Health Technology Assessment Report 8

The use of epoetin alfa before orthopaedic surgery in patients with mild anaemia

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Health Technology Assessment Report 8

The use of epoetin alfa before orthopaedic surgery in patients with mild anaemia

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1 EXECUTIVE SUMMARY

This Health Technology Assessment (HTA) makes recommendations to NHSScotland on the use of epoetin alfa.

This drug is licensed for use in patients with mild anaemia (haemoglobin concentration of 10-13 grams per decilitre (g/dL)) before planned orthopaedic surgery with expected moderate blood loss, to reduce exposure to allogeneic blood transfusion.

The Scottish Arthroplasty Project Annual Report (NHSScotland, 2005) showed that in 2004 there were 4,664 primary hip and 3,875 primary knee replacements, and 760 revision hip and 275 revision knee replacements. Some of these patients will have mild anaemia and thus be consistent with the indication. A recent study of blood bank records from a Scottish hospital showed that 20% of such patients are transfused during their admission.

Patients with existing anaemia are more likely to require a peri-operative blood transfusion. Such patients should have the underlying cause of their anaemia identified and treated at the time of referral to the orthopaedic service. In many cases this will involve iron therapy to improve the haemoglobin levels. Checking anaemia at the time of referral affords time to treat it. Delaying the identification of anaemia reduces the time period within which the condition can be addressed. Failure to treat existing anaemia may result in surgery being delayed but there is no evidence that surgery in Scotland would be postponed for the mild anaemia relevant to this indication.

An alternative therapy for some patients with preoperative anaemia and with adequate iron stores is treatment with epoetin alfa by three or four weekly injections prior to surgery. Treatment with epoetin alfa in conjunction with iron supplementation has been shown to be clinically effective in reducing the need for transfusion in patients undergoing elective orthopaedic surgery. A recent survey showed that the major barrier to widespread use of epoetin alfa is its high cost.

Allogeneic blood transfusions, being blood donated from a donor, are associated with risk of infections including hepatitis B and C and HIV, adverse reactions and transfusion errors. The risk of many of these adverse events has decreased considerably over the last decade due to initiatives such as the implementation of universal leucodepletion of donor blood cells, improved testing methods and enhanced training for medical staff handling blood. The Scottish National Blood Transfusion Service (SNBTS) and NHSScotland have continuing programmes of work to improve transfusion practice in Scotland.

Using epoetin alfa to correct preoperative anaemia thus offers the potential to reduce the number of transfusions and conserve blood stocks. Reducing the number of patients receiving allogeneic blood transfusion also reduces the risk to patients and, by avoiding adverse events, reduces the costs to NHSScotland. This HTA examined whether administering epoetin alfa is cost effective, by comparing the cost of treatment with the potential costs avoided by reducing the number of allogeneic blood transfusions. It also considers the cost of using epoetin alfa as a blood sparing technology and compares that cost to the current cost of a unit of blood.

The cost of a course of epoetin alfa is about £1,350. In comparison the cost of a unit of standard red blood cells is around £130. This is the charge that the English National Blood Transfusion Service makes to hospitals in England and Wales. In Scotland there are no explicit charges between SNBTS and hospitals for blood components. In addition, hospitals incur handling, laboratory and administration costs that add a further £100 to the cost of a unit, giving a total cost per unit of red blood cells of about £230.

Certain groups, primarily Jehovah’s Witnesses will not accept allogeneic blood transfusion for religious reasons. In other patient groups, matching blood for allogeneic transfusion may be problematic. Currently, these patients benefit from a range of management strategies that do not involve allogeneic blood transfusion.

Methods

This HTA takes account of the clinical and cost effectiveness evidence comparing epoetin alfa with standard care, and considers the potential impact on patients and on NHSScotland. Evidence identified by literature searching and provided by experts, patient interest groups and the manufacturer was critically appraised and expert staff undertook robust analyses. Review by health professionals, other experts and wide public consultation ensure that all views are considered.

Results and conclusions

The clinical evidence showed that administering epoetin alfa before operations was effective at reducing the number of patients who required transfusion compared with placebo and the mean number of units transfused declined by 0.5-0.7 units per patient. However, there was no reduction in the number of units used per transfused patient and hence the benefit was primarily in fewer patients being transfused. None of the studies reported significant differences in length of stay or postoperative infection rates as a result of using epoetin alfa.

The studies were in settings with different transfusion policies from those currently in use across Scotland; in particular the standard care arms had higher transfusion rates than those observed in Scotland. It is thus unclear to what extent the clinical effectiveness results can be generalised to Scotland.

Published evidence on the cost effectiveness of epoetin alfa showed that the incremental cost per life year gained is extremely high. The main conclusion from each study was using epoetin alfa in orthopaedic surgery is not cost effective.
A key factor in cost effectiveness in some settings was the risk of developing nosocomial bacterial infections. As Scotland has implemented universal leucodepletion of donor blood cells, it was decided to develop a cost-utility model to estimate the incremental cost effectiveness of epoetin alfa in the Scottish setting. The results confirmed that using epoetin alfa was not cost effective, having a cost per quality adjusted life year of over £21 million.

The analyses also considered whether it was cost effective to use epoetin alfa as a blood sparing treatment. The cost of transfusing a unit of blood would have to rise from around the current level of £230 to over £2,750 before using epoetin alfa became cost effective.

Sensitivity analyses show the results are robust to extreme changes in parameter values. However, if there is a material increase in the risk from an adverse event, for example if the risk of variant Creutzfeldt-Jacob disease (vCJD) should increase, then it may be informative to update the analyses. Alternatively, if the price of epoetin alfa should fall, for example with the launch of a generic formulation, or if the demand for blood were to outstrip supply, then again it may be worth re-running the model to reflect the new parameters.

The introduction of clinical standards for blood transfusions may change management practices and encourage the greater use of blood sparing technologies to include use of blood salvage techniques, anti-fibrinolytic drugs, acute normovolaemic haemodilution and optimising preoperative haemoglobin level using iron or epoetin alfa. The economic model could be adapted to compare these technologies.

**Recommendations**

Epoetin alfa is not recommended for general use by NHSScotland to reduce exposure to allogeneic blood transfusion in patients with mild anaemia prior to major elective orthopaedic surgery.

Epoetin alfa is recommended for restricted use within NHSScotland. It is a possible treatment option for patients with mild anaemia prior to major elective orthopaedic surgery who cannot receive blood transfusion, either due to their religious convictions or because suitable blood is unlikely to be available.

**Resource implications of recommendations**

These recommendations are not estimated to change resource use in NHSScotland.
2 INTRODUCTION

This document makes recommendations to NHSScotland based on a completed Health Technology Assessment (HTA), on the potential use of epoetin alfa prior to major elective orthopaedic surgery to reduce the subsequent exposure of patients to allogeneic blood transfusion. Use would be restricted to patients with mild anaemia (haemoglobin concentrations of 10-13 grams per decilitre (g/dL)), when an autologous predonation programme is not available and moderate surgical blood loss (900-1800 mL) is expected. Section 3 of the document provides information on NHS Quality Improvement Scotland (NHS QIS) and on the HTA process.

The main types of orthopaedic surgery where epoetin alfa might benefit patients are in hip and knee replacements. Background on the numbers of primary and revision hip and knee replacements, the presentation of anaemia, and comparison of the use of epoetin alfa with other blood sparing technologies is provided in Section 4. Clinical evidence on the use of epoetin alfa in the orthopaedic setting is summarised in Section 5 and economic analyses are presented in Section 6. Patient issues are considered in Section 7. Section 8 discusses the findings and presents the recommendations.
3 BACKGROUND ON NHS QUALITY IMPROVEMENT SCOTLAND

NHS QIS was set up by the Scottish Parliament in 2003 to take the lead in improving the quality of care and treatment delivered by NHSScotland. NHS QIS sets standards, monitors performance and provides NHSScotland with advice, guidance and support on effective clinical practice and service improvements.

Health Technology Assessment

HTA is an internationally recognised process used by NHS QIS to advise NHSScotland about a specific health intervention, eg medicine, equipment or diagnostic test. HTA evaluates the clinical and cost effectiveness of the various ways in which a particular intervention can be used, comparing alternatives where appropriate. Patient and organisational issues are also considered.

Evidence is identified by literature searching and assimilating expert evidence, the views of patient interest groups and manufacturers. The evidence is then critically appraised and robust analyses are undertaken by expert staff. Surveys may also be undertaken to ascertain current clinical practice and patient preferences.

NHS QIS staff from a variety of disciplines conduct the assessment, with considerable input from health professionals expert in the particular area of interest (see Appendix 1). Peer review and wide public consultation ensures that all views are considered.
4 SETTING THE SCENE

4.1 Orthopaedic surgery in Scotland

The Scottish Arthroplasty Project’s Annual Report, 2005 presented the national trends in the number of orthopaedic operations performed by NHSScotland over the years 1992-2004 (NHSScotland, 2005). The report described a gradual increase in the number of primary hip and knee replacements over the period, with 4,664 hip and 3,875 knee operations performed in 2004. The recent trend in the revision of hip and knee replacements is downwards, with 760 hip and 275 knee procedures in 2004. The majority of these operations were performed electively.

These procedures are frequently associated with substantial blood loss, requiring transfusion of allogeneic red blood cells. It was estimated that in 2003-2004, these four procedures used about 5,250 units of red blood cells, equivalent to 15% of the total red blood cells used in Scotland (Dr B Perry, Director of the NHSS Better Blood Transfusion Programme, SNTBS, personal communication, November 2005). Table 4-1 shows the number of episodes, percentage transfused and number of red blood cell units transfused per episode for the major four types of elective orthopaedic surgery (Dr B Perry, personal communication, November 2005).

Patients undergoing revision procedures are thus more likely to receive a red cell blood transfusion and receive a higher number of units during each transfusion.

SNBTS plans to publish such information on a range of surgical procedures in Scotland (Dr B Perry, personal communication, November 2005).

A UK guideline for the management of surgical patients recommends that, ideally, transfusion is avoided for appropriate procedures (Murphy et al., 2001). As preoperative haemoglobin concentration is a prognostic indicator of transfusion risk (Aderinto & Brenkel, 2004), appropriate investigation and treatment of the condition is required prior to elective surgery (Murphy et al., 2001). In addition, the combination of anaemia with other co-morbidities increases mortality, emphasising the need for effective treatment prior to orthopaedic procedures (Carson et al., 1996).

4.2 Current management of anaemia in elective orthopaedic surgery

Anaemia is a reduction in the concentration of erythrocytes or haemoglobin in the blood and occurs when there is an imbalance between blood loss (through bleeding or destruction) and blood production (Dorland’s Illustrated Medical Dictionary, Dorland’s illustrated medical dictionary, 2000). The World Health Organisation states that anaemia exists in adults whose haemoglobin levels are lower than 13 g/dL (males) or 12 g/dL (females). Anaemia of differing severity is graded as shown in Table 4-2.

        Table 4-1  Surgical blood use in orthopaedic surgery 2003-04

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Number of episodes</th>
<th>% Episodes transfused</th>
<th>Red blood cells units /episode transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary hip replacement</td>
<td>3,758</td>
<td>26.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Primary knee replacement</td>
<td>2,888</td>
<td>14.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Revision hip replacement</td>
<td>578</td>
<td>63.3</td>
<td>4.0</td>
</tr>
<tr>
<td>Revision knee replacement</td>
<td>223</td>
<td>32.7</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Table 4-2  Grading systems for anaemia

<table>
<thead>
<tr>
<th>Severity</th>
<th>World Health Organisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (WNL*)</td>
<td>≥11.0 g/dL</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>9.5 to 10.9 g/dL</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>8.0 to 9.4 g/dL</td>
</tr>
<tr>
<td>Grade 3 (serious/severe)</td>
<td>6.5 to 7.9 g/dL</td>
</tr>
<tr>
<td>Grade 4 (life-threatening)</td>
<td>&lt; 6.5 g/dL</td>
</tr>
</tbody>
</table>

* WNL = within normal limits

Note number of recorded episodes are similar to, but slightly lower than, the numbers recorded in the Scottish Arthroplasty Project Annual Report.
treatment. Treatment options depend on the cause of anaemia and include replacement of iron, vitamin B₁₂, or clotting factors and treatment of the cause of the condition. Failure to treat anaemia may result in surgery being postponed but there is no evidence that in Scotland surgery is being delayed because of mild anaemia as defined in the indication for epoetin alfa. However, failure to treat more severe anaemia in sufficient time to allow the iron deficiency to be addressed does impact adversely on surgical lists (Mr A Muirhead, Consultant Orthopaedic Surgeon, NHS Ayrshire and Arran, personal communication, March 2006).

The main treatment for postoperative anaemia is allogeneic blood transfusion to quickly reverse the condition. The Guidance recommends that patients should not normally be transfused if their haemoglobin concentration is above 10 g/dL. A strong indication for transfusion is a haemoglobin concentration below 7 g/dL. Patients who are symptomatic and have haemoglobin concentrations between these levels should also be transfused.

Alternative blood sparing approaches applicable to elective orthopaedic procedures include autologous donation, where blood is collected from the patient prior to surgery and re-infused during the procedure as required (Toy et al., 1987). However, serial phlebotomy can result in progressive haemodilution causing iatrogenic anaemia (British Orthopaedic Association, 2005) and increases the likelihood of the patient requiring perioperative transfusion (Faris & Ritter, 1998; Forgie et al., 1998). The collection of adequate amounts of blood by pre-donation can, therefore, be challenging and is not routinely recommended for primary joint arthroplasties (British Orthopaedic Association, 2005).

Other blood sparing strategies include acute normovolaemic haemodilution, the use of anti-fibrinolytic drugs, cell salvage and erythropoietin (Scottish Intercollegiate Guidelines Network, 2001). Slappendel et al. (2003) undertook a review of over 28,860 orthopaedic surgery patients in a hospital in Maastricht to determine the effectiveness of combining several measures, to include administering epoetin alfa, in a protocol, with the objective of reducing the number of red cell transfusions. This study reported an 80% reduction in red blood cell use, but it was not possible to attribute a specific proportion of the reduction to any one factor. Rather, the study showed that using a range of methods can reduce the need for transfusions. However, this HTA is limited to considering the clinical and cost effectiveness of epoetin alfa.

4.3 Availability of red blood cells for transfusion

A major issue associated with the use of allogeneic blood is the maintenance of sufficient stocks. The problems associated with falling numbers of donors has been exacerbated by the recent exclusion in the UK of previously transfused individuals, as a result of concerns over VCJD transmission (Hartley & Robinson, 2004). This may have resulted in a loss of 3.2% (52,000) of blood donors. The average age of patients receiving blood transfusion is 63 years, and it has been estimated that the increasing size of the aging population will lead to an increase of 4.9% in the annual red blood cell demand by 2008 (Thomas et al. ed., 2004). One reason for this increased demand is the likelihood that the numbers of hip and knee replacement will continue to rise. In addition, the costs associated with collecting and producing a unit of red blood cells are estimated to have risen from £47 in 1998 to over £120 in 2004, as a result of the requirement for more stringent safety testing (Wilson et al., 2005). Given the increasing concerns over the availability of allogeneic blood and cost considerations, alternative approaches to dealing with blood loss during orthopaedic surgery are required (British Orthopaedic Association, 2005).

The Scottish Executive Health Department have taken various steps to improve the management of blood stocks to ensure blood is used in a clinically appropriate way and according to safe standard procedures (Scottish Executive Health Department, 2003; Scottish Executive Health Department, 2005; Scottish Executive Health Department, 1999). A key part of the strategy to improve practices is the NHSScotland Better Blood Transfusion Programme (www.betterblood.org.uk). Further support is provided by the introduction of clinical standards for blood transfusions. These include standards to trace every unit of blood donated and to optimise use of blood (NHS Quality Improvement Scotland, 2005a). These initiatives support the work of SNBTS in providing blood products for safe transfusion in Scotland.

Such measures recognise that whilst currently in Scotland blood supplies exceed demand, with over 250,000 donations given each year (NHS Quality Improvement Scotland, 2005a), this position may not continue in the medium term (Scottish National Blood Transfusion Service, 2004).

4.4 Epoetin alfa (epoetinum alfa or erythropoietin alfa)

Epoetin alfa is a hormone produced by renal cells in response to hypoxia, and stimulates erythroid stem cell precursors in the bone marrow to proliferate and differentiate. The resulting erythrocytes are released into the circulation. Epoetin alfa (Eprex®, Janssen-Cilag), the human recombinant form of erythropoietin alfa, is licensed in the UK to treat: anaemia in patients with renal failure, anaemia in adults receiving cancer chemotherapy, patients with mild anaemia prior to elective orthopaedic surgery to reduce the risk of allogeneic blood transfusion, or to increase autologous blood volumes as part of a predonation programme (British National Formulary 50, 2005). This HTA focuses on the use of epoetin alfa prior to elective orthopaedic surgery.

4.5 Treatment indications

The licensed orthopaedic uses for Eprex® (Janssen-Cilag, 2005) are:

- To increase the yield of autologous blood from patients in a predonation programme. Treatment is only given to patients with mild anaemia (haemoglobin concentration of between 10-13 g/dL.
with no iron deficiency) if blood saving procedures are not available or are insufficient as a large volume of blood (four or more units of blood for females or five or more units for males) may be needed.

- To reduce exposure to allogeneic blood transfusion in non-iron deficient adults at high risk of transfusion complications, prior to major elective orthopaedic surgery. Use is restricted to patients with mild anaemia (haemoglobin concentration of between 10-13 g/dL) where an autologous predonation programme is not available and when moderate blood loss (900-1800 mL) is expected.

The range of haemoglobin levels within the licensed indication encompasses the WHO grade of mild and ‘within normal limits’. In this document the haemoglobin concentrations between 10-13 g/dL are defined as ‘mild anaemia.’ In Scotland, little use is made of predonation programmes, therefore only the second indication is considered in this HTA.

4.6 Treatment regimen

It is recommended that patients scheduled for orthopaedic surgery receive subcutaneous epoetin alfa at a dose of 600 IU/kg given weekly for 3 weeks prior to surgery and on the day of surgery, with iron supplementation. An alternative regimen is 600 IU/kg given for 15 days, starting 10 days before surgery.

4.7 Product price

The net vial price of epoetin alfa (Eprex®, Janssen-Cilag) is £7.96 for 1,000 units in an injection pre-filled syringe; £15.92 for 2,000 units; £23.88 for 3,000 units; £31.84 for 4,000 units; £39.81 for 5,000 units; £47.77 for 6,000 units; £63.69 for 8,000 units; and £79.61 for 10,000 units (British National Formulary 50, 2005). For a person weighing 70 kilograms a course of four weekly treatments costs about £1,340 compared to a cost of £2,510 for the recommended daily regimen.

4.8 Orthopaedic use of epoetin alfa

Epoetin alfa is clinically effective in the management of mild anaemia (haemoglobin level of between 10-13 g/dL) prior to surgery, (British Orthopaedic Association, 2005). The level of use of erythropoietin in the orthopaedic setting varies greatly between countries, with 1% of hospitals in Australia using the treatment, 43% in the United States and 51% in Japan from 1995-1997 (Fergusson et al., 1999). This study noted that orthopaedic erythropoietin use in Scotland during this period was estimated to occur in 6% of hospitals.

The SIGN Guidelines (Scottish Intercollegiate Guidelines Network, 2001) recommended that:

- Erythropoietin use should be targeted to patients aged under 70 years who are scheduled for major blood losing surgery and who have a presenting haemoglobin <130g/L.
- Erythropoietin be used to prepare patients who have objections to allogeneic transfusion for surgery that involves major blood loss.

These recommendations only assessed the clinical evidence base for erythropoietin use and considered a wider indication than specified by the licence.
5 CLINICAL EFFECTIVENESS

5.1 Introduction

This chapter studies the effectiveness of epoetin alfa in adults with mild anaemia (haemoglobin concentration of between 10-13g/dL) scheduled to undergo major orthopaedic surgery. The assessment considered the rate of transfusion, amount of blood transfused, length of hospital stay, rate of infection and the incidence of adverse events. The effectiveness of epoetin alfa alone was compared with that of standard hospital practice. Section 5.2 describes the methodology used to extract information from the published literature and to carry out statistical analyses. The findings are described in Section 5.3 and discussion and conclusions follow in Section 5.5 and 5.5. The assessment was carried out in accordance with the SIGN guidance for systematic reviews (Scottish Intercollegiate Guidelines Network, 2004).

5.2 Methodology

5.2.1 Evidence sources

Evidence was obtained from a variety of sources including published and grey literature, and information from manufacturers and clinical experts.

Literature search

Initial scoping searches to establish the quantity and quality of existing literature considering the use of epoetin alfa in surgical patients were performed in September 2004. These were updated in June 2005, to include blood management in surgical patients. Particular attention was paid to finding studies by other HTA organisations, systematic reviews, research in progress, guidelines and policy documents. A full list of information sources is presented in Appendix 2.

The results of the scoping searches led to the decision to undertake a comprehensive systematic literature search for primary studies relating to the use of epoetin alfa specifically in orthopaedic surgery. Only studies in orthopaedic surgery were included to correspond to the licensed indication in the Summary of Product Characteristics (SPC). The search was performed in June-September 2005. Orthopaedic search terms were identified by: using the MeSH thesaurus, consulting with experts and confirming the procedures listed by North Glasgow Trust in their Blood Transfusion Guidelines Maximum Blood Ordering Schedule http://www.ngt.org.uk/transfusion/appendix7.htm. From the scoping work, it was anticipated that the quantity of literature retrieved would be small, therefore the search was not restricted by study design, language or date.

The strategy used to search the MEDLINE, EMBASE and CINAHL databases through the OVID multi-file interface is presented in Appendix 2. This strategy was modified for the other databases used (see also Appendix 2). A complete listing of strategies can be obtained by contacting NHS QIS.

Literature was also identified using the British Library's Table of Contents alerts service, by citation searching on key papers, and from scanning the bibliographies of retrieved items.

A flow diagram showing the number of records identified and then included in the report and analysis is given in Appendix 2.

5.2.2 Selection criteria

Studies were selected according to the inclusion/exclusion criteria listed in Table 5-1.

5.2.3 Methodology for analyses

This section defines the analyses carried out followed by a description of the methods used to perform them.

Table 5-1 Selection criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>Orthopaedic surgery: Preoperative autologous donation not used.</td>
<td>Other surgery and indications</td>
</tr>
<tr>
<td>Intervention</td>
<td>Epoetin alfa given subcutaneously presurgery, either at: 600 IU/kg or 40 KU once per week for 4 weeks prior to surgery ('weekly'), or 300 IU/kg once a day for 10 days prior to surgery and 4 days post surgery ('daily').</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>Placebo or control.</td>
<td>Other blood saving interventions</td>
</tr>
<tr>
<td>Design</td>
<td>Randomised controlled trials (RCTs) with some evidence of blinding Systematic review of RCTs.</td>
<td></td>
</tr>
<tr>
<td>Endpoint(s)</td>
<td>Transfusion (yes or no).</td>
<td>Absence of this endpoint</td>
</tr>
<tr>
<td>Language</td>
<td>English</td>
<td>Foreign</td>
</tr>
<tr>
<td>Dates</td>
<td>All</td>
<td></td>
</tr>
</tbody>
</table>
Analyses

The primary analysis related to adult patients with haemoglobin concentrations of 10-13 g/dL prior to major orthopaedic surgery reflecting the licensed indication. Data from all studies providing information on transfusion rates for this group of patients were included. The primary endpoint was whether or not patients were transfused. The amount of blood transfused, length of hospital stay and infection rates formed secondary endpoints. Additional analyses of the primary endpoint were carried out to determine whether clinical effectiveness varied according to surgery type (primary or revision), dosage regime (weekly or daily) and baseline study transfusion rate. Baseline study transfusion rate represents the background rate of transfusion in the study setting and is defined as the rate of transfusion observed in placebo or control patients. The analysis to determine its effect on efficacy was performed because transfusion practices varied between countries (Weber et al., 2005) and orthopaedic surgeons had advised that there was a recent trend towards less frequent transfusion. This trend was apparent in data from the SNBTS. As the transfusion rate in Scotland is currently lower than seen in the placebo arms of all the studies selected it was desirable to determine whether the effectiveness of epoetin alfa was altered when there was a reduction in the tendency to transfuse.

Meta analyses were used to combine information across studies in each analysis.

Statistical methods

Transfusion (yes or no) was assessed using a generalised linear mixed model (GLMM) with a binomial error function. Treatment effects (epoetin alfa or placebo/control) were fitted as fixed effects and the trial by treatment interaction as random effects. Heterogeneity between studies was assessed by testing the significance of the study by treatment variance component, using a likelihood ratio test. Publication bias was assessed by calculating the correlation between the standard error of the treatment effect (reflecting the study size) and the size of the treatment effect. A significant positive correlation would indicate that smaller studies were more likely to produce larger treatment effects, and hence show a publication bias.

To determine whether the treatment effect varied between patient subgroups, interactions between treatment and subgroups were additionally included in the generalised linear mixed model. Subgroups were considered based on surgery type (primary or revision), dose regimen (daily or weekly), and baseline study transfusion rate. A separate treatment effect estimate for each subgroup was produced.

The amount of blood transfused was analysed using a fixed effects meta analysis model. Only three trials recorded this endpoint and it was not, therefore, appropriate to use a random effects model.

Results are presented in terms of odds ratios with 95% confidence intervals for transfusion and mean treatment differences for the amount of blood transfused, again with 95% confidence intervals. The models were fitted using the MIXED and GLIMMIX procedures in the SAS software package.

Quality assurance

A selection of studies and statistical analyses were quality assured by internal NHS QIS staff. Peer review also provided an external check on quality.

5.3 Results

5.3.1 Studies included

One systematic review and four randomised controlled trials satisfied the inclusion/exclusion criteria.

The systematic review (Laupacis & Fergusson, 1998) considered the effectiveness of epoetin alfa in cardiovascular and orthopaedic surgery. Patients with all levels of baseline haemoglobin and all epoetin alfa dosing regimes were included in this review, though some dose levels fell below those in the licensed indication. Three studies considered the use of epoetin alfa alone in orthopaedic surgery. These studies were included in the current assessment along with a fourth study, Feagan et al. (2000), which was published later.

An additional study, Weber et al. (2005), did not fully meet the inclusion criteria, as the treatment allocation was not blind and patients were allowed to undergo preoperative autologous donation. However, preoperative autologous donation was only available in two of the six countries (France and Germany), representing 21% of study population and was only received by 5% of total study population. The study was excluded from the main meta-analyses; however, since it was a large and recent study covering several countries, and including patients with the exactly required baseline haemoglobin range, a second set of meta-analyses were additionally performed including it.

Details of the studies considered in the assessment are presented in Table 5-2. Treatment arms not consistent with the licence were excluded from analyses, these are square bracketed in Table 5-2. In addition to the outcomes listed in Table 5-2, all studies reported thrombotic and other adverse events.

Faris (1996), De Andrade et al. (1996) and Weber et al. (2005) provided data for patients with baseline haemoglobin 10-13 g/dL. The COPES (Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993) and Feagan et al. (2000) studies provided data for a slightly different baseline haemoglobin range and are included in the analyses. COPES provided data for haemoglobin levels <13.5g/dL, however very few patients (6 of 208) had haemoglobin levels <10g/dL. Feagan et al. (2000) included patients with baseline haemoglobin levels of 9.8-13.7g/dL. The studies either included all types of orthopaedic procedures or just hip and knee surgery. However, in studies of all orthopaedic procedures the...
majority of patients underwent knee or hip surgery. All studies included patients scheduled to receive revision or primary surgery. Two studies were performed in the US (Faris (1996) and De Andrade et al. (1996)), two in Canada (Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993) and Feagan et al. (2000)) and one Weber et al. (2005) in six, mainly European, countries. Patients received iron supplementation concurrently in all studies except Weber et al. (2005). In this study, iron was received by all epoetin alfa patients but only administered to control patients if in line with local hospital policy. This resulted in 76% of the controls receiving iron supplementation.

All the studies analysed data using an intention to treat approach and included data from all patients who had undergone surgery.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Number of patients</th>
<th>Treatment groups</th>
<th>Baseline haemoglobin level</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laupacis &amp; Fergusson (1998)</td>
<td>Orthopaedic and cardiovascular surgery</td>
<td>684 (3 studies)</td>
<td>1. Epoetin alfa (all doses and regimes) 2. Placebo</td>
<td>All levels</td>
<td>Transfusion</td>
<td>Systematic review including COPES, Faris et al. and De Andrade et al.</td>
</tr>
<tr>
<td>COPES (1993)</td>
<td>Elective hip replacement</td>
<td>208</td>
<td>1. Epoetin alfa (daily) 2. Placebo 10 to 5 days before surgery then daily epoetin alfa] 3. Placebo</td>
<td>All levels Patients with levels &lt;13.5 g/dL studied separately</td>
<td>Transfusion Units of blood transfused Length of stay</td>
<td>Canada All patients received oral iron.</td>
</tr>
<tr>
<td>Faris (1996)</td>
<td>Orthopaedic surgery with expected blood loss 2 units, patients unable or unwilling to participate in the study.</td>
<td>200</td>
<td>1. (daily) 2. 100IU/kg daily 3. Placebo</td>
<td>&lt;15. 1013 Patients with levels 10-13g/dL studied separately</td>
<td>Transfusion</td>
<td>US All patients received oral iron</td>
</tr>
<tr>
<td>De Andrade et al. (1996)</td>
<td>Knee and hip</td>
<td>316</td>
<td>1. Epoetin alfa (daily) [2. Epoetin alfa 100 IU/kg daily] 3. Placebo</td>
<td>All levels Patients with levels 10-13 g/dL studied separately</td>
<td>Transfusion Units of blood transfused Length of stay</td>
<td>US All patients received oral iron. Analysis by hip and knee, and haemoglobin group.</td>
</tr>
<tr>
<td>Weber et al. (2005)</td>
<td>Orthopaedic (all types)</td>
<td>685</td>
<td>1. Epoetin alfa (weekly) 2. Control</td>
<td>9.8-13.7 g/dL</td>
<td>Transfusion (yes or no) Length of stay Post-operative infection</td>
<td>Netherlands, France, Germany, Sweden, Belgium and Australia. Preoperative autologous donation available in France and Germany (21%). Epoetin alfa group received oral iron, control group received iron depending on hospital policy.</td>
</tr>
</tbody>
</table>

1Daily = 300 IU/kg epoetin alfa given daily from 10 days prior to surgery to 4 days following surgery.
2Weekly = 40 K U or 600 IU/kg epoetin alfa given weekly 3 or four 4 prior to surgery up until surgery.
[Treatment groups] that received doses not consistent with the SPC and were excluded from analyses.
5.3.2 Primary endpoints

The incidence of transfusion in patients with baseline haemoglobin of 10-13g/dL is shown in Table 5-3. Meta-analyses showed that patients receiving epoetin alfa had a significantly lower likelihood of undergoing transfusion than patients receiving placebo (p=0.007 excluding Weber et al., p=0.0002 including Weber et al.). The odds ratio of transfusion for patients receiving epoetin alfa was about seven times less than that for patients receiving placebo. There was no significant evidence of heterogeneity between the studies (study by treatment variance component=0.0, p=1.0), or of publication bias (p=0.5).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Epoetin alfa</th>
<th>Placebo or control</th>
<th>Odds ratio (95% CI) for EPO vs placebo/control</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPES (1993)</td>
<td>33 (10/30)</td>
<td>74 (23/31)</td>
<td>0.174 (0.058-0.526)</td>
</tr>
<tr>
<td>Faris (1996)</td>
<td>14 (3/22)</td>
<td>78 (21/27)</td>
<td>0.045 (0.010-0.206)</td>
</tr>
<tr>
<td>De Andrade et al. (1996)</td>
<td>16 (5/32)</td>
<td>45 (13/29)</td>
<td>0.228 (0.069-0.759)</td>
</tr>
<tr>
<td>Feagan et al. (2000)</td>
<td>11 (5/44)</td>
<td>45 (35/78)</td>
<td>0.158 (0.056-0.442)</td>
</tr>
<tr>
<td>Weber et al. (2005)</td>
<td>12 (55/460)</td>
<td>46 (107/235)</td>
<td>0.167 (0.114-0.244)</td>
</tr>
<tr>
<td>Meta analysis - excluding</td>
<td></td>
<td></td>
<td>0.148 (0.058-0.375)</td>
</tr>
<tr>
<td>Weber et al.</td>
<td></td>
<td></td>
<td>0.162 (0.111-0.238)</td>
</tr>
<tr>
<td>- including Weber et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 5-1  Forest plot corresponding to the percentage of patients transfused and odds ratios for patients with mild anaemia.
Type of surgery (revision or primary)

Results were only available according to type of surgery in COPES (Canadian Orthopedic Perioperative Erythropoietin Study Group (COPES), 1993) and Weber et al. (2005). However, only Weber et al. gave results for patients with haemoglobin concentrations of 10-13 g/dL. Treatment effects were not significantly associated with type of surgery in either study.

Dose regimen

There was no significant interaction between treatment effect and whether patients received a daily or weekly dosing regimen (p=0.6). Results are presented by dose regimen in Table 5-6.

Table 5-4 Placebo or control study transfusion rates and treatment odds ratios

<table>
<thead>
<tr>
<th>Reference</th>
<th>Transfusion policy</th>
<th>Transfusion rate</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPES (1993)</td>
<td>A 15% loss of intravascular volume and: - unstable haemoglobin levels or - a stable haemoglobin level &lt;9 g/dL.</td>
<td>0.44</td>
<td>0.174 (0.058-0.526)</td>
</tr>
<tr>
<td>Faris (1996)</td>
<td>At surgeon's discretion. Effort made to avoid transfusion if haemocrit&gt;27%.</td>
<td>0.38</td>
<td>0.045 (0.010-0.206)</td>
</tr>
<tr>
<td>De Andrade et al. (1996)</td>
<td>At surgeon's discretion. 91% of patients transfused had haemoglobin &lt;9 g/dL and 38% had high intra-operative blood loss.</td>
<td>0.25</td>
<td>0.228 (0.069-0.759)</td>
</tr>
<tr>
<td>Feagan et al. (2000)</td>
<td>At surgeon's discretion. Usual practice to transfuse only if patient symptomatic and not on the basis of haemoglobin levels.</td>
<td>0.21</td>
<td>0.158 (0.056-0.442)</td>
</tr>
<tr>
<td>Weber et al. (2005)</td>
<td>If haemoglobin level below that specified in hospital protocol. If no protocol haemoglobin level &lt;8 g/dL used.</td>
<td>0.08</td>
<td>0.167 (0.114-0.244)</td>
</tr>
</tbody>
</table>

*As presented in Table 5-3

Table 5-5 Frequency of transfusion and odds ratios by surgery type

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Reference</th>
<th>Transfused % (n/total)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Epoetin alfa</td>
<td>Placebo or control</td>
</tr>
<tr>
<td>Primary</td>
<td>COPES (1993)</td>
<td>20 (13/66)</td>
<td>43 (29/67)</td>
</tr>
<tr>
<td></td>
<td>Weber et al. (2005)</td>
<td>11 (48/421)</td>
<td>45 (96/213)</td>
</tr>
<tr>
<td>Revision</td>
<td>COPES (1993)</td>
<td>45 (5/11)</td>
<td>45 (5/11)</td>
</tr>
<tr>
<td></td>
<td>Weber et al. (2005)</td>
<td>21 (8/39)</td>
<td>50 (11/22)</td>
</tr>
</tbody>
</table>

Table 5-6 Frequency of transfusion and odds ratio by dose regime

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Reference</th>
<th>Transfused % (n/total)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Epoetin alfa</td>
<td>Placebo or control</td>
</tr>
<tr>
<td>Daily</td>
<td>COPES (1993)</td>
<td>33 (10/30)</td>
<td>74 (23/31)</td>
</tr>
<tr>
<td></td>
<td>De Andrade et al. (1996)</td>
<td>14 (3/22)</td>
<td>78 (21/27)</td>
</tr>
<tr>
<td></td>
<td>Faris (1996)</td>
<td>16 (5/32)</td>
<td>45 (13/29)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>Feagan et al. (2000)</td>
<td>11 (5/44)</td>
<td>45 (35/78)</td>
</tr>
<tr>
<td></td>
<td>Weber et al. (2005)</td>
<td>12 (55/460)</td>
<td>46 (107/235)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis (including Weber et al.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.3.3 Secondary endpoints

Units of blood transfused

Results for the amount of blood transfused in patients with mild anaemia are shown in Table 5-7 for studies where this was recorded. Although Faris (1996) recorded the amount of blood transfused, he did not distinguish patients with a baseline haemoglobin concentration of 10-13 g/dL and this study is not, therefore included in the analysis. Patients receiving epoetin alfa required significantly less transfused blood than patients receiving placebo (p<0.0001 in analyses including and excluding Weber et al. (2005)).

Although not an endpoint for this study, Weber et al. (2005) provided results in terms of number of units transfused per transfused patient and reported no significant difference. These results are used within the health economic model (Section 6).

Length of hospital stay and infection rates

COPES (1993), De Andrade et al (1996) and Weber et al (2005) all considered the length of hospital stay and reported no significant difference between the epoetin alfa and placebo treatment groups. However, COPES and De Andrade did not have the power to detect clinically significant differences. The largest study (Weber et al.) had the power to detect a mean difference between groups of greater than 1.5 days.

Weber et al. was the only study to report postoperative infection rates (9.4% on epoetin alfa and 10.6% on control) and did not show a statistically significant difference between treatment groups. However, the study only had the power to detect a difference of more than 70% and was likely to miss smaller but clinically significant differences.

Figure 5-2 Forest plot corresponding to the frequency of transfusion and odds ratio by dose regime

Table 5-7 Mean units of blood transfused

<table>
<thead>
<tr>
<th>Reference</th>
<th>Units transfused per patient mean± SD, n</th>
<th>Mean difference in number of units transfused (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feagan et al. (2000)</td>
<td>0.3 ± 0.7 (44)</td>
<td>0.700 (0.363-1.037)</td>
</tr>
<tr>
<td>Weber et al. (2005)</td>
<td>0.152 ± 0.227 (458)</td>
<td>0.493 (0.403-0.583)</td>
</tr>
<tr>
<td>Meta-analysis</td>
<td>0.646 ± 0.671 (253)</td>
<td></td>
</tr>
<tr>
<td>- including Weber et al.</td>
<td></td>
<td>0.510 (0.427-0.591)</td>
</tr>
</tbody>
</table>

* The standard error of the difference (used to determine 95% CI) was calculated as √(SD₁²/n₁ + SD₂²/n₂)

* The mean number of red blood cell units transfused was cited per transfused patient. The data were converted to a mean for all patients using:
  \[
  \text{mean} = \text{mean}_t \times n_t/n \quad \text{varall} = (SD_t^2 \times (n_t - 1)) + \text{mean}_\text{all}^2 \times (n_\text{all} - n_t) / (n_\text{all} - 1) \\
  \text{mean}_\text{all} = \text{mean units transfused for transfused patients/total number of patients} \\
  n_t = \text{number transfused/total number of patients} \\
  SD_t = \text{standard deviation for transfused patients.}
  \]
5.3.4 Adverse events

Rates of thrombotic and all adverse events are summarised in Table 5-8. Data are only presented for epoetin alfa dosage regimens consistent with the licensed indication (40 K U or 600 IU/kg in four weekly doses prior to surgery, or 300 IU/kg daily for 10 days prior to surgery and 4 days post surgery), to correspond with statistical analyses.

None of the studies showed a statistically significant difference between the treatment groups, however they lacked the power to detect clinically significant differences. Thus, there was insufficient information to assess the safety of epoetin alfa in orthopaedic surgery.

The systematic review by (Laupacis & Fergusson, 1998) reported adverse event rates from two cardiac surgery studies. In d’Ambra (1997) the incidence of thrombotic events was 23% in patients receiving epoetin alfa and 29% in patients receiving placebo. Death occurred in 6% (7 of 126) of patients receiving epoetin alfa compared with 0% (0 of 56) in patients receiving placebo, however this difference was not statistically significant (p=0.10). Sowade et al. (1997) reported deaths in 11% (4 of 38) of patients in each treatment group. Although safety has also been reported in the literature for other indications for epoetin alfa such as renal and cancer, this has not been reviewed as part of this HTA.

Figure 5-3  Forest plot of mean units of blood transfused

Table 5-8  Incidence of thrombotic events and all adverse events in patients undergoing orthopaedic surgery

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Reference</th>
<th>Event rate % (n/total)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Epoetin alfa</td>
<td>Placebo or control</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>COPES (1993)</td>
<td>12 (5/78)</td>
<td>6 (8/77)</td>
</tr>
<tr>
<td></td>
<td>Faris (1996)</td>
<td>3 (2/60)</td>
<td>9 (6/69)</td>
</tr>
<tr>
<td></td>
<td>De Andrade et al. (1996)</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td></td>
<td>Weber et al. (2005)</td>
<td>0.4 (2/460)</td>
<td>0.4 (1/237)</td>
</tr>
<tr>
<td>All</td>
<td>COPES (1993)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Faris. (1996)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>De Andrade et al. (1996)</td>
<td>6 (7/112)</td>
<td>8 (8/108)</td>
</tr>
<tr>
<td></td>
<td>Feagan et al. (2000)</td>
<td>8.5</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Weber et al. (2005)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
5.4 Discussion

The meta analysis findings showed epoetin alfa to be an effective treatment for reducing the incidence of transfusion in patients with mild anaemia prior to orthopaedic surgery. However, the studies reviewed considered situations where anaemia treatment and transfusion policies differ from those in Scotland and it is unclear to what extent results can be generalised to Scotland. Using data available from Ibrahim (2004) the transfusion rate for patients undergoing hip or knee replacement surgery with Hb 10-13g/dL in Scotland is estimated to be 37%. This is lower than the transfusion rate of 45% for patients receiving placebo reported in Weber et al. (2005) and there is therefore a possibility that the effectiveness of epoetin alfa in the Scottish population could differ slightly from that reported due to the difference in transfusion rates. Additionally, in Scotland, patients with a haemoglobin level of greater than 10g/dL are unlikely to be treated for anaemia inferring that under current practice few patients are likely to be treated with epoetin alfa.

While it is not possible to study treatment effectiveness in relation to all factors that underlie transfusion policy, the absence of a relationship with baseline transfusion rate lends some support to the hypothesis that the effectiveness of epoetin alfa is unrelated to transfusion policy.

The odds ratio of a treatment benefit for epoetin alfa during primary surgery was almost half that demonstrated for revision surgery, but this difference was not statistically significant. However, as only two studies reported results according to the type of surgery the meta-analyses lacked the power to detect clinically significant differences.

The SPC (Janssen-Cilag, 2005) recommends that a weekly dosage regime is used for epoetin alfa, and that the daily regime is appropriate when there is a medical need to shorten the lead time to surgery to less than 3 weeks. The subgroup analyses indicated that there was no difference in effectiveness between weekly and daily dosage regimes.

5.5 Conclusions

Epoetin alfa was shown to be an effective treatment for preventing transfusion and reducing the amount of transfused blood required by patients with mild anaemia prior to orthopaedic surgery. There was insufficient evidence to assess whether effectiveness differed when comparing primary and revision surgery. Effectiveness was not related to dose regime or to study baseline transfusion rate. There was insufficient evidence to assess the safety of epoetin alfa in patients with mild anaemia undergoing orthopaedic surgery.
6 COST EFFECTIVENESS

This section summarises the cost effectiveness evidence available from the published literature. Section 6.2 describes the literature search, Sections 6.3, 6.4 and 6.5 describe the results and sensitivity analyses of the economic model, whilst Sections 6.6 and 6.7 present the discussion and conclusions.

6.1 Introduction

This section evaluates the cost effectiveness of epoetin alfa treatment in adults with mild anaemia before orthopaedic surgery. Epoetin alfa was compared with standard hospital practice, usually involving iron supplementation.

6.2 Sources of evidence

6.2.1 Literature search

Initial scoping searches to identify economic evaluations relating to the use of epoetin alfa in surgical patients were undertaken in September 2004. These were updated in August 2005 and the remit was broadened to include the overall management of blood in surgical patients. The NHS Economic Evaluation Database (NHS EED), the Health Economics Evaluation Database (HEED) and websites of major international health economics research units were searched for relevant economic evaluations.

Following scoping, consideration was given to performing an extensive systematic literature search to identify: existing economic evaluations, relevant models, costs and other inputs for economic models. To retrieve all useful economic information, it was thought necessary to broaden the population group from that used for the clinical effectiveness analyses. A search targeting all patients undergoing surgery, excluding those with cancer, was trialled in the MEDLINE database but resulted in a large number of irrelevant hits. The decision was therefore taken to restrict the search to patients receiving orthopaedic surgery. These results comprised a subset of those retrieved during the clinical effectiveness search, and so a separate full-scale search was not performed. Instead the clinical effectiveness data were examined for relevant economic information.

A small number of additional studies were identified by scanning the bibliographies of retrieved items, through the use of alert services, by members of the HTA Topic Group and as part of the submissions process.

A flow chart showing the literature identified and included in the report is given in Appendix 2.

Study selection criteria

Studies were excluded if no data were reported on the costs and outcomes, including quality of life parameters, for presurgical epoetin alfa use in patients with anaemia awaiting orthopaedic surgery.

The electronic search yielded 614 references. Full text citations were obtained for 66, and the others were excluded as irrelevant on the basis of title and or abstract alone. Four studies (Coyle et al., 1999; Coyle et al., 1998; Marchetti & Barosi, 2000; MacLaren & Sullivan, 2005), were included in the final analyses. The others were excluded primarily because they did not address both costs and benefits. The MacLaren study was set in intensive care units rather than orthopaedic surgery, but a summary of it was provided because its model structure was used to inform the NHS QIS cost effectiveness model structure.

None of the studies were performed in the UK and the values of key parameters, particularly the attributable risk of adverse events following a blood transfusion did not generalise to Scotland. Therefore the results of the literature review cannot be used as direct evidence to inform decisions in the Scottish setting.

Overview of studies

The selected literature comprised three economic evaluations considering the use of epoetin alfa in surgery which are summarised in Appendix 3. These studies show that the incremental cost per life year gained from using epoetin alfa is extremely high, ranging from US $7 million in Marchetti & Barosi (2000) to Can $66 million in Coyle at al. (1999). Extensive sensitivity analyses demonstrated that the results were robust. The main conclusion of each study was that the use of epoetin alfa is not cost effective in orthopaedic surgery.

The fourth study by MacLaren & Sullivan (2005) is also summarised in Appendix 3. This study used data from two independent USA trials considering the use of epoetin alfa in intensive care units. These gave costs per quality adjusted life year (QALY) of US $34,088 and US $47,149. The most important factor in cost effectiveness was the risk of developing nosocomial bacterial infections. The risk of infection is higher in intensive care units than for orthopaedic surgery (Janssen Cilag, personal communication, 28th March 2006) and thus studies of measures to reduce blood borne infections are likely to be more cost-effective in such units. The results cannot therefore be generalised to orthopaedic surgery. In addition, Scotland, unlike the USA, has implemented universal leucodepletion of blood cells in part to reduce the risk of bacterial infections. The study noted that if a leucodepletion strategy was implemented in the USA it would minimise the benefits associated with epoetin alfa.

In the absence of finding studies from the literature that generalise to Scotland and recognising that none of the above studies use clinical effectiveness data from the recent systematic reviews, it was decided to develop an economic model to inform on the cost effectiveness of epoetin alfa in this indication.
6.3 Economic model

6.3.1 Methodology

The economic modelling methodology adopted is presented in ‘Guidance for manufacturers’ (NHS Quality Improvement Scotland, 2005b). Best practice recommends that economic evaluations adopt a societal perspective (Drummond and McGuire ed., 2001). None of the studies from the literature review adopted a societal perspective, primarily because of the lack of available data. Coyle et al. (1998) noted that such costs are likely to be small given the mean age of the orthopaedic surgery population. The authors chose to test the sensitivity of the results to these costs by using extreme cost of disease values in their sensitivity analyses. A similar approach was adopted in this economic modelling and all resource use was, therefore, considered from the NHS perspective.

The Drummond checklist for assessing economic evaluations was used to validate the evaluation (Drummond and McGuire ed., 2001). The literature selection process, values of parameters and model structure have all been quality assured by an independent reviewer. All inconsistencies have been resolved. Peer review also provided an external check on quality.

6.3.2 Form of analysis and comparator

Decision tree analysis was used to model the costs and effectiveness of using epoetin alfa in comparison with standard practice. The clinical path within the tree depicts patients receiving or not receiving allogeneic blood. For those patients receiving transfusions there is a risk of contracting a transfusion related illness (Appendix 4).

Scottish current practice was used as the comparator and was assumed to be consistent with the placebo or control comparator, primarily used in the clinical effectiveness arm (see Section 5.3.1).

The model estimated the lifetime costs and benefits for each treatment arm, with the main costs being associated with epoetin alfa administration, blood transfusion and transfusion-related illnesses. The main benefits were greater life expectancy and quality of life as a result of fewer adverse events from allogeneic blood transfusions in the active arm. Costs were expressed in pounds sterling (£), at 2005 prices and a 3.5% discount rate was applied to both costs and benefits, in accordance with Treasury Guidance.

Cost effectiveness findings were expressed as an incremental cost per QALY and cost of an avoided transfusion. The base case adopted the profile for a typical orthopaedic patient as a mean age of 67.7 years with a 38:62 male to female ratio (Aderinto & Brenkel, 2004).

6.3.3 Model inputs

Clinical effectiveness data

The economic model incorporated the incidence of elective and emergency joint replacement operations (both primary and revision for hip and knee) recorded in NHSScotland for the year to March 2004 (NHSScotland, 2005) as presented in Table 6-1. The proportion of episodes transfused and the mean red blood cell units transfused for each type of operation over the same period was obtained from Scottish National Blood Transfusion Service (Dr B Perry, Director of the NHSS Better Blood Transfusion Programme, SNBTS, personal communication, 31st October 2005). Subgroup analysis by presurgery haemoglobin level was not possible.

Table 6-2 reproduces data concerning the clinical effectiveness rates observed in the Weber trial (Weber et al., 2005) and identifies the clinical benefit of epoetin alfa associated with primary and revision surgery. An alternative data source is the COPES study (Canadian Orthopedic Perioperative Erythropoietin Study Group (COPEG), 1993). However, this was published in 1993 and is less representative of current treatment practice.

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Number of operations in 2003/04</th>
<th>Number of operations in 2003/04</th>
<th>Mean red cell units used per operation transfused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee primary</td>
<td>3,875</td>
<td>14.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Hip primary</td>
<td>4,664</td>
<td>26.1</td>
<td>2.6</td>
</tr>
<tr>
<td>Knee revision</td>
<td>275</td>
<td>32.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Hip revision</td>
<td>760</td>
<td>63.3</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Table 6-2 Clinical effectiveness of epoetin alfa and its impact on transfusion rates

<table>
<thead>
<tr>
<th>Type of operation</th>
<th>Transfused (trial data) %</th>
<th>Operations transfused %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo or control</td>
<td>Epoetin alfa</td>
<td>Current in Scotland*</td>
</tr>
<tr>
<td>Knee primary</td>
<td>45.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Hip primary</td>
<td>45.1</td>
<td>11.4</td>
</tr>
<tr>
<td>Knee revision</td>
<td>50.0</td>
<td>20.5</td>
</tr>
<tr>
<td>Hip revision</td>
<td>50.0</td>
<td>20.5</td>
</tr>
</tbody>
</table>

*From Table 6-1
No data on the reduction in the mean number of red blood cell units transfused per transfused patient was available following epoetin alfa treatment in the Scottish setting. However, the Weber trial (Weber et al., 2005) reported that the number of units transfused per transfused patient was similar in the epoetin alfa (2.36 units) and the standard care (2.41 units) treatment arms. Thus, the base case assumed that there was no change in the mean number of units transfused per transfused patient and this assumption was explored in sensitivity analyses.

Adverse events from blood transfusion in the UK

Since 1996, systematic reporting of transfusion complications and errors to the Serious Hazards of Transfusion (SHOT) scheme has developed an evidence base that can be used to estimate the risks associated with blood transfusion in the United Kingdom (UK). Risks can be grouped into those associated with viral infections or non-viral adverse reactions.

Risk of transfusion transmitted viral infections reactions

Dr B McClelland, Strategy Director, SNBTS, advised that the risk of transfusion transmitted viral infection is very low as a result of current blood testing strategies. The reported risk of transfusion transmitted hepatitis B, hepatitis C and HIV in the UK are presented in Table 6-3.

In Scotland all donated blood is leucocyte filtered, compared with only 6% in the studies used for cost effectiveness analysis. Jensen et al. (1996) reported that patients transfused with leucocyte depleted blood had significantly fewer postoperative infections than those transfused with whole blood.

Risk of non viral adverse reactions

Estimates of the major risks from other transfusion related adverse events as reported to the SHOT scheme for 1996-2004 were provided by Dr B McClelland and are presented in Table 6-4.

No risk of adverse events from variant Creutzfeldt-Jacob disease (vCJD) are included in the model. At the end of December 2005, around 150 people in Britain have died from definite or probable vCJD, with a further six alive with the diagnosis (National Institute for Health and Clinical Excellence, 2006). During 2004, there were 20 cases (18 in England and two in Scotland) reported to the CJD Incidents Panel of people receiving blood components who later developed vCJD (CJD Incidents panel, 2004). Red blood cells have a lower risk of carrying the disease than other blood components. (CJD Incidents panel, 2004). Such incidents and related research into the transmission of vCJD by blood transfusions have increased concerns about the risk of contracting vCJD from blood transfusions (CJD Incidents panel, 2004). If the public health risk of transmission of vCJD through transfusions of red blood cells increases then the model parameters should be updated to reflect this risk.

Table 6-3 Estimated frequency of infectious donations by marker, per million donations issued (also shown as 1 in x per million donations issued): UK 2002-2003

<table>
<thead>
<tr>
<th>Donations from:</th>
<th>HIV</th>
<th>Hepatitis C</th>
<th>Hepatitis B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Per million</td>
<td>1 in x million</td>
<td>Per million</td>
</tr>
<tr>
<td>All donors</td>
<td>0.22</td>
<td>4.58</td>
<td>0.05</td>
</tr>
<tr>
<td>New donors</td>
<td>0.50</td>
<td>1.98</td>
<td>0.19</td>
</tr>
<tr>
<td>Repeat donors</td>
<td>0.19</td>
<td>5.38</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 6-4 Estimated frequency of non viral adverse reactions per 100,000 components issued

<table>
<thead>
<tr>
<th>Type of reaction / event</th>
<th>Total number of incidents reported 1996-2004 in the UK</th>
<th>Average per year in the UK</th>
<th>Calculated risk per 100,000 blood component units issued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incorrect blood component transfused (IBCT)</td>
<td>1832</td>
<td>229</td>
<td>7</td>
</tr>
<tr>
<td>ABO incompatible transfusions (included in IBCT)</td>
<td>249</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Death as a result of IBCT</td>
<td>20</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Transfusion related lung injury (TRALI)</td>
<td>162</td>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>Fatal TRALI</td>
<td>36</td>
<td></td>
<td>0.1</td>
</tr>
<tr>
<td>Acute transfusion reaction</td>
<td>267</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Transfusion – transmitted infection (including bacterial)</td>
<td>47</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Total adverse reactions / events</td>
<td>2628</td>
<td>329</td>
<td>10</td>
</tr>
<tr>
<td>Total transfusion related deaths</td>
<td>99</td>
<td>12</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Cost of adverse events and associated loss in quality of life and life expectancy

The cost of an adverse event following allogeneic blood transfusion was assumed to comprise three components: the lifetime cost to treat the disease, the associated loss in quality of life during the remaining years of life and, if relevant, the reduced life expectancy.

The costs of adverse events following allogeneic red blood cell transfusion were taken from MacLaren & Sullivan (2005) and Huber et al. (1997) converted to pounds sterling and indexed to 2005 prices using a retail price index measure of inflation excluding housing costs (http://www.statistics.gov.uk/STATBASE/tsdataset.asp?vlnk=229&More=N&All=Y). These data are from American studies and different patient groups but in the absence of British data were used. Sensitivity analyses indicate the results and conclusions from the model are not sensitive to these costs.

Mean utility values for the viral infections were taken from Tengs and Wallace. (2000). No utility values were found in the literature for events arising from non viral reactions. A utility loss of 0.5 for the year of the event was assumed. The sensitivity of the result to this assumption was tested in sensitivity analyses.

The loss in life years from a transfusion-related death was estimated using life tables (http://www.gad.gov.uk/Life_Tables/docs/wltscom0204.xls) for a patient with a mean age of 67.7 years (Aderinto & Brenkel, 2004). Patients who contracted HIV were assumed to have half the life expectancy of other 67.7 year olds. The resulting costs and effects from adverse events are presented in Table 6-5.

<table>
<thead>
<tr>
<th>Type of infection / reaction / event</th>
<th>Cost of disease or fatality (£)</th>
<th>Loss in life expectancy (years)</th>
<th>Loss in utilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>7,470</td>
<td>7.56</td>
<td>0.43 per year</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>16,640</td>
<td></td>
<td>0.43 per year</td>
</tr>
<tr>
<td>HIV</td>
<td>38,705</td>
<td></td>
<td>0.35 per year</td>
</tr>
<tr>
<td>Incorrect blood component transfused of which fatal</td>
<td>1,350</td>
<td>15.12</td>
<td>0.5 initial year</td>
</tr>
<tr>
<td>Transfusion related lung injury (TRALI) of which fatal</td>
<td>1,350</td>
<td>15.12</td>
<td>0.5 initial year</td>
</tr>
<tr>
<td>Acute transfusion reaction</td>
<td>1,350</td>
<td></td>
<td>0.5 initial year</td>
</tr>
<tr>
<td>Transfusion-transmitted infection (including bacterial)</td>
<td>105</td>
<td></td>
<td>0.5 initial year</td>
</tr>
<tr>
<td>Others</td>
<td>1,350</td>
<td>14,515</td>
<td>15.12</td>
</tr>
</tbody>
</table>

a MacLaren & Sullivan (2005)  b Huber et al. (1997)

Dosage and cost of an epoetin alfa treatment course

It is recommended that epoetin alfa is administered at an initial dose of 600 IU/kg for 3 weeks prior to surgery and on the day of surgery. Assuming the mean weight of an orthopaedic patient to be 70 kg then the cost of a course of epoetin alfa treatment is approximately £1,340. This cost has been adopted in the model. No sensitivity analyses have been conducted on using the higher cost of the daily regime (£2,510).

Treatment could be administered at a GP surgery at a cost per visit of £24 (Netten and Curtis ed., 2005) or at an orthopaedic outpatients clinic at a cost per visit of £82 (Information and Statistics Division Scotland (ISD), 2005). It is assumed patients are not trained to self-administer the drug given there are only three injections required per cycle.

Cost of a blood transfusion

The National Blood Transfusion Service in England and Wales has stated that the 2005 cost of a unit of red blood cells is £132 (National Blood Service, 2005). This cost includes the costs incurred by the National Blood Service in collecting, testing, processing and issuing red blood cells. The NHS Health Boards incur further costs to include the cost of handling the units from the hospital blood bank to the wards, laboratory tests on the patient and administering the blood.

In 2003, Varney and Guest (2003) estimated that the annual cost to the NHS attributable to blood transfusions (excluding hospital length of stay) were £222 (£235 at 2005 prices) per unit. Adopting this value implies an add-on cost of around 80% for these hospital-based costs. This level is consistent with other values found in the literature (Wilson et al., 2005; Forbes et al., 1991). It is also consistent with advice from Professor Ian Franklin (National Medical & Scientific Director, SNBTS, personal communication, November 2005) that the add-on costs within the hospital setting could be up to 100% of the...
cost of a unit of red blood cells. He also noted that the cost per unit of red blood cells is likely to be lower in Scotland than in England and Wales. However, the higher value of £235 per unit has been used in the model.

6.4 Results

The results from the base case analysis show an incremental cost effectiveness ratio of £21.2 million per QALY and a net discounted cost per transfusion avoided of £2,520 (see Table 6-6). The incremental cost per QALY is similar to those in the literature for a similar population and confirms that, in Scotland, using epoetin alfa in this indication is not cost effective.

6.5 Sensitivity analyses

6.5.1 Sensitivity analyses: one way changes in parameter values

One way sensitivity analyses were conducted to inform on factors which might make epoetin alfa use cost effective for this indication and the results are presented in Appendix 3. The results were most sensitive to the number of units transfused, the price of epoetin alfa and the cost of blood.

However, the price of epoetin alfa would need to fall by about 95% or the cost of blood would need to rise to over £2,750 per unit, before the use of epoetin alfa became cost effective.

Other sensitivity analyses showed that should epoetin alfa be sufficiently effective as to prevent all transfusions then the cost per QALY would fall to £14.1 million. Thus, even if the entire benefit of an 80% reduction in the use of allogeneic red blood cells as reported in Slappendel (2003) could be attributed to the adoption of epoetin alfa, with no benefit from measures such as introducing a robust algorithm, with pre-defined transfusion values, and cell salvage, then using the drug would still not be cost-effective.

If the cost of transfusion related infections or if the risk of an adverse event from a blood transfusion rose by a factor of 100 fold then the cost per QALY would remain over £21 million. Increasing the loss in annual quality of life to 0.95 for patients who contract hepatitis B, hepatitis C or HIV, or suffer a blood transfusion related adverse event reduces the cost per QALY to £14.2 million. The results are not sensitive to changes in the discount rate. Discounting costs by 6% and benefits by 1.5% reduces the incremental cost per QALY slightly to £20.9 million.

Table 6-1 shows that blood loss is greater in knee and hip revisions than in primary surgery. Restricting the administration of epoetin alfa to this group improved the cost per QALY to £6.9 million.

Given the improbability of these events it was deemed unnecessary to undertake full probability sensitivity analyses and the results were judged as robust for all reasonable ranges of costs and benefits.

Table 6-6 Discounted costs and benefits and incremental cost per QALY

<table>
<thead>
<tr>
<th></th>
<th>£13,494,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional costs of epoetin alfa</td>
<td></td>
</tr>
<tr>
<td>Less savings from: avoided blood transfusions</td>
<td>£1,148,000</td>
</tr>
<tr>
<td>: avoided infection costs</td>
<td>£1,000</td>
</tr>
<tr>
<td>Net costs</td>
<td>£12,345,000</td>
</tr>
<tr>
<td>Gain in QALYs</td>
<td>0.6</td>
</tr>
<tr>
<td>Incremental cost per QALY</td>
<td>£21,193,000</td>
</tr>
</tbody>
</table>

(Note costs are rounded to nearest thousand pounds)

Table 6-7 Sensitivity analyses of one way changes in parameter values

<table>
<thead>
<tr>
<th>Change in parameter value</th>
<th>Incremental cost per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>£21,193,000</td>
</tr>
<tr>
<td>Reduction in epoetin alfa costs from £79.96 to £2.95 for 10,000 units</td>
<td>£25,000</td>
</tr>
<tr>
<td>Increase in cost of blood from £235 to £2,750 per unit</td>
<td>£28,000</td>
</tr>
<tr>
<td>All blood transfusions avoided with epoetin alfa</td>
<td>£14,127,000</td>
</tr>
<tr>
<td>Cost of transfusion related infections rise by a factor of 100 (equivalent to risk of adverse event rising by 100 )</td>
<td>£21,061,000</td>
</tr>
<tr>
<td>Loss in QALY of 0.95 for hepatitis B, C and HIV and for 1 year for other transfusion related events</td>
<td>£14,182,000</td>
</tr>
<tr>
<td>Use in revision hip and knee operations only</td>
<td>£6,899,000</td>
</tr>
<tr>
<td>Discount rate of 6% for costs and 1.5% for benefits</td>
<td>£20,934,000</td>
</tr>
</tbody>
</table>

Costs are rounded to nearest thousand pounds
6.5.2 Sensitivity analyses: additional hospitalisation costs

Some studies have noted that consequences for patients receiving blood transfusions could be increased infection rates and delayed postoperative recovery (Weber et al., 2005). Weber et al reported that the mean time to discharge was 10.8±5.5 days for 704 patients undergoing orthopaedic surgery. There was no significant difference in the discharge time between epoetin alfa treated patients and the control group but transfused patients stayed in hospital longer than non transfused patients (12.9 days vs 10.2 days) as shown in Table 6-8.

Weber et al. (2005) noted that the length of hospital stay was determined by a number of factors, including reimbursement issues, availability of home nursing and family support. It was agreed at a meeting with the manufacturer of epoetin alfa and HTA clinical experts on the 8 September 2005, that it was not appropriate to include length of stay savings in the model because of the wide diversity of factors influencing discharge and lack of evidence of effect. However, for a sensitivity analysis, an additional 2.7 days (12.9-10.2) worth of hospital costs were assumed for 1,655 additional patients who receive a blood transfusion in the standard care arm. A cost of £540 per day was used, being the mean gross costs of a 24-hour orthopaedic inpatient stay for the year to 31 March 2005 (Information and Statistics Division Scotland (ISD), 2005), updated for 6 months inflation. This results in a cost for epoetin alfa per QALY of over £17.1 million.

6.6 Discussion

This economic evaluation has reviewed the literature on the cost effectiveness of epoetin alfa and modelled its use in Scotland. The existing studies retrieved from the literature search all reported that using epoetin alfa in this indication was not cost effective. The study by MacLaren & Sullivan (2005), set in intensive care units, reported a range of costs per QALY that were below $50,000 and which might thus be considered by some decision makers to be cost-effective. However, the risk of infections is higher in this setting so the results do not generalise to orthopaedic surgery. The other studies used clinical effectiveness data that has been superceded by the publication of several systematic reviews in this area, primarily from Weber et al. (2005) and Feagan et al. (2000). Thus, an economic model was developed using data from various sources to examine the cost effectiveness of using epoetin alfa treatment in patients with preoperative haemoglobin concentrations of 10-13 g/dL.

Several limitations are associated with the parameter values used. The estimates of clinical effectiveness are generated from meta-analysis of published trials and Section 5 discusses the issues surrounding pooling trial data and generalising these trials to the Scottish setting. For example, the Weber trial (Weber et al., 2005) excluded patients whose operations were delayed by more than 10 days. The main clinical benefit of epoetin alfa is seen when the planned dose is administered 3-4 weeks prior to surgery; delaying the surgery will reduce the clinical effectiveness of the drug and thus benefit to the patient. Other possible reasons for reduced clinical effectiveness compared with trials include: failure to administer therapy over the three to four week cycle and inappropriate provision of other aspects of care. Of particular relevance is the administration of adjunctive iron therapy to provide adequate iron stores to facilitate the increased erythropoiesis.

The trials also report a higher incidence of transfusions in the control group than the current rate in Scotland. The difference in transfusion rates may be a function of timing since the transfusion rates have been falling in Scotland or may reflect different underlying clinical practices or different patient groups. This poses some uncertainty for the economic model. However, as the sensitivity analyses demonstrate, even if epoetin alfa avoided all blood transfusions its use would still not be cost effective.

The probability of adverse events occurring following blood transfusion were derived from a passive reporting system in which under-reporting is likely. There is no routine surveillance to estimate the actual rates of adverse events and reactions. However, the risks from red cell blood transfusions may be overestimated for two reasons. Firstly, the calculations assume that all blood components have the same risk profile. Transfusion related lung injury and severe allergic reactions (included within acute transfusions reactions) are four to six times more likely to occur following administration of plasma or platelets than red cells. Secondly, in some cases, the causal relationship between the reaction and the transfusion is not definitive, particularly in the case of fatal reactions, where there may be other contributory factors (Dr B McClelland, SNBTS, personal communication, Nov 2005).

Measures are in place to reduce the risk of vCJD being transmitted through blood transfusions (Scottish National Blood Transfusion Service, 2004), supported by considerable on-going research. Thus, this economic evaluation assumed the risk of vCJD being transmitted is virtually zero. Should this risk increase then the economics of using epoetin alfa will change and the analyses should be updated.

The costs of infectious diseases were taken from the literature and converted into sterling, but there are no published costs considering management of such diseases in Scotland. Where possible, cost estimates have been compared to equivalent values in England (Department of

Table 6-8 Mean time to discharge (days)

<table>
<thead>
<tr>
<th></th>
<th>Epoetin alfa (days)</th>
<th>Standard Care (days)</th>
<th>Total (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfused</td>
<td>15.5</td>
<td>10.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Non transfused</td>
<td>11.5</td>
<td>9.4</td>
<td>10.2</td>
</tr>
</tbody>
</table>

2 Time to discharge is defined as number of days between surgery and discharge from hospital where surgery was performed.
Health, 2005) and in all cases the costs used in the model were higher than those reported for managing similar conditions in England.

The economic evaluation used the number of episodes reported for each procedure to inform the modelling. However, not all of the patients included would have had preoperative haemoglobin levels consistent with epoetin alfa treatment. Moreover, in Scotland not all patients with haemoglobin levels of 10-13 g/dL would routinely have their anaemia treated. For example, in April 2005 the Guidelines on ‘Blood conservation in elective orthopaedic surgery’ (British Orthopaedic Association, 2005) established a strategy to investigate and/or treat underlying anaemia where patients had preoperative haemoglobin concentrations of <12 g/dL. However, changing the number of patients treated in the model does not alter the findings when expressed as a cost per QALY or cost per transfusion avoided.

Studies have shown that the risk of developing nosocomial bacterial infections is the most important determinant of cost effectiveness. Investing in leucodepleting blood cell technology minimises the risk of such infections and thus reduces the potential benefit of epoetin alfa treatment (MacLaren & Sullivan, 2005). In Scotland, leucodepletion has been routine for several years and thus the infection risk is greatly reduced, further limiting the potential benefit from epoetin alfa treatment.

There may be some benefits from using epoetin alfa routinely in preoperative patient management which have not been identified. These could include the possibility of fewer delayed operations and last minute cancellations when the patient presents at the preoperative assessment or on the day of surgery with untreated anaemia. However, compliance with the British Orthopaedic Association’s Guidelines on preoperative management at the time of referral could achieve the same outcome.

6.7 Conclusions

Clinical effectiveness analyses identified the evidence base that quantifies the benefits of administering epoetin alfa in patients with preoperative haemoglobin concentrations of 10-13 g/dL. The primary outcome measure was the number of units of allogeneic blood not required for transfusion as a result of treatment. This section has combined the effectiveness data with drug costs, the savings from viral infections and adverse events avoided and the resultant improvement in QALYs. Modelling, and the associated sensitivity analyses, confirmed literature findings that the use of epoetin alfa in patients with anaemia prior to orthopaedic surgery is not cost effective, as judged by a cost per QALY outcome measure. Moreover, using epoetin alfa as a blood sparing technology is not an effective use of NHS resources.
7 OTHER ISSUES RELEVANT TO CLINICAL AND COST EFFECTIVENESS EVIDENCE

7.1 Patient Issues

This section considers important concerns for anaemic patients who require orthopaedic surgery that is often associated with a risk of high blood loss. It identifies issues that may affect a minority of patients, affecting the benefit that can be derived. A review of the literature identified that issues important to the patient centred on the relative safeties of epoetin alfa and allogeneic blood transfusion. In addition, specific patient groups for whom administration of epoetin alfa may be a high priority were identified as Jehovah’s Witnesses, those with serious anxieties about the transfusion of allogeneic blood and patients with multiple antibodies (Scottish Intercollegiate Guidelines Network, 2001).

Literature search

Searches of major bibliographic databases (MEDLINE, MEDLINE In-Process EMBASE, CINAHL, Science Citation Index) and selected websites were performed in August 2005, to identify the primary literature to inform this section of the HTA, and to supplement evidence from the secondary literature retrieved during clinical effectiveness analysis.

The searches of the primary literature used several different approaches, but were unsuccessful in identifying a distinct body of literature relevant to patient issues. Whilst this section uses the secondary literature, it focuses most heavily on discussions with representatives from the Hospital Liaison Committee for Jehovah’s Witnesses. The representatives also provided relevant literature on the use of epoetin alfa and other blood sparing technologies.

7.1.1 Comparative risks of allogeneic blood transfusion and epoetin alfa

Concerns associated with allogeneic blood transfusion include the possibility of transmission of infectious agents and the occurrence of transfusion reactions and procedural error. In order to reduce exposure to allogeneic transfusion the SIGN Guideline No. 54, produced in 2001, recommends that patients undergoing major elective surgery have a full blood count performed to allow those presenting with anaemia to be investigated and treated prior to the procedure.

The increased stringency of serological screening of donated blood has resulted in a dramatic reduction in the incidence of transfusion transmitted infection, with only one report of infection being referred to the Serious Hazards of Transfusion (SHOT) scheme in 2004 (Stainsby et al., 2004). In addition, there is a low risk of adverse transfusion reactions and a more substantial risk of procedural error. The SHOT report highlights some of the strategies now in place to further decrease problems associated with administrative errors. SIGN (2001) also recommends that relevant British guidelines on the administration of blood and blood components and the management of transfused patients should be implemented.

The incidence of all possible transfusion-associated complications in Scotland is low, with one serious event occurring per 67,000 transfusions (Scottish Intercollegiate Guidelines Network, 2001). However, this is at odds with public perception, with patients increasingly refusing transfusion as a result of safety concerns (Kirschman, 2004). During discussions concerning possible transfusion requirements, it is important that these safety concerns are fully addressed. All patients should receive information on the realistic level of risk from allogeneic blood (NHS Quality Improvement Scotland, 2005a).

The use of epoetin alfa to increase red blood cell levels overcomes the safety issues associated with transfusion but, in patients undergoing orthopaedic surgery, may be associated with a low incidence of hypertension and deep vein thrombosis. As a result, patients with uncontrolled hypertension or severe coronary, peripheral arterial, carotid or cerebral vascular disease, including those with recent myocardial infarction, cerebral vascular event or a baseline haemoglobin concentration >13 g/dL should not receive epoetin alfa (Janssen-Cilag, 2005). The SIGN Guidelines (2001) note that the trials of epoetin alfa have very strict entry criteria and have not recruited a sufficiently large number of patients to be able to detect important adverse effects of low incidence and SIGN recommended that further research is conducted in this area.

The efficacy of epoetin alfa in the presurgical setting is affected by the patient’s ability to draw on iron stores (Rutherford et al., 1994). Patients receiving epoetin alfa usually receive oral or intravenous iron therapy but no optimal iron support schedule has been identified (Scottish Intercollegiate Guidelines Network, 2001).

7.1.2 Treatment compliance

Treatment with epoetin alfa requires weekly subcutaneous injection, iron supplementation and regular blood tests, raising the possibility that compliance may be an issue. However, following discussion with Jehovah’s Witnesses, it was considered that the advantages of epoetin alfa treatment over transfusion were likely to promote compliance.

7.1.3 Specific patient groups

The major group for whom allogeneic blood transfusion is not acceptable is the Jehovah’s Witnesses. Their religious convictions require that medical management should be through the adoption of non blood medicine (Hospital Information Services for Jehovah’s Witnesses, 2003). Epoetin alfa is recognised as an effective therapy to optimise red blood cell production (http://www.watchtower.org/medical_care_and_blood.htm).

In 2002, the Royal College of Surgeons in England and Wales drew up a Code of Practice for ‘The surgical management of Jehovah’s Witnesses’ (Royal College of Surgeons of England, 2002). The code noted that surgical teams should consider the use of recombinant human erythropoietin to correct perioperative anaemia.
Representatives of the Glasgow Hospital Liaison Committee for Jehovah’s Witnesses advised that, in their view, clinicians in Scotland are now adopting strategies that avoided recourse to allogeneic blood. Such strategies include administering epoetin alfa. The potential side effects and intensive treatment regimen were considered minor issues when balanced with the option of blood-free surgery (Mr Harry Crawford & Mr Peter Warden, Hospital Liaison Committee for Jehovah’s Witnesses, personal communication, 23rd August 2005). These views were consistent with those of surgeons and anaesthetists expressed at the Topic Group meeting of April 2005.

Patients with multiple red cell alloantibodies also require consideration, as compatible blood for transfusion may be difficult to find. The presence of multiple antibodies also increases the level of transfusion risk in these patients, who may also be at higher risk of anaemia and infection if the presence of antibodies indicates immunocompromised status. Treatment with epoetin alfa reduces the risks associated with orthopaedic surgery for this patient group.

7.1.4 Clinical standards for blood transfusions

NHS QIS has recently consulted on draft clinical standards for blood transfusions (NHS Quality Improvement Scotland, 2005a). These contain standards that are regarded as essential to improve the recording of transfusions episodes, traceability of donor units and patient identification. The standards also recommend that before any transfusion the potential risks and benefits of, and alternatives to, transfusions are discussed between the clinician and the patient in advance of transfusions. Information should also be available in leaflets. In event of an emergency, clinicians should comply with any advance decision document specifying the patient’s wishes with regard to blood transfusions.

Adopting such management practices may encourage greater use of blood sparing technologies that seek to avoid blood transfusions unless absolutely clinically necessary. There are several such technologies to include use of blood salvage techniques, anti-fibrinolytic drugs, acute normovolaemic haemodilution and optimising preoperative haemoglobin level using iron or epoetin alfa.
8 PRINCIPAL FINDINGS, LIMITATIONS AND RECOMMENDATIONS

This section considers the principal findings (Section 8.1), the need for further research (Section 8.2), limitations and uncertainties (Section 8.3), and makes evidence based recommendations (Section 8.4) concerning epoetin alfa treatment.

8.1 Principal findings

8.1.1 Scope of the HTA

The HTA focuses on the optimal use in Scotland of epoetin alfa within the licensed indication of reducing the need for allogeneic blood transfusions in non-iron deficient adults, with mild anaemia (haemoglobin 10-13 g/dL), at risk of transfusion complications, prior to major orthopaedic surgery. It considered clinical effectiveness, cost effectiveness and patients’ needs and preferences. It did not consider organisational issues, other than including a cost for three visits to a primary care setting for administration of epoetin alfa in the economic model.

8.1.2 Summary of findings

Clinical evidence showed that the preoperative administration of epoetin alfa, compared with placebo, is effective in reducing the number of patients who require transfusion but that the number of units of blood transfused per patient transfused does not alter. The mean number of units of blood transfused reduces by 0.5-0.7 units per patient (Table 5-4). None of the studies selected reported significant differences in length of stay or postoperative infection rates as a result of using epoetin alfa.

In Scotland, a study of the preoperative predictors of allogeneic blood transfusion following hip replacement showed that a preoperative haemoglobin ≤12 g/dL increased the likelihood of allogeneic blood transfusion by more than threefold (Aderinto & Brenkel, 2004). This finding supports the British Orthopaedic Association recommendation that local referral protocols should aim to identify and treat anaemia before preoperative assessment (British Orthopaedic Association, 2005). These Guidelines only recommend epoetin alfa use in patients with religious objections regarding the use of allogeneic blood, or at times when blood supplies are inadequate. The clinical findings described in Section 5 are unlikely to be applicable where these or similar recommendations on transfusion triggers are incorporated into local treatment protocols.

The studies selected from the literature review of cost effectiveness all reported that the incremental cost per life year gained by using epoetin alfa is extremely high, ranging from US $7 million (Marchetti & Barosi, 2000) to Can $66m in (Coyle et al., 1999). Extensive sensitivity analyses demonstrated that the results were robust. The main conclusion of each study was that use of epoetin alfa is not cost effective in orthopaedic surgery. MacLaren & Sullivan (2005) identified the most important factor influencing cost effectiveness in the intensive care setting was the risk of developing nosocomial bacterial infections. Scotland has implemented universal leucodepletion of donor blood cells, thereby reducing the potential infections and thus the likelihood that using epoetin alfa would be cost effective.

The cost effectiveness model compared epoetin alfa with standard care for patients undergoing primary and revision hip and knee procedures. Key parameters in the model included: the risk of infection and immunological reactions derived from a British register, the cost of treating these events, the percentage of patients requiring transfusion and the mean blood use per transfusion using data from the Scottish National Blood Transfusion Service, and the cost of blood. The findings confirmed that using epoetin alfa was not cost effective, having a cost per QALY of over £21 million. The cost of a unit of blood would have to rise to over £2,750 before using epoetin alfa became cost effective for this patient group.

However, there may be patient groups for whom these findings do not apply. Patient needs and preferences were informed by discussions with representatives from the Jehovah’s Witnesses who also provided an extensive literature base. No further studies were found from the systematic literature search. Jehovah’s Witnesses cannot accept allogeneic blood transfusions because of their religious convictions and their surgical management using alternative clinical strategies, including epoetin alfa, is now general practice (Mr Harry Crawford & Mr Peter Warden, Hospital Liaison Committee for Jehovah's Witnesses, personal communication, 23 August 2005).

There may be other patients for whom allogeneic blood transfusions is problematic, particularly those with red cell alloantibodies. In such patients the most effective clinical strategy may be to manage the patient without recourse to allogeneic blood transfusion, and may include treatment with epoetin alfa.

In conclusion, the evidence base suggests that for the majority of patients with haemoglobin concentrations of 10-13 g/dL that require orthopaedic surgery associated with moderate blood loss, administering epoetin alfa preoperatively is not cost effective. Use of the treatment should be reserved for a select group of patients for whom allogeneic blood transfusions are not suitable.

8.2 Further research

No further research is recommended at this juncture as the results of the economic model proved very robust. Epoetin alfa is not cost effective except under extreme circumstances: for example the cost of treatment would need to fall by over 95% before its use would fall within conventional thresholds of cost effectiveness.

However, should there be a material increase in the risk of transmission of existing or new diseases through blood transfusions, for example of transmitting vCJD, then the existing economic analyses should be updated. The resultant costs and benefits may be useful to assess the value of potential investments in blood transfusion activities, for example the introduction of a new screening test.
Alternatively, if the price of epoetin alfa falls materially, for example should a lower priced generic formulation become available then again it may be worth updating the cost effectiveness analyses.

The introduction of clinical standards for blood transfusions may change management practices and encourage the greater use of blood sparing technologies to include use of blood salvage techniques, anti-fibrinolytic drugs, acute normovolaemic haemodilution and optimising preoperative haemoglobin level using iron or epoetin alfa. The economic model could be adapted to compare these technologies.

8.3 Limitations and uncertainties

There were no major deficiencies in the published clinical and cost effectiveness evidence base.

These analyses included the costs of managing the known complications associated with allogeneic blood transfusions. However, the improved safety of donated blood has reduced the incidence of such events. It is conceivable that additional transfusion related complications, particularly vCJD, could emerge or rates of transfusion administration errors could rise materially, such that the type and number of adverse events would increase significantly. Sensitivity analyses indicate that the current incidence of adverse events from allogeneic blood transfusion is so small that the findings remain valid even when assuming an event rate many times higher than currently observed.

The cost of managing any adverse clinical event following allogeneic blood transfusion is uncertain, in part because such events are very rare and cost data are not routinely collected. The utility measure does not assess the impact of patients’ anxiety over the potential risks of receiving allogeneic blood transfusion and may, therefore, underestimate the benefits of epoetin alfa. Sensitivity analyses indicated that the modelled results are not sensitive to large changes in the parameter values adopted for the cost of disease or utility values.

There is also uncertainty concerning the level of resources, such as the length of hospital stay, as trials were not powered to detect differences. No trial found a trend in this direction. However, it may be that epoetin alfa does reduce the length of hospital stay but that this benefit is masked by factors such as availability of family members to act as carers, discharge procedures and societal issues. Sensitivity analyses indicated that the conclusions are not sensitive to including a cost saving from a shorter duration of 2-3 days in hospital for patients who benefit from epoetin alfa.

Trials were also underpowered to compare postoperative infection rates and the risk of adverse events, particularly thrombolytic events.

The analyses attributed no benefit to patients attending a clinic for weekly epoetin alfa treatment for 3 weeks prior to surgery. It may be that information gained during such visits could inform decisions and reduce the numbers of cancelled procedures. However, this benefit could also be achieved by optimising preoperative patient management in the GP and pre-assessment settings.

The analyses assumed the supply of blood to be sufficient to meet demand and that elective surgery is not delayed or postponed as a result of blood shortages. This is currently the position in Scotland. Should blood shortages become an issue and lead to an increase in the price of blood, the results from the economic model could be used to compare the cost per transfused unit saved by epoetin alfa treatment with the higher blood price.

The analyses assume that the appropriate measure of benefit is the incremental cost per additional QALY. The manufacturer, Janssen-Cilag, has commented that this is not an appropriate measure to use because there are no survival benefits associated with epoetin alfa treatment and that improving quality of life is not a key driver in a clinician’s decision to treat patients. Rather the driver is to reduce the likelihood of requiring blood transfusions, in accordance with Government policy. This aspect is addressed by identifying the cost of each unit of red cells saved by administering epoetin alfa. This is over £2,500 per unit. This can be compared to the current cost of administering a unit of red blood cells of around £235.

8.4 Recommendations

Epoetin alfa is not recommended for general use by NHSScotland to reduce exposure to allogeneic blood transfusion in patients with mild anaemia prior to major elective orthopaedic surgery.

Epoetin alfa is recommended for restricted use within NHSScotland. It is a possible treatment option for patients with mild anaemia prior to major elective orthopaedic surgery who cannot receive blood transfusion either due to their religious convictions or because suitable blood is unlikely to be available.

Resource implications of recommendations

These recommendations are not estimated to change resource use in NHSScotland.
9 ACKNOWLEDGEMENTS

NHS QIS is very grateful to all experts and peer reviewers (Appendix 1) who generously gave of their time to scope the project, appraise the evidence and inform this Report.

Thanks also to Janssen-Cilag who submitted evidence at the outset and who provided access to information during the assessment.
10 REFERENCES


APPENDICES
## APPENDICES

### Appendix 1  Experts and Peer Reviewers

**EXPERTS**

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Hospital</th>
</tr>
</thead>
<tbody>
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<td>Dr Graeme Hilditch</td>
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<td>Mr Vipin Zamvar</td>
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<td>Royal Infirmary of Edinburgh</td>
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<tr>
<td>Mr Andrew Muirhead</td>
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<tr>
<td>Dr Campbell Tait</td>
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</tr>
</tbody>
</table>

**PEER REVIEWERS**

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<th>Position</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Royal Infirmary of Edinburgh at Little France</td>
</tr>
</tbody>
</table>
Appendix 2 Literature search for clinical effectiveness

Databases: MEDLINE, MEDLINE IN PROCESS, EMBASE, CINAHL
Platform: OVID Multifile
Coverage:
MEDLINE: up to May Week 3 2005
EMBASE: 2005 Week 22
CINAHL: May Week 3 2005
MEDLINE IN PROCESS: May 31st 2005
Search run: 1 June 2005

Search Strategy:
1 exp erythropoietin/ use mez
2 recombinant erythropoietin/ use emez
3 erythropoietin/ use emez
4 erythropoietin/ use nursing
5 epoade.tw.
6 epogen.tw.
7 epokine.tw.
8 epoxitin.tw.
9 eryto.tw.
10 procrit.tw.
11 epoetin.tw.
12 epoetin.tw.
13 eprex.tw.
14 erythropoetin.tw.
15 erythropoetin.tw.
16 or/1-15
17 orthopedics/
18 exp orthopedic procedures/ use mez
19 exp orthopedic surgery/ use emez
20 exp orthopedic surgery/ use nursing
21 hip.tw.
22 knee.tw.
23 arthrosopic.tw.
24 (bone adj2 length$).tw.
25 ilizarov.tw.
26 osteogenesis.tw.
27 bone transplant$.tw.
28 bone graft$.tw.
29 diskectomy.tw.
30 discectomy.tw.
31 fracture?.tw.
32 skeletal fixation.tw.
33 (leg adj2 length$).tw.
34 osteosynthetic$.tw.
36 osteotom$.tw.
37 tendon?.tw.
38 bone surgery.tw.
39 bone resection?.tw.
40 fasciotom$.tw.
41 hemipelvectomy$.tw.
42 ligament?.tw.
43 amputat$.tw.
44 arthrodesis.tw.
45 spinal fusion.tw.
46 spine fusion.tw.
47 spondylodesis.tw.
48 spondylodesynthesis.tw.
49 laminectomy$.tw.
50 arthroplasty.tw.
51 ligamentoplasty$.tw.
52 muscle resection?.tw.
53 muscle transposition?.tw.
54 cartilage.tw.
55 foot.tw.
56 feet.tw.
57 (neck adj2 surg$).tw.
58 (shoulder adj2 surg$).tw.
59 kyphoplast$.tw.
60 vertebroplasty.tw.
61 (hand$ adj2 surg$).tw.
62 arthroplasty.tw.
63 bursectomy.tw.
64 capsulotomy.tw.
65 meniscectomy.tw.
66 synovectomy.tw.
67 acetabuloplasty.tw.
68 periost$ graft$.tw.
69 (spine adj2 surg$).tw.
70 (spinal adj2 surg$).tw.
71 laminoplasty.tw.
72 tenotomy.tw.
73 laminotomy.tw.
74 foraminotomy.tw.
75 (joint adj2 replac$).tw.
76 joint surgery.tw.
77 orthopedic?.tw.
78 orthopaedic?.tw.
79 prosthesis.tw.
80 (fixation adj1 pelvi?).tw.
81 (acetabul$ adj1 fracture?).tw.
82 (fixation adj1 femur).tw.
83 (fixation adj1 femoral).tw.
84 elbow.tw.
85 ((femoral or femur) adj2 nail?).tw.
86 (fixation adj1 tibia?).tw.
87 (bone adj1 biops$).tw.
88 (bone adj1 graft$).tw.
89 hemiarthroplasty.tw.
90 or/17-89
91 16 and 90

Sources

Secondary literature, policy documents

- Health Technology Assessment Database, via the Cochrane Library
- NICE (National Institute for Clinical Excellence), www.nice.org.uk/
- NCCHTA (National Coordinating Centre for Health Technology Assessment), www.ncchta.org/
- NHS Centre for Reviews and Dissemination, University of York, www.york.ac.uk/inst/cri/crd/
- Birmingham Technology Assessment Group, Department of Public Health and Epidemiology, University of Birmingham, www.publichealth.bham.ac.uk/wmhtag/
- ScHARR (School of Health and Related Research), University of Sheffield, www.shef.ac.uk/~scharr/publications.htm
- South and West R&D Directorate, DEC reports, www.doh.gov.uk/research/swrd/rd/publicat/dec/
- Health Services Research Unit (HSRU), www.abdn.ac.uk/hsru/
- ECRI, www.ecri.org/
• Cochrane Database of Systematic Reviews (CDSR), via the Cochrane Library
• Database of Abstracts of Reviews of Effectiveness (DARE), via the Cochrane Library
• SIGN (Scottish Intercollegiate Guidelines Network), www.sign.ac.uk/
• ARIF (Aggressive Research Intelligence Facility), www.bham.ac.uk/arif/
• Health Evidence Bulletins, Wales, http://hebw.uwcm.ac.uk/
• TRIP, www.tripdatabase.com/
• Bandolier, www.jr2.ox.ac.uk/bandolier/
• Health Evidence Network, www.euro.who.int/HEN
• Clinical Evidence, www.clinicalevidence.com/ceweb/conditions/index.jsp
• Prodigy, www.prodigy.nhs.uk/
• NeLH Guidelines Finder, http://libraries.nelh.nhs.uk/guidelinesFinder/
• SEHD, www.show.scot.nhs.uk/sehd
• SHOW, www.show.scot.nhs.uk/
• Chief Scientist Office (CSO), www.show.scot.nhs.uk/cso/
• Public Health Institute of Scotland, www.phis.org.uk/
• Department of Health, www.dh.gov.uk/Home/fs/en
• NHS Economic Evaluation Database (NHS EED), via the Cochrane Library
• Health Economic Evaluation Database (HEED)

Primary literature including ongoing research

• MEDLINE (OVID)
• MEDLINE In-Process and Other Non-Indexed Citations (OVID)
• EMBASE (OVID)
• WEB OF SCIENCE (ISI)
• CINAHL (OVID)
• Cochrane Central Register of Controlled Trials (CCRCT), Cochrane Library
• Current Controlled Trials, www.controlled-trials.com/
• Clinical trials.gov, http://clinicaltrials.gov/
• NRR (National Research Register), www.nrr.nhs.uk/
• Centerwatch, www.centerwatch.com
• Trials Central, www.trialscentral.org/
• CRISP (Computer Retrieval of Information on Scientific Projects), www-commons.cit.nih.gov/crisp/
Flow chart of literature selection process

1. Systematic literature search for clinical and cost effectiveness literature (614)
2. Evaluate records against inclusion and exclusion criteria
3. Potentially relevant records (113)
   - Potentially relevant articles from literature search (110)
   - Articles not available (3)
4. Records excluded (331)
5. Obtain articles for further examination
6. Total number of potentially relevant articles (152)
7. Articles from other sources e.g. Submission process, zetoc alerts, scanning bibliographies (42)
8. Studies potentially suitable for meta-analysis (87)
9. Articles referenced in the report (54)
10. Articles reviewed but not referenced in report (98)
11. Excluded studies (81)
12. Included studies (6)
Appendix 3  Overview of economic evaluations

This appendix summarises one Canadian economic evaluation of epoetin alfa use in orthopaedic surgery, two on its use in orthopaedic and cardiac surgery, and one study where the treatment was used in a wider group of critically ill patients.

Economic analysis of erythropoietin use in orthopaedic surgery (Coyle et al., 1999)

This study used data from the Canadian setting in a decision model to assess the clinical and cost effectiveness of erythropoietin:

- to reduce the risk of patients receiving perioperative allogeneic red cell transfusion during orthopaedic surgery compared with no intervention;
- and to augment preoperative autologous donation compared with preoperative autologous donation alone.

The parameters used in the model included: the risk of allogeneic blood cell transfusion, the cost of blood, the likelihood of developing transfusion related disease, the cost of such diseases, the impact of these diseases on patient morbidity and mortality, and the clinical effectiveness of erythropoietin in reducing transfusion risk. The clinical effectiveness parameter values came from a meta-analysis of published randomised trials. Values for the other parameters were obtained by systematic literature review.

The results of using erythropoietin compared with no intervention showed a benefit of 0.000024 life years gained, at an incremental cost of Can $1,588 million, giving an incremental cost per life year gained of Can $66.3 million. Using erythropoietin to augment preoperative autologous donation had a cost per life year gained of Can $329 million. Detailed sensitivity analyses informed the conclusion that the use of erythropoietin in either orthopaedic indication was not cost effective.

Economic analysis of erythropoietin in surgery (Coyle et al., 1998)

A Canadian health technology report evaluated the clinical and cost effectiveness of erythropoietin in orthopaedic and cardiac surgery. The relevant interventions, modelling approach and data sources were similar to those reported in (Coyle et al., 1999). The orthopaedic results showed a cost per life year gained of Can $55 million comparing erythropoietin with no intervention and Can $296 million when using erythropoietin to augment preoperative autologous donation. Extensive sensitivity analyses demonstrated that the results were robust and the report concluded that the use of erythropoietin in orthopaedic surgery was not cost effective.

Cost effectiveness of epoetin and autologous blood donation in reducing allogeneic blood transfusions in coronary artery bypass graft surgery (Marchetti & Barosi, 2000)

This study used Italian data in a decision tree model to compare epoetin with no intervention in reducing patients’ risk of receiving perioperative allogeneic red blood cell transfusions during coronary artery bypass graft surgery. Each strategy was tested with and without autologous blood donation. The cost effectiveness of epoetin alone was more than US $7 million per QALY. This fell to approximately US $5 million when epoetin was used with preoperative autologous donation.

The estimated cost per transfusion avoided was $1,095, which is approximately four times the estimated cost of blood.

None of the sensitivity analyses, some using extreme values such as assuming all patients were transfused, proved cost effective.

Cost-effectiveness of recombinant human erythropoietin for reducing red blood cells transfusions in critically ill patients (MacLaren & Sullivan, 2005)

This study used decision analysis to estimate the cost effectiveness of using erythropoietin to reduce red blood cell transfusion in intensive care units. The model used data from two independent trials which compared administering erythropoietin with giving blood transfusion to critically ill patients.

Both studies administered epoetin alfa when haematocrit levels fell below 38% using a dose of 40,000 units weekly or a daily dose of 23,000 units for 5 days and then on alternate days. Blood was transfused according to clinical judgment in one study and to maintain a haematocrit level of 27% in the other.

The results gave costs per QALY of $34,088 and $47,149.

Sensitivity analyses showed that the model was most sensitive to the risk of nosocomial bacterial infections. The authors concluded that use of epoetin alfa appears cost effective in this setting.

The study noted that the USA has not implemented universal leucodepletion of donor red blood cells. Such a strategy would reduce the risk of bacterial infections and minimise the benefits associated with epoetin alfa.
Orthopaedic surgery with pre-operative haemoglobin levels of between 10 & 13g/100ml
Do nothing
A
IBCT fatal
Virus infection
Survive
Fatal
Lung infection
Survive
Fatal
Transfusion reaction
Survive
Fatal
Bacterial or other infection
Survive
Fatal
No IBCT

IBCT - Incorrect Blood Component Transfusion
GLOSSARY
12 GLOSSARY

**Alloantibodies**
Antibodies to donor platelets.

**Allogeneic**
Blood from the same species but not the same individual so that when the blood is introduced into a body it stimulates the production of an antibody.

**Anaemia**
Reduction in the concentration of erythrocytes or haemoglobin in the blood.

**Anti-fibrinolytic drugs**
Agents are used to treat serious bleeding.

**Arthroplasties**
Surgical procedures in which the diseased parts of a joint are removed and replaced with new, artificial parts.

**Autologous predonation programme**
Planned donation of units of blood by a person before surgery for use should a transfusion be required.

**Binomial error function**
The binomial distribution function specifies the number of times (x) that an event occurs in n independent trials where p is the probability of the event occurring in a single trial. The error term is the difference between the observed values and those obtained by fitting a binomial function.

**Cell salvage**
A technique to recover any "spilt" blood from the operative field using a sucker to return blood to a bypass reservoir and following filtration to remove particulate debris, it can be re-transfused.

**Concomitant iron therapy**
To accompany a second therapy with a dosage of iron.

**Decision tree**
A diagram that enables all possible options to be identified in a structured and efficient manner to assist decision makers.

**Deep vein thrombosis**
The formation of a blood clot in a deep vein such as the femoral vein in the leg.

**Epoetin alfa**
A drug in a class of medications called erythropoiesis stimulating proteins. It works by causing the bone marrow (soft tissue inside the bones where blood is made) to make more red blood cells.

**Erythrocytes**
Red blood cells that form the largest population of blood cells and carry out the exchange of oxygen and carbon dioxide between the lungs and the body tissues.

**Erythroid stem cells**
Relatively undifferentiated cells that retain the ability to divide and cycle throughout post natal life to provide cells that can become specialised and replace those that die or are lost.

**Erythropoiesis**
The formulation or production of red blood cells.

**GLIMMIX procedure**
Statistical software within the SAS package which fits generalized linear mixed models.

**Haematocrit tests**
A test that measures the total volume that red blood cells take up in the blood.

**Haemodilution**
An increased plasma volume, leading to low haematocrit.

**Haemoglobin**
Haemoglobin carries oxygen around your body.

**Health Technology Assessment (HTA)**
An international recognised methodology to synthesise the clinical and cost effectiveness of comparative technologies, together with their implications for the NHS and patients.

**Hypertension**
High blood pressure being the force of the blood against the artery walls.

**Hypoxia**
A condition associated with a deficiency of oxygen in inhaled gases or in arterial blood and/or in the tissues.

**Immunocompromised**
Incapon of developing a normal immune response.

**Leucocyte filtered**
The passage of blood through a filter to remove leucocytes.

**Leucodepletion**
Removal of donor white blood cells from blood.

**Meta-analyses**
A technique for combining the results of several reported results of primary studies.

**NHS Quality Improvement Scotland (NHS QIS)**
A special health board set up by the Scottish Executive to act as the lead organisation in improving the quality of healthcare delivered by NHSScotland.

**Non-iron deficient anaemia**
Anaemia that has a cause other than a shortage of iron.
Normovolaemic haemodilution
Increase in the fluid content of the blood associated with a resulting decrease in erythrocytes.

Nosocomial bacterial infections
A bacterial infection that is acquired in a hospital or a long-term care facility.

PAD
The preoperative donation of blood with the aim of minimising the need for a transfusion of blood donated from another person.

Perioperative transfusion
A blood transfusion delivered during the period from time of hospitalisation for surgery to time of discharge.

Phlebotomy
To puncture a vein for the purpose of withdrawing blood.

Placebo
A preparation having no specific pharmacological activity against the patients illness and given solely for the psychophysiological effects of the treatment, particularly in a clinical trial.

Primary surgery
First surgical procedure.

QALY
Quality Adjusted Life Year; 1 QALY is the equivalent of 1 year of life in full health.

Red cell alloantibodies
Red blood cell that can be clinically significant in patients with transfusion reactions when such cells react with the patient’s own cells.

Revision surgery
Subsequent surgical procedure.

Sensitivity analysis
Tests to inform how the results of a model change with changes in the assumed parameter values.

Serology
The science that deals with the properties and reactions of serums especially blood plasma.

Subcutaneous injection
An injection into the fatty tissue directly under the skin.

Thrombotic events
A clinical event caused by the aggregation of blood factors, primarily platelets and fibrin which cause a vascular obstruction at the point of its formation.

vCJD transmission
Creutzfeldt-Jakob disease (vCJD) is a rare and fatal human neurodegenerative condition. Patients can contract the disease by mechanisms such as contaminated surgical equipment.

Vial
A sealed sterile container that contains a drug.