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Economic Analysis of Erythropoietin Use in Surgery

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Summary

Allogeneic blood transfusions are associated with risks of developing infectious disease such as human immune deficiency virus (HIV) and Hepatitis B and C as well as the risk of serious hemolytic reactions. There is also concern that currently unknown infectious agents might be transmitted by blood. Thus, there is great interest in methods of decreasing the use of allogeneic transfusion. This interest has continued despite the likelihood that the transmission of HIV and hepatitis has decreased markedly in the last decade due to deferral of high risk donors and more sophisticated methods of testing for the viruses.

Peri-operative use of blood in elective surgery (e.g. hip arthroplasty and open heart surgery) accounts for a substantial amount of all blood used; although the amount of blood received per patient has reduced significantly in recent years due to improved surgical practices. Erythropoietin (EPO) is one of the techniques available to reduce patients' requirements for allogeneic blood. EPO stimulates the bone marrow to produce red blood cells which, on average, allows autologous donors to donate more blood than without EPO. If EPO is given pre-operatively to patients who do not donate autologous blood, their mean hemoglobin at the time of operation is higher than those who do not receive EPO, thus reducing the requirement for perioperative transfusions.

A decision analytic model was created to assess the cost-effectiveness of erythropoietin (EPO) compared to no intervention in orthopedic surgery and as an augmentation to preoperative autologous donation (PAD) for both orthopedic and cardiac surgery.

The benefit of EPO in reducing allogeneic blood transfusions was estimated by a systematic review of published studies. Without pre-donation, EPO reduced the proportion of orthopedic surgery patients receiving allogeneic transfusion by 51% (from 48% to 24%). With predonation, EPO reduced the proportion of patients receiving allogeneic transfusions by 37% (from 17% to 11%) in orthopedic surgery and by 60% (from 32% to 13%) in cardiac surgery.

The decision analysis incorporated the reduction in allogeneic blood transfusions with the costs and effects associated with treatment and transfusion, and with transfusion related disease. In the base case scenario, EPO led to only modest incremental benefit compared to no intervention for orthopedic surgery (0.000029 life years gained). As an augmentation to PAD, EPO led to modest benefits in both cardiac (0.000043 life years) and orthopedic (0.000007 life years) surgery. For EPO compared to no intervention in orthopedic surgery, the incremental cost per life year gained was $55 million. For EPO to augment PAD, the incremental cost per life year gained was $296 million for orthopedic surgery and $35 million for cardiac surgery.

Detailed sensitivity analysis was conducted varying the rates of transfusion in the control group, the risks of transfusion related illnesses, and the quality of life and life expectancy with transfusion related illnesses. However, the cost-effectiveness ratio did not fall to a level generally considered acceptable. The conclusion of this report is that the use of EPO in reducing perioperative allogeneic transfusions is not cost-effective by conventional criteria.

1. Background and Objectives

1.1 Background

There has been great interest in methods of decreasing the use of allogeneic blood transfusion, mainly due to the risks of transmission of infectious agents (such as HIV and Hepatitis B and C) with allogeneic transfusion. There is also concern that currently unknown infectious agents might be transmitted by blood in the future. This interest has continued despite the likelihood that the transmission of these agents has decreased markedly in the last decade due to deferral of high risk donors and better methods of testing for the viruses. With blood transfusions, there is an additional risk of serious hemolytic reactions due to the mismatch of blood products.

Peri-operative use of blood in elective surgery (e.g. hip arthroplasty and open heart surgery) accounts for a substantial amount of all blood used. Technologies available to minimize peri-operative allogeneic transfusion include modifying the surgical technique, peri-operative management and transfusion threshold; predonation of autologous blood (PAD); cell salvage (both intra and post-operative); an anesthetic technique called acute normovolemic hemodilution (ANH); drugs that decrease blood loss (aprotinin, tranexamic acid (TXA), epsilon aminocaproic acid (EACA)); and erythropoietin (EPO).

The focus of this report is to assess the cost-effectiveness of EPO. EPO stimulates the bone marrow to produce red blood cells which, on average, allows autologous donors to donate more blood than without EPO. If EPO is given pre-operatively to patients who do not donate autologous blood, their mean hemoglobin at the time of operation is higher than those who do not receive EPO, potentially reducing the requirement for perioperative transfusions. We will refer to the former use as **EPO to augment PAD** and the latter as **EPO alone**.

In Canada, pre-operative use of EPO is approved for both EPO alone and for EPO to augment PAD. Both indications are restricted to patients undergoing major surgery who have a pre-operative hemoglobin between 100 and 130 g/l. In addition EPO to augment PAD is restricted to patients who are expected to require more blood than they can donate without EPO (EPREX Product Monograph 1996).

1.2 Current Clinical Evidence

Current evidence on the efficacy of EPO in surgery is limited. As part of the International Study of Perioperative Transfusion (ISPOT), meta analyses of all randomized trials (including abstracts and unpublished studies) of technologies to reduce exposure to allogeneic transfusions are being done (Bryson et al. 1997, Forgie et al. 1997, Laupacis et al. 1997). The meta analysis involved computerized searches of the MEDLINE and EMBASE databases as well as searches of the grey literature. The focus of the meta analyses was to identify the effect of technologies on the proportion of patients receiving allogeneic transfusions. Thus, only studies which provided data on the proportion of patients receiving allogeneic blood were used in the meta analyses.

The meta analysis concerning EPO was conducted by identifying all studies with erythropoietin as a text word published before May 1997. Only randomized trials that described the proportion of patients receiving allogeneic transfusions were included. The outcome was expressed as an odds ratio : an OR less than 1.0 suggested that EPO decreased exposure to allogeneic blood an OR greater than 1.0 would suggest that EPO increased exposure to allogeneic blood. This meta analysis has been submitted to the British Journal of Surgery for publication.

Three randomized trials were found assessing EPO alone in orthopedic surgery (a total of 684 patients) (COPES 1993, DeAndrade et al. 1996, Faris et al. 1996) and two randomized trials were found assessing EPO alone in cardiac surgery (a total of 108 patients) (D'Ambra et al. 1992, Sowade et al. 1996). The odds ratio (OR) was 0.38 (95% CI : 0.24 - 0.63) in the orthopedic studies, and 0.09 (0.03 - 0.28) in the cardiac studies.

There were 11 trials of EPO to augment PAD in orthopedic surgery (total of 825 patients) (Goodnough et al. 1989, van Bormann et al. 1991, Mercuriali et al. 1993, Beris et al. 1993, Biesma et al. 1993, Goodnough et al. 1994, Schlaeppi et al. 1994, Biesma et al. 1994, Yuen and Matthews 1995, Price et al. 1995, Tryba et al. 1995) and 5 trials of EPO to augment PAD in cardiac surgery (total of 224 patients) (Watanabe et al. 1992, Kulier et al. 1993, Schmoekel et al. 1993, Kulier et al. 1993, Hayashi et al. 1994, Walpoth et al. 1995). The OR was 0.42 (0.28 - 0.62) in the orthopedic studies and 0.25 (0.08 - 0.82) in the cardiac studies. The ORs for high dose EPO (total dose > 1800 units/kg) and low dose

EPO were similar (OR 0.41 and 0.48 respectively). There was a non-statistically significant trend for subcutaneous EPO to be more effective than intravenous EPO (OR 0.32 and 0.52 respectively).

There was no statistically significant evidence of serious side effects from EPO. However, there were not enough patients in the meta-analysis of orthopedic studies to exclude a small but clinically important increase in the risk of post-operative deep venous thrombosis. Also, in one study of EPO alone for cardiac surgery, 3% of patients had a death associated with a thrombotic or vascular event while on EPO, compared with none in the placebo-treated group (D'Ambra et al. 1992, EPREX product monograph 1996).

None of the randomized trials compared EPO directly with other methods of minimizing peri-operative transfusion such as PAD. However, one small study (sample size 76 patients) randomized patients undergoing radical prostatectomy to PAD, ANH, or ANH plus EPO (Monk et al. 1995). The proportion of patients receiving allogeneic blood was lowest in the ANH plus EPO group although this was not statistically significant. Another small study in patients undergoing orthopedic or vascular surgery (total sample size 80) received different combinations of PAD, ANH and EPO (Lefevre et al. 1995) There were no differences in the quantity of allogeneic blood received among groups (indeed there was a trend towards the EPO patients receiving more blood).

A further finding of the meta analysis was that the total dose of EPO, dose of EPO per injection, number and timing of doses, method of delivery (subcutaneous or intravenous) and the use of oral or intravenous iron differed markedly among published randomized trials[1].

1.3 Current Economic Evidence

As another component of ISPOT, a systematic review of all published economic evaluations of the technologies to minimize peri-operative allogeneic transfusion was conducted (submitted to British Journal of Surgery). There were no economic evaluations of EPO. The majority of evaluations of other technologies were of poor quality. The best quality studies are of PAD (Etchason et al. 1995, Birkmeyer et al. 1993 and 1994), which showed that PAD does not meet conventional criteria for cost-effectiveness. For example, Etchason found the cost/quality adjusted life year (QALY) was $235,000 for hip arthroplasty, and $494,000 for CABG. In his analysis, the risks of HIV and hepatitis were considerably higher than the current risks. When the cost-utility ratios were re-calculated using the current risks in the United States, the cost per QALY for PAD for hip arthroplasty was now $2,900,000 (personal communication Dr. Jeff Etchason).

Most of the studies assumed that allogeneic blood does not increase the likelihood of post-operative infections. Blood transfusions have been shown to be immunosuppresive in patients receiving transplants, but the data regarding peri-operative patients are not clear

[1] For EPO to augment PAD, the total dosage for cardiac patients ranged from 600 to 6400 units/kg whilst the total dosage for orthopedic patients ranged from 300 to 5400 units/ kg. For EPO alone, the total dosage for orthopedic patients ranged from 1500 to 4500 units /kg. EPO was given subcutaneously in 13 out of the 21 studies.

(McAllister 1997). If allogeneic transfusions increase the frequency of clinically implemented infections the cost-effectiveness of PAD could change markedly.

1.4 Study Objectives

We examined the cost-effectiveness of the peri-operative use of EPO in two situations:

1. EPO alone in patients with a pre-operative hemoglobin between 100 and 130 g/l; and
2. EPO to augment PAD in patients with a pre-operative hemoglobin between 100 and 130 g/l who are not expected to predonate their complete peri-operative needs without EPO.

The cost-effectiveness of EPO to augment PAD was assessed for both orthopedic (hip arthroplasty) and cardiac (CABG and valvular replacement) surgery patients. The analysis of EPO alone was confined to orthopedic patients, because EPO for cardiac patients has only been studied in two small studies, one of which found a concerning (but non-statistically significant) increase in thrombolitic deaths (D'Ambra et al. 1992, Sowade et al. 1996).

2. METHODS

2.1 Treatment comparators

The following comparisons were made:

1. EPO alone versus no intervention in orthopedic surgery
2. EPO to augment PAD versus PAD in orthopedic surgery
3. EPO to augment PAD versus PAD in cardiac surgery
4. PAD versus no intervention in orthopedic surgery
5. EPO alone versus PAD in orthopedic surgery

The choice of comparators follows the recommendations of the Canadian guidelines by focusing on the most common alternative practice and the minimum or "do nothing" alternative (CCOHTA 1994). For the analysis of EPO alone, the most commonly used comparator is the "do nothing" strategy - i.e. the use of allogeneic blood when clinically indicated[2]. Thus, the principal analysis is of the cost-effectiveness of EPO alone versus no therapy (both groups receive allogeneic blood when clinically indicated). However, the most common alternative practice to "do nothing" is the use of PAD. Thus, we conducted a secondary analysis of the cost-effectiveness of EPO alone versus PAD as well as an analysis of PAD versus no intervention. For the analysis of the cost-effectiveness of EPO

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[2] In a survey of transfusion practices in Canadian hospitals, only 16% of hospitals reported that they had an autologous blood donation program, and only 44% of hospitals reported that they handled autologous blood from the Red Cross. Of those using blood from the Red Cross only 22% reported that use by MDs was "moderate or very high" (Commission of Inquiry on the Blood System in Canada 1995).

to augment PAD, the obvious comparator is PAD alone.

Two regimens of EPO were considered. Regimens were based on the high dose and low-doses regimens recommended in a consensus statement of international experts on the use of EPO in surgery (Messmer 1996) which were similar to the manufacturer's recommended doses (EPREX product monograph 1996).

For all comparisons, the base case regimen was the lower dose of EPO: 300 units/kg given subcutaneously twice weekly for three weeks for a total of 6 doses, supplemented with 300 mg of oral iron sulfate three times a day for three weeks prior to surgery. The mean weight of patients undergoing orthopedic and cardiac surgery were obtained from the meta analysis (72.5 kg for orthopedic surgery patients and 72.0 for cardiac surgery). Thus, orthopedic patients would receive a total of 130 500 IU of EPO compared to 129 660 IU for cardiac patients.

If EPO was demonstrated to be cost-effective, sensitivity analysis would be conducted based on higher dose regimens: 600 units/kg given subcutaneously weekly for three weeks prior to surgery and on the day of surgery (four doses in total), supplemented with 300 mg of oral iron sulfate three times a day for three weeks prior to and two weeks post surgery for EPO alone ; and 600 units/kg given subcutaneously bi-weekly for three weeks prior to surgery (six doses in total), supplemented with 300 mg of oral iron sulfate three times a day for three weeks prior to and two weeks post surgery for EPO to augment PAD.

For all analyses, the mechanisms of collecting and administrating PAD and allogeneic blood were assumed to be similar to those detailed in a recent Canadian study of the costs of blood transfusions (Tretiak et al. 1996).

2.2 Perspective

Ideally, the principal viewpoint of the analysis would be from the societal perspective. However, due to a lack of available data, the base case estimates for the costs associated with transfusion related illnesses did not include the associated indirect costs. Such costs are likely to be small given the mean age of the populations under study (56 for cardiac surgery and 65 for orthopedic surgery); although there may be costs to informal caregivers. However, sensitivity analysis was conducted using extreme values for the costs of disease which would incorporate any indirect costs.

2.3 Form of Analysis

Analysis was conducted using decision trees representing the main consequences of treatment and the associated costs and effectiveness (Figures 1 and 2). The clinical path within the tree depicts patients receiving or not receiving allogeneic (and if appropriate autologous) transfusions: those receiving transfusions then have a risk of contracting a transfusion related illness.

Costs and outcomes were calculated for each terminal node of the trees, which allowed estimation of the expected costs and outcomes for each of the regimens compared. From this, the cost-effectiveness of the alternative regimens can be assessed.

For the base case analysis the profile of a typical orthopedic and cardiac surgery patient was identified. The weight of patients was assumed to be the mean weight of patients from the systematic review of published studies detailing transfusions received. The age and sex of the patients was obtained from a review of relevant patients treated at the Ottawa Civic Hospital (40 patients) and the University of Ottawa Heart Institute (186 patients), due to the poor reporting of this data in the published studies.

- for orthopedic surgery, a 65 year old woman weighing 72.5 kg
- for cardiac surgery, a 56 year old man weighing 72.0 kg.

2.4 Analytic Horizon

The decision analysis modeled the life time costs and effects for each intervention. Immediate costs associated with each transfusion regimen and lifetime costs of transfusion related illnesses were estimated. In addition, the effect of transfusion related illnesses on life expectancy was assessed.

2.5 Outcome measures

The principal effectiveness measure was life years gained with the regimens being assessed in terms of the incremental cost per life year gained. A secondary surrogate effectiveness measure was the number of allogeneic blood units avoided.

Patients' expected life years were calculated within the decision analysis as follows:

1. The proportion of patients receiving red cell transfusions and the quantity of units received for each intervention (no intervention, EPO, PAD and EPO to augment PAD) was obtained by pooling studies contained within the meta analysis. Each study within the meta analysis was reviewed and only data from studies with all necessary information were extracted. Studies were then systematically reviewed to identify the effect of EPO and PAD on the proportion of patients receiving allogeneic and autologous transfusions and the quantity of blood received. (Appendix 1)
2. Data on transfusions were then combined with data on the risk of transfusion related illnesses and their effect on life expectancy to estimate expected life years for each comparator. Data on the likelihood of transfusion related illnesses and their effects on life expectancy was obtained from a detailed literature review (Appendix 5).

There were no published studies comparing EPO alone versus PAD. Thus, for this comparison the transfusions received for the PAD intervention was taken from the comparison of PAD to no intervention. Transfusions received for EPO was then estimated based on the relative benefits of EPO and PAD in reducing the risks of allogeneic transfusions compared to no intervention and the quantity of allogeneic blood transfused (see Appendix 2).

Separate analyses were conducted using data on blood use and pre-donation from the Ottawa Civic Hospital and the University of Ottawa Heart Institute for the years 1995-1997. The rationale for this analysis is to estimate the effectiveness of technologies using actual rather than trial transfusion rates; thus, allowing for any Hawthorne effects and allowing the use of more recent data given changes in transfusion rates. Thus, for this analysis, the quantity of transfusions received were obtained for 40 orthopedic surgery patients and 186 cardiac surgery patients who predonated blood. The quantity of transfusions for no intervention, EPO alone and EPO to augment PAD were estimated based on modeling the data for PAD patients according to the relative frequency of allogeneic transfusions and the effect on the quantity of blood transfused from the systematic review (see Appendix 2). Data were then combined with risks and effects of transfusion illnesses to estimate life expectancy.

2.6 Costs

Cost items measured and valued were the costs of EPO, the costs of allogeneic and autologous blood collection and delivery, and the costs associated with transfusion related illnesses (Hepatitis B and C, HIV, hemolytic reactions and febrile reactions). All costs were converted to 1996 Canadian dollars.

In our base case analysis, the costs associated with EPO included only the costs of the drug and the costs of iron supplements. If in the base case analysis EPO was cost-effective, sensitivity analysis including the costs of administration and the costs of any additional tests (such as regular CBC) required would be conducted. The dosages for EPO and supplementary iron adopted for this analysis were detailed previously. The list price of a 20,000 IU vial of EPO ($267) was obtained from the pharmacy department of the Ottawa Civic Hospital. We assumed that should patients require less than full vial of EPO, the remaining EPO would be used in the treatment of other patients.

The cost of PAD and allogeneic transfusions was derived from a recently published Canadian study (Tretiak et al. 1996). The study involved the collection of cost data from eight hospitals and six red cross blood centres in four provinces. For allogeneic and autologous blood, costs include the costs of collection, production, distribution and delivery. These costs incorporate the costs of donor recruitment and time, testing and screening, overheads and consumables. The costs of allogeneic blood also include the costs of wastage. For the purposes of this study, the costs associated with wastage in PAD were excluded given that the analytic framework included the number of units donated not just the number received. A literature search was conducted to identify other studies containing estimates of the costs of blood products, for comparison with our base values (Appendix 3).

Estimates of the costs of transfusion related illnesses were obtained from a review of the published literature (Appendix 4). To be included, studies had to provide details of the lifetime costs of disease and the methodology used to calculate the costs. The main criteria for the choice of which data source to use was the most recent Canadian data if acceptable methodological quality; however if no Canadian data were available the most recent complete data from other countries would be used.

2.7 Discounting

Future costs and outcomes were discounted at a 5% rate (CCOHTA 1994).

2.8 Sensitivity analysis

The range of sensitivity analysis to be conducted was highly dependent on the results of the base case analysis of the cost-effectiveness of EPO.

If EPO was shown to be cost-effective, detailed univariate sensitivity analysis would be conducted to assess the robustness of the study's results to changes in the main assumptions. Major parameters which would be subject to univariate sensitivity analysis will include:- the dose and cost (including administration) of EPO, proportion of patients transfused, the mean units transfused, the discount rate, the risks and costs of transfusion related illnesses and the costs of blood products. Sensitivity analysis would employ the range of parameter estimates obtained from the various literature reviews. Further analysis would be conducted based on the most and least favourable scenarios in terms of the cost-effectiveness of EPO and using threshold analyses to determine values for key parameters associated with cost-effectiveness ratios of <$100,000, <$50,000, <$20,000 and $10,000 per life year gained.

However, if the base case analysis concluded that EPO was not cost-effective (more than $100 000 per life year gained), it would not be worthwhile to conduct detailed sensitivity analysis incorporating scenarios which would make EPO even less attractive. Thus, sensitivity analysis would focus on identifying whether EPO would become cost-effective only under more favourable scenarios. Such scenarios would include higher risks of transfusion related illnesses (including allowance for indirect costs and possible compensation claims), higher costs of allogeneic blood, extreme quality of life effects of transfusion related illnesses (including secondary infection of partners), higher proportions of patients receiving allogeneic transfusions in the control groups. possible decrease in patient length of stay with EPO and greater benefit in terms of reducing the relative risk of receiving allogeneic transfusions.

2.9 Allowance for Regional Variation

If EPO was found to be cost-effective, analysis would be conducted incorporating differences in the cost of EPO across provinces. If EPO was not cost-effective, analysis would be conducted to identify the threshold cost of EPO required for a cost-effectiveness ratio of $100 000 per life year gained.

3. Results

3.1 Quantity of Transfusions Received

A systematic review of all relevant published studies detailing the quantity of transfusions received was undertaken (Appendix 1). There was no consistent difference between different dosage regimens for EPO in the effect on transfusions received. For example, in the review of studies comparing EPO to no intervention in orthopedic surgery two studies included comparisons of different doses of EPO. In one study patients receiving the higher dose of EPO were less likely to receive allogeneic transfusions (23.4% versus 30.2%); however, in the other study the opposite was observed (25.0% versus 16.7%). Thus, data on all EPO regimens were pooled in determining the clinical effects.

Both EPO alone and EPO to augment PAD significantly reduce the requirement for patients to receive allogeneic blood (Tables 1). EPO alone reduced the proportion of patients receiving allogeneic transfusions in orthopedic surgery on average by 50.7% (48.3% of patients transfused to 23.8% of patients transfused) with a range between studies of 30.0% to 60.5%. EPO to augment PAD reduced the proportion receiving allogeneic blood in orthopedic surgery by 37.5% (16.8% to 10.5%) with a range of 36.1% to 100%. EPO to augment PAD reduced the proportion receiving allogeneic blood in cardiac surgery by 59.8% (31.6% to 12.7%) with a study range of 4.75% to 100%.

However, PAD alone was more effective in reducing the proportion receiving allogeneic blood than EPO alone with a reduction compared to no intervention of 78.4% (from 35.8% to 4.7%) with a study range of 75.3% to 86.7%.

For patients who were transfused, the quantity of blood received varied by intervention (Table 2). The use of EPO alone in orthopedic surgery (2.63 units reduced to 2.26 units) leads to a reduction in the quantity of allogeneic blood in those transfused. However, this was not the case for EPO to augment PAD in both cardiac surgery (5.5 units increased to 5.8 units) and orthopedic surgery (2.11 units increased to 2.46 units).

3.2 Risks of Transfusion Related Illness

Risks of transfusion related illnesses were obtained from a systematic review of the literature (Table 3). For HIV, hepatitis B and Hepatitis C, the base case risks were obtained from a study by Schreiber et al. (1996). For HIV the base case risk was 2/1 000 000 units of allogeneic blood transfused, with a range from other studies of 1.33/1 000 000 to 16.7/1 000 000. For Hepatitis B, the risk was 16/1 000 000 (range 5/1 000 000 to 300/1 000 000). For Hepatitis C the risk was 10/ 1 000 000 (range 9.7/1 000 000 to 660/1 000 000). It is evident from the data extracted that these risks have fallen considerably over recent years due to more sophisticated testing of allogeneic blood (Appendix 5).

The risks of hemolytic transfusion reactions associated with all transfusions (both allogeneic and autologous) was derived from the article by Linden and Kaplan (1992). For a non-fatal hemolytic reaction the risk was 52.6/1 000 000 units transfused (range 52.6/1 000 000 to 166.7/1 000 000). The risk of a fatal hemolytic reaction was 1.67/1 000 000 (range 1/100 000 to 1.67/1 000 000). The risk of a febrile reaction was estimated to be 1/100 units (Walker 1987) which approximates the recent findings of Gibis (1997).

For patients who did not contract any transfusion related infections, life expectancy was assumed to be the same as an average Canadian with the same age and sex as the surgery patient as detailed previously (Statistics Canada 1994). Discounted life expectancies for Canadian patients with HIV was obtained from a paper by Gold et al. (1996). Life expectancies for patients developing Hepatitis B and Hepatitis C were derived from the hazard function derived by Dusheiko et al. (1995) for chronic hepatitis patients in the UK. For sensitivity analysis, an extreme analysis was conducted assuming no life expectancy with transfusion related diseases.

3.3 Costs

All costs were converted into 1996 Canadian dollars (Tables 4 and 5)

The cost of receiving a unit of allogeneic blood was $210; and the cost of predonating one unit of blood was $277 (Tretiak et al. 1996). These estimates were broadly in the middle of the range of costs obtained from other published studies : $78 to $410 for allogeneic blood and $101 to $415 for predonating blood (Appendix 3).

The base case cost of treatment by EPO was derived assuming the patients' base case weight. The cost of EPO was $1743 for orthopedic surgery patients and $1730 for cardiac surgery. The cost of the larger dose regimen would be $3486 and $2595 respectively.

The literature review found few articles on the costs of transfusion related illnesses. (Appendix 4). The cost per case of HIV in Canada was derived from the study by Gold (1996) - $87 290. Alternative valuations ranged from $28 341 to $283 823.

Only three studies were identified that provided lifetime costs of Hepatitis B (Dusheiko 1995, Struve and Giesecke 1993, Wong et al. 1995). Our base case estimates of the lifetime costs of Hepatitis B and C ($19 141 and $15 621 respectively) were derived from the Dusheiko study (1995); the only study to in addition provide estimates of the lifetime costs of Hepatitis C. However, the estimates from this study pertain to the costs of chronic hepatitis which is manifest in approximately 50% of infected cases. Thus, the estimate may be an over estimate of the costs associated with Hepatitis and will be biased in favour of EPO. Other studies were identified which examined the cost-effectiveness of strategies to reduce the incidence of Hepatitis (Wiebe et al. 1997, Krahn and Detsky 1993, Margolis et al. 1995, Bloom et al. 1993). However, it was not possible to derive an estimate of the average lifetime costs of disease from these studies.

There are no published papers detailing the costs of hemolytic or febrile reactions. Thus, the cost per case for both a non-fatal and fatal hemolytic reaction was taken from an abstract (Sonnenburg 1996). Costs were $136 and $36 936 respectively. The cost of a febrile reaction was the average cost per febrile reaction of 306 non-leukemia patients identified in a chart review of patients treated at the Ottawa General Hospital - $90 (Gibis 1997).

3.4 Cost-effectiveness

The baseline variables used in the decision analysis are detailed in Table 7.

In the analysis based on transfusion rates from the systematic review, EPO alone and EPO to augment PAD both lead to a significant reduction in the number of units of allogeneic blood received (Tables 8 and 9). The number of units per patient was reduced by interventions incorporating EPO from 1.26 units to 0.54 units for EPO alone in orthopedic surgery, from 0.35 to 0.26 for EPO to augment PAD in orthopedic surgery and from 1.74 units to 0.74 units for EPO to augment PAD in cardiac surgery.

However, despite this, EPO led to only a small incremental benefit in life years gained. For orthopedic surgery patients, EPO alone increased life expectancy compared to no intervention by 0.000029 life years. For orthopedic surgery patients, EPO to augment PAD increased life expectancy by 0.000007 life years compared to PAD alone. For cardiac surgery patients EPO to augment PAD increased life expectancy by 0.000043 life years compared to PAD alone.

Interventions incorporating EPO were always more costly than their comparator. For orthopedic surgery patients, EPO alone cost $1857 per patient compared to $269 for no intervention. For orthopedic surgery patients who predonated blood, EPO to augment PAD cost $2903 per patient compared to $968 for PAD alone. For cardiac surgery patients, EPO to augment PAD cost $2515 per patient compared to $995 for PAD alone.

The incremental cost per life year gained for EPO compared to no intervention in orthopedic surgery was $55 million. For EPO to augment PAD, the incremental cost per life year gained was $296 million for orthopedic surgery and $35 million for cardiac surgery.

Analysis based on actual transfusion rates within the Ottawa Civic Hospital and the University of Ottawa Heart Institute, was less favourable towards EPO (Table 11). Due to the substantially lower proportion of patients receiving allogeneic transfusions in the control group, the benefits from any reduction in transfusion rates were smaller. EPO alone in orthopedic surgery led to a gain of only 0.000015 life years and EPO to augment PAD in cardiac surgery led to a gain of only 0.000 004 life years. Consequently the cost-effectiveness ratios for these two comparisons were also greater: respectively $109 million and $396 million per life year gained. EPO to augment PAD in orthopedic surgery was ineffective leading to a shorter life expectancy than PAD alone; largely due to the increased use of autologous blood resulting in an increase in fatal hemolytic reactions.

In our base case analysis, PAD alone for orthopedic surgery patients led to a decrease in the mean number of allogeneic units received : from 1.22 units to 0.32 units. However, it led to a substantial increase in the total number of units received: from 1.22 units to 2.26 units per patients. The benefits to life expectancy of the reduced risk of illnesses related to allogeneic transfusions (HIV and hepatitis B and C) is outweighed by the increased risk of fatal hemolytic reactions. Thus, the effect of PAD alone compared to no intervention was to reduce life expectancy in patients by 0.000007 years.

3.5 Sensitivity Analysis

The range of parameter estimates identified in the various literature searches is detailed in Table 6. However, given the unfavourable results for EPO in the base case analysis, sensitivity analysis focused on identifying scenarios under which EPO may be considered cost-effective (Table 12). This analysis assumed that a value of $100 000 per life year or QALY gained was a minimally acceptable ratio (Laupacis et al. 1993).

Sensitivity analysis was conducted based on quantity of transfusions received within the systematic review; given that analysis with lower transfusion requirements led to more unfavourable results. Analyses focused on the comparison of EPO alone to no intervention in orthopedic surgery and EPO to augment PAD for both cardiac and orthopedic surgery. Initial analyses were conducted as follows:

Scenario 1. Assuming the same quantity of transfusions received but with the highest risks of HIV and hepatitis, and the highest costs for HIV, hepatitis and allogeneic blood (Table 6).

Scenario 2. Assuming extreme effects of hepatitis and HIV on patients quality of life (utility = 0) from the time of transfusion, and assuming full quality of life for all other health states (utility =1).

Scenario 3. Assuming a combination of the above.

Under the first scenario, the cost per life year gained for the interventions incorporating EPO was reduced (range $2.6 million to $42.4 million). Under the second scenario, the cost per QALY gained for the interventions incorporating EPO ranged from $3.7 million to $48.5 million. Combining the first two analyses, led to a cost per QALY in orthopedic surgery of $150 000 for EPO alone and $1.6 million for EPO to augment PAD. In cardiac surgery , the cost per QALY of EPO to augment PAD was $90 000. Thus, in only one of these extreme scenarios did the inclusion of EPO lead to a ratio less than $100,000 per life year gained.

The second scenario is equivalent to conducting an extreme analysis relating to the life expectancy of patients with transfusion related disease : i.e. patients with disease die immediately. Thus, adopting the extreme assumption regarding life expectancy which favoured treatment with EPO led to cost-effectiveness ratios which did not meet our criteria for minimal acceptability.

Analyses were also conducted to assess the effect of changing the proportion of patients receiving allogeneic transfusions. An extreme analysis was conducted assuming all patients without EPO received allogeneic transfusions and all patients with EPO received no transfusions. However, the cost per life year gained from the use of EPO was still high: range $3.1 million to $19.4 million.

Our base case estimates of the costs of HIV and Hepatitis include only estimates of the direct costs of disease. Thus, an extreme analysis was conducted to assess the effects of the indirect costs of disease by adopting an extreme analysis by assuming the total cost of the diseases were $1 million each. Under this assumption the cost per life year gained was reduced only moderately to $ 54.2 million (from $ 54.9 million) for EPO alone in orthopedic surgery and $ 296.0 million (from $ 296.4 million) and $ 34.8 million (from $35.4 million) for EPO to augment PAD in orthopedic and cardiac surgery respectively.

Additional analysis was conducted to assess the impact of the infection of partners by patients who developed HIV from blood transfusion. We adopted an extreme analysis assuming that for each patient, one partner would also be affected with HIV and will incur the same costs and effects associated with HIV as the patient. This assumption reduced the cost per life year gained but the range was still high ; $28.1 million to $261.3 million.

Threshold analysis was conducted to determine the cost of EPO required for the cost per life year gained to be reduced to $100 000 per life year or QALY (Table 10). Under the base case analysis, the threshold value for EPO in orthopedic surgery was $158 for EPO alone. For EPO to augment PAD in orthopedic surgery, a threshold value would be less than $0. The threshold value for EPO in cardiac surgery was $214.

Further analysis focused on whether EPO would be cost-effective if targeted at patients with an increased capacity to benefit. Analysis was conducted under the extreme scenario assuming that it was possible to identify patients who would require 5 units of allogeneic blood and that by treating these patients with EPO they would not require any allogeneic transfusion. Under these assumptions the cost per life year gained from EPO was $3.5 million. Sensitivity analysis was also conducted assuming a younger patient population with an increased capacity to benefit (i.e. more potential life years would be lost from transfusion related infections). The base case analysis was repeated assuming a 30 year old patient. The cost per life year gained was lower than for the older patient population but was still considerably greater than $100 000 (actual range $28.2 million to $194 million).

Further sensitivity analysis was conducted to assess the sensitivity of the study's results to assumptions relating to the effect of EPO on the use of other health care resources. Analysis focused on identifying the threshold value required for the reduction in bed-days needed for patients receiving treatment with EPO so that cost-effectiveness ratios were reduced to less than $100 000 per life year gained. Assuming a cost per bed-day of $500, EPO alone would be cost-effective if it led to a reduction in mean length of stay in hospital of more than 3.17 bed days. Under a similar assumption, EPO to augment PAD would be cost-effective if it led to reductions of more than 3.9 bed days for orthopedic patients and 3.0 bed-days for cardiac patients. However, it must be noted that there is no evidence available to suggest that EPO reduce the length of hospital stay.

The final sensitivity analysis examined the threshold value for the costs of HIV which would be required for the cost-effectiveness ratios for EPO to fall below $100 000 per life year gained. This analysis addresses concerns regarding both the recent escalating costs of treatment for HIV/AIDS and any effects of compensation claims arising from infection. The threshold value for EPO alone in orthopedic surgery was $1.1 billion. For EPO to augment PAD in orthopedic surgery, the threshold value was $10.0 billion, and for EPO to augment PAD in cardiac surgery the threshold value was $0.8 billion.

3.6 Global Impact of EPO Adoption

The potential financial impact of EPO was examined by estimating its impact on hip arthroplasties and coronary artery bypass surgery.

Statistics Canada (Surgical Procedures and Treatments, 1992-93) estimates that the total number of hip arthroplasties conducted for the year 1992-93 was 22 638. The Heart & Stroke Foundation of Canada (Heart Disease and Stroke in Canada, 1995) estimate a total of 15 034 coronary artery bypass surgeries for the same period.

Not all surgery patients will be eligible for treatment with EPO. Assuming 10% of hip arthroplasty patients were treated with EPO alone, based on our base case analysis, the additional annual costs to the Canadian health care system compared to no intervention would be $3.6 million with the potential benefit of 0.05 life years gained. If 10% of all CABG patients were treated with EPO to augment PAD, the additional annual costs compared to PAD alone would be $2.3 million with the potential benefit of 0.07 life years gained.

4. Discussion

The main results of our study, question the appropriateness on economic grounds of the use of EPO to avoid perioperative transfusions. Under the assumptions contained in our decision analytic model, the inclusion of EPO leads to only modest incremental benefits (0.000007 to 0.000043 life years gained). Consequently, the cost per life year gained are considerable ($35 million to $296 million).

There is no consensus about the maximum magnitude for a cost-effectiveness ratio that can be considered acceptable. Tentative guidelines have been proposed whereby studies reporting values of over $100 000 per QALY gained may be considered weak evidence for adoption (Laupacis et al. 1992). Studies reporting values greater than $100 000 per QALY gained have included evaluations of non-ionic contrast media in patients at low risk of side effects and the treatment of asymptomatic hyperlipidemia with cholestyramine (Goel et al. 1989, Weinstein and Stason 1982). Following this argument, we have based our sensitivity analysis on the assumption that a cost per life year gained of $100 000 could be considered the maximum magnitude of a ratio that is acceptable. Given the magnitude of the ratios identified in this study, in this context EPO clearly does not fall under a level which is conventionally considered cost-effective.

We conducted detailed sensitivity analysis varying the rates of transfusion in the control group, the risks of transfusion related illnesses, and the costs, quality of life and life expectancy of transfusion related illnesses. We also explored the effects of the secondary infection of partners by patients who developed transfusion related illnesses. In all cases, analysis focused on extreme scenarios which improved the apparent cost-effectiveness of EPO. However, the cost-effectiveness ratios under these scenarios still did not meet the above criteria for cost-effectiveness.

One factor which may be limiting the cost-effectiveness of EPO, is the reduction in the requirement for allogeneic transfusions during surgery. In the past, when allogeneic units transfused per patient were higher, interventions such as EPO may have been more cost-effective. Thus, it may be hypothesized that the use of EPO could be targeted to patients at high risk of allogeneic transfusions. However, even under extreme assumptions of the number of units received and the positive effects of EPO, EPO was still not cost-effective.

Another factor affecting the cost-effectiveness of EPO is the reduction in risks of transfusion related infections such as HIV and hepatitis. However, analysis incorporating the highest recorded risks of infection were still not favourable towards EPO.

Given the typical age of patients requiring orthopedic and cardiac surgery another factor affecting their capacity to benefit from the use of EPO is the increased life expectancy of patients with HIV and hepatitis. Thus, analysis of younger patients, with a greater capacity to benefit was conducted but again the results were more than $100 000 per life year gained.

The above factors identify a major issue regarding interventions to reduce the need for allogeneic blood transfusions: the little benefit to be obtained. For example, for a female orthopedic patient aged 65, based on all patients in the no intervention groups of our systematic review, the discounted life expectancy with no intervention was only 0.000 041 discounted life years less than if there were no risks related to transfusions. Thus, the potential benefit to be obtained from interventions such as EPO are very small, and to be cost-effective the cost of EPO must be significantly smaller than it currently is. Assuming that an intervention could avert all costs associated with allogeneic transfusions and obtain maximum benefits in terms of life years gained, the intervention would have to cost no more than $218 for the cost-effectiveness ratio to be less than $100 000.

An additional finding of this study is the danger in using surrogate clinical endpoints in economic evaluation. The main impetus of the use of EPO is the reduction of allogeneic blood transfusions due to the associated risk of illness. Assessing the cost-effectiveness of interventions in terms of the cost per unit of allogeneic blood avoided may lead to erroneous conclusions. The incremental costs for EPO and EPO to augment PAD do not in the first instance appear considerable (range of $1 500 to $21 500 in our base case analysis). However, when cost-effectiveness is assessed in terms of life years gained the benefits in the reduction of allogeneic blood received appear less important.

EPO may be cost-effective if it leads to a reduction in the use of other health care resources during the period immediately post surgery. Sensitivity analysis identified that EPO may be cost-effective if it leads to a reduction in average length of stay of more than

3 days per patient. However, there is no evidence available to suggest that this is indeed the case.

Willingness to pay techniques have been suggested as an appropriate measure to assess society's preferences with respect to avoidance of risk (Donaldson 1990). However, there is a lack of consensus on how such techniques can be used with respect to the questions asked and the population sample (Pauly 1995). In particular there is indecision over whether values should be obtained for holistic programs (i.e. the administration of EPO) or the consequences of the program (i.e. a life year gained). Clearly, the former approach would be more complex requiring patients to consider the relative benefits of treatment while the latter allows the patient only to consider the end product of treatment; namely the effects on quality of life and life expectancy. In addition there are a number of criticisms of the use of willingness to pay including framing effects related to the choice of values for closed-ended questions, the lack of incentive to individuals to give reasonable values and individual's inexperience in considering the value of health care. Thus, the technique's appropriateness may be limited in this analysis, given that we are already able to estimate the costs and benefits of treatment with EPO.

There are several limitations of our study which must be addressed.

The optimal dose of EPO is unknown. Within the systematic review of transfusion received, there were no statistically significant differences in efficacy between lower and higher doses of EPO. However, given the results of the threshold analysis for the cost of

EPO, to be cost-effective the dosage of EPO would have to be substantially lower than currently recommended, without any loss in efficacy.

Our analysis assumed that the supply of allogeneic blood products will be sufficient to meet the level of demand. Sometimes elective surgery has been postponed due to shortages in local blood supply. It is unclear what impact the use of EPO by a small proportion of potential transfusion recipients would have on the total blood supply. Also, it is not clear that surgery for patients treated by EPO or who have pre-donated blood would continue during periods of shortages given that there would be a continued risk that patients may have heavy blood requirements.

Our analysis also did not consider the uncertainty over whether EPO has a small but clinically important effect upon post operative arterial thrombosis rates (D'Ambra 1992). However, any analysis which considered such effects would make EPO less cost-effective than our current estimates.

We also did not consider the public's trust in the blood system and the effect on patient's quality of life of any anxiety over the risk of receiving allogeneic blood. However, given the current low risks of infections from blood and the continual reduction in the proportion of patients transfused such anxiety may be reduced if patients were made aware of the reduced magnitude of such risks. It may be contentious to suggest that policy decisions should be made based on the lack of knowledge concerning the actual risks and health effects.

We are also unable to predict whether currently unknown infections are transmitted by allogeneic blood. However, the analysis incorporating the highest recorded estimates of the risks of transfusion related illnesses provide insight into the effect of increased risks on the cost-effectiveness ratio. Any unknown disease would have to have an extremely high prevalence rate in the population to make an impact on the study results.

In this study, we did not compare EPO to any other technologies to decrease peri-operative allogeneic transfusion, such as aprotinin, TXA or cell salvage. Meta-analyses of RCTs have shown that these technologies are effective.

Some RCTs have suggested that peri-operative allogeneic transfusions increase the frequency of post-operative bacterial infection. A recent meta-analysis is inconclusive, but there is a possibility that the risk of bacterial infections may increase. Since such infections are expensive to treat (Gibis 1997), such an increase could improve the cost-effectiveness of EPO.

We have assumed that the risks of hemolytic transfusion reactions are the same for autologous and allogeneic blood. To our knowledge there are no data addressing this issue, although the process of processing autologous blood is more complex, thus making it reasonable to conclude the risks are similar. Because patients who predonate blood are more likely to receive any transfusion, the increased risk of hemolytic reactions negate some of the benefits of the decrease in HIV and hepatitis. However, even if patients who predonate autologous blood receive the same amount of blood as non donors, the cost effectiveness ratios are still unattractive.

Two recent studies have suggested that EPO used along with ANH may decrease the requirement for allogeneic transfusions (Monk et al. 1994, Goodnough 1997). However, since the efficacy of ANH itself has not been established (Bryson et al. 1997) and since the number of patients within these studies was small, we have not evaluated EPO for this indication.

In conclusion, we have attempted within the sensitivity analysis to address most of these perceived limitations. We must still conclude that the use of EPO to prevent perioperative allogeneic transfusions is not cost-effective because detailed sensitivity analysis adopting scenarios more favourable to EPO did not change the conclusions reached.

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Table 1: Percentage Relative Reduction in Proprotion of Patients Receiving Allogeneic Blood

	% relative reduction in proportion of patients receiving allogeneic blood		
	Included Studies [1]	All Studies [2]	Individual Study Range [3]
EPO vs. No intervention (orthopedic)	50.7 (n=2)	52.6 (n=3)	30.0 - 60.5
EPO+PAD vs. PAD (orthopedic)	37.5 (n=6)	44.8 (n=9)	36.1 - 100.0
EPO+PAD vs. PAD (cardiac)	59.8 (n=2)	67.3 (n=5)	4.75 - 100
PAD vs. No intervention (orthopedic)	78.4 (n=2)	78.4 (n=2)	75.3 - 86.7

[1] Included studies are studies within the original meta analysis which reported mean number of units received and, where appropriate, predonated. Studies are combined irrespective of dosage of EPO used.

[2] All studies are all studies within the meta analysis, irrespective of whether mean number of units received were reported.

[3] Range of relative risks from individual included studies.

Table 2: Number of Allogeneic Blood Units per Patient Receiving Allogeneic Transfusion

	Included Studies	Range
EPO vs. No intervention (orthopedic)		
No Intervention	2.63	2.61 - 2.64
EPO	2.26	2.26 - 2.27
EPO+PAD vs. PAD (orthopedic)		
PAD	2.11	1.2 - 3.0
EPO+PAD	2.46	0 - 4.0
EPO+PAD vs. PAD (cardiac)		
PAD	5.50	2.2 - 6.0
EPO+PAD	5.80	0 - 7.25
PAD vs. No intervention (orthopedic)		
PAD	2.16	0.6 - 2.3
No intervention	1.79	1.24 - 2.3

Table 3: Risk of Transfusion Related Illness

Illness	Risk	Source
Hemolytic reactions	52.6/1 000 000	Linden 1992
Fatal hemolytic reactions	1.67/1 000 000	Linden 1992
Hepatitis B	16/1 000 000	Schreiber 1996
Hepatitis C	10/1 000 000	Schreiber 1996
HIV	2/1 000 000	Schreiber 1996
Febrile Reactions	1/100	Walker 1993

Table 4: Lifetime cost of Transfusion Related Illnesses

Illness	Source	Country	Cost [1]
HIV/AIDS	Gold 1996	CAN	$87 290
Hepatitis B	Dusheiko 1995	UK	$19 141
Hepatitis C	Dusheiko 1995	UK	$15 621
Fatal hemolytic reaction	Sonnenberg 1996	USA	$36 936
Non-fatal hemolytic reaction	Sonnenberg 1996	USA	$136
Febrile Reaction	Gibis 1997	CAN	$90

[1] Values converted to 1996 Canadian dollars and discounted at 5% per annum

Table 5: Cost of Interventions

	Source	Cost [1]
Cost per unit of allogeneic blood transfused	Tretiak 1996	$210
Cost per unit of autologous blood predonated	Tretiak 1996	$277
Cost of EPO regimen for cardiac surgery	Ottawa Civic Hospital Pharmacy	$1730
Cost of EPO regimen for orthopedic surgery	Ottawa Civic Hospital Pharmacy	$1743

[1] Values converted to 1996 Canadian dollars

Table 6: Potential Range for Sensitivity Analysis

Variable	Range
Risk of non-fatal hemolytic reaction	52.6/1 000 000 - 166.7/1 000 000
Risk of fatal hemolytic reaction	1/1 000 000 - 1.67/1 000 000
Risk of Hepatitis B	5/1 000 000 - 300/1 000 000
Risk of Hepatitis C	9.7/1 000 000 - 660/1 000 000
Risk of HIV	1.33/1 000 000 - 16.7/1 000 000
Costs of hepatitis B and C	$15 621 - $45 570
Costs of HIV	$28 341 - $283 823
Cost of per unit predonated	$101 - $415
Cost of unit of allogeneic blood	$78 - $410

Full range of studies presented in appendices 3, 4 and 5.
Costs in 1996 Canadian Dollars.

Table 7 Variables Used in Decision Analysis

Variable	Description	Definition	
		Orthopedic	**Cardiac**
cBlood	Cost of allogeneic unit transfused	210	210
cPAD	Cost of PAD unit donated	277	277
cFHemo	Cost per case of fatal hemolytic reaction	36936	36936
cFR	Cost per case of febrile reaction	90	90
cHemo	Cost per case of hemolytic reaction	136	136
cHepB	Cost per case of Hepatitis B	19141	19141
cHepC	Cost per case of Hepatitis C	15621	15621
cHIV	Cost per case of HIV	87290	87290
cEPO	Cost of EPO	1743	1730
Lnothing	Discounted life expectancy	13.0378	14.0024
Lfhemo	Life expectancy after fatal hemolytic reaction	0	0
Lhepb	Discounted life expectancy for case of Hepatitis B	12.7213	13.6525
LhepC	Discounted life expectancy for case of Hepatitis C	12.6813	13.5807
LHIV	Discounted life expectancy for case of HIV	8.4761	8.4761
pTrans	Probability of receiving allogeneic blood	see Tables 8 and 9	see Tables 8 and 9
pPAD	Probability of receiving predonated blood	see Tables 8 and 9	see Tables 8 and 9
uPADr	Units of PAD received	see Tables 8 and 9	see Tables 8 and 9
unitPAD	Units of blood predonated	see Tables 8 and 9	see Tables 8 and 9
UnitsTrans	Units of allogeneic blood received	see Tables 8 and 9	see Tables 8 and 9
TotUnits	Total number of units transfused	unitsTrans+uPADr	unitsTrans+uPADr
pFHemo	Probability of fatal hemolytic reaction	(1/600000)*TotUnits	(1/600000)*TotUnits
pFR	Probability of febrile reaction	(1/100)*unitsTrans	(1/100)*unitsTrans
pHemo	Probability of hemolytic reaction	(1/19000)*TotUnits	(1/19000)*TotUnits
pHepB	Probability of Hepatitis B	(16/1000000)*unitTrans	(16/1000000)* unitTrans
pHepC	Probability of Hepatitis C	(10/1000000)* unitTrans	(10/1000000)* unitTrans
pHIV	Probability of HIV	(2/1000000)* unitTrans	(2/1000000)* unitTrans

Costs in 1996 Canadian Dollars.

Table 8 : Estimated Blood Use :Systematic analysis transfusion rates

Surgery	Analysis	Groups	% per group	Units of Allogeneic	Units of PAD donated	Units of PAD received
Orthopedic	EPO [2] vs. Allogeneic	Allogeneic - no transfusion	51.7	0	0	0
		- allogeneic	48.3	2.63	0	0
		EPO - no transfusion	76.2	0	0	0
		- allogeneic	23.8	2.26	0	0
Orthopedic	PAD [1] vs. EPO to augment PAD	PAD - no transfusion	10.0	0	3.22	0
		- autologous only	73.2	0	3.22	2.73
		- autologous + allogeneic	16.8	2.11	3.22	3.22
		EPO + PAD - - no transfusion	10.0	0	3.99	0
		- autologous only	79.5	0	3.99	2.96
		- autologous + allogeneic	10.5	2.46	3.99	3.99
Cardiac	PAD vs. EPO to augment PAD	PAD - no transfusion	10.0	0	2.26	0
		- autologous only	58.4	0	2.26	2.18
		- autologous + allogeneic	31.6	5.5	2.26	2.26
		EPO + PAD - no transfusion	10.0	0	2.27	0
		- autologous only	77.3	0	2.27	2.27
		- autologous + allogeneic	12.7	5.8	2.27	2.27
Orthopedic	PAD vs. Allogeneic	Allogeneic - no transfusion	32.0	0	0	0
		- allogeneic	68.0	1.79	0	0
		PAD - no PAD	10.0	0	2.22	0
		- PAD alone	75.3	0	2.22	2.15
		- PAD + allogeneic	14.7	2.16	2.22	2.22
Orthopedic	PAD [1] vs. EPO [2]	PAD - no transfusion	10.0	0	2.22	0
		- autologous only	75.3	0	2.22	2.15
		- autologous + allogeneic	14.7	2.16	2.22	2.22
		EPO - no transfusion	66.4	0	0	0
		- allogeneic	33.6	1.55	0	0

[1] Data on proportions of PAD patients based on actual data from published studies for the specific comparisons.

[2] Data on proportions of EPO patients transfused differ between comparisons. For the comparison with no intervention, data are obtained from the published studies. For the comparison with PAD, data are derived from modeling the relative risk and quantity of allogeneic blood received (see Appendix 2).

Table 9: Estimated Blood Use: Non-Trial Transfusion Rates [1]

Surgery	Analysis	Groups	% per group	Units of Allogeneic	Units of PAD donated	Units of PAD received
Orthopedic	EPO vs. Allogeneic	Allogeneic - no transfusion	63.5	0	0	0
		- allogeneic	36.5	1.84	0	0
		EPO - no transfusion	82.0	0	0	0
		- allogeneic	18.0	1.58	0	0
Orthopedic	PAD vs. EPO to augment PAD	PAD - no transfusion	21.1	0	2.5	0
		- autologous only	71.0	0	2.5	1.72
		- autologous + allogeneic	7.9	2.22	2.5	2.5
		EPO + PAD - - no transfusion	21.1	0	3.1	0
		- autologous only	74.0	0	3.1	1.88
		- autologous + allogeneic	4.9	2.58	3.1	3.1
Cardiac	PAD vs. EPO to augment PAD	PAD - no transfusion	27.3	0	2.78	0
		- autologous only	64.7	0	2.78	1.83
		- autologous + allogeneic	8.0	2.29	2.78	2.78
		EPO + PAD - no transfusion	27.3	0	2.78	0
		- autologous only	69.5	0	2.78	1.95
		- autologous + allogeneic	2.8	2.41	2.78	2.78
Orthopedic	PAD vs. Allogeneic	Allogeneic - no transfusion	63.5	0	0	0
		- allogeneic	36.5	1.84	0	0
		PAD - no PAD	21.1	0	2.5	0
		- PAD alone	71.0	0	2.5	1.72
		- PAD + allogeneic	7.9	2.22	2.5	2.5
Orthopedic	PAD vs. EPO	PAD - no transfusion	21.1	0	2.5	0
		- autologous only	71.0	0	2.5	1.72
		- autologous + allogeneic	7.9	2.22	2.5	2.5
		EPO - no transfusion	82.0	0	0	0
		- allogeneic	18.0	1.58	0	0

[1] For orthopedic surgery, baseline transfusion rates were based on a review of medical records for 40 autologous patients treated at the Ottawa Civic Hospital. For cardiac patients, baseline transfusion rates based on a database of 186 autologous patients treated at the Ottawa Heart Institute.

Table 10: Cost-Effectiveness Results : Systematic Analysis Transfusion Rates

Surgery	Intervention	Life Years	Incremental Life Years	Allogeneic Units	Units Avoided	Cost ($)	Incremental Cost ($)	Incremental Cost per Life Year Gained	p
Orthopedic	EPO	13.037779	0.000 029	0.54	0.72	1857	1588	54 920 000	
	None	13.037750		1.26		269			
Orthopedic	EPO+PAD	13.037730	0.000 007	0.26	0.09	2903	1935	296 360 000	
	PAD	13.037723		0.35		968			
Cardiac	EPO+PAD	14.002320	0.000 043	0.74	1.00	2515	1520	35 390 000	
	PAD	14.002277		1.74		995			
Orthopedic	None	13.037752	0.000 007	1.22		258	-424	Dominant	
	PAD	13.037745		0.32	0.90	682			
Orthopedic	EPO	13.037779	0.000 034	0.52		1853	1171	34 190 000	
	PAD	13.037745		0.32	0.20	682			

[1] Threshold value is the cost of EPO required for the cost per life year gained to equal $100 000.

Table 11: Cost Effectiveness Results: Non-Trial Transfusion Rates [1]

Surgery	Intervention	Life Years	Incremental Life Years	Cost ($)	Incremental Cost ($)	Incremental Cost per Life Year Gained
Orthopedic	EPO	13.037789	0.000 015	1803	1661	108 660 000
	None	13.037773		142		
Orthopedic	PAD	13.037762	0.000 001	730	-1899	Dominant
	EPO+PAD	13.037761		2629		
Cardiac	EPO+PAD	14.002363	0.000 004	2515	1706	395 610 000
	PAD	14.002359		809		
Orthopedic	None	13.037773	0.000 011	142	-588	Dominant
	PAD	13.037762		730		
Orthopedic	EPO	13.037789	0.000 027	1803	1073	40 470 000
	PAD	13.037762		730		

[1] For orthopedic surgery, baseline transfusion rates based on a review of medical records for 40 autologous patients treated at the Ottawa Civic Hospital. For cardiac patients, baseline transfusion rates based on a database of 186 autologous patients treated at the Ottawa Heart Institute.

Table 12: Results of Sensitivity Analysis

Scenario	Cost per Life Year (QALY) Gained		
	EPO vs. No Intervention (orthopedic)	EPO+PAD vs. PAD (orthopedic)	EPO+PAD vs. PAD (cardiac)
Highest reported risks and costs of transfusion related illnesses transfusion risks and highest reported costs of allogeneic blood	4 490 000	42 350 00	2 550 000
Utility of patients with HIV and hepatitis =0, for other states =1	5 610 000	48 470 000	3 670 000
Combination of the above	150 000	1 550 000	90 000
Younger patients (age=30)	38 670 000	204 860 000	28 370 000
All patients without EPO require allogeneic transfusions, none with EPO	11 430 000	19 380 000	3 130 000
All patients require 5 units of allogeneic blood without EPO, none with EPO	3 470 000	N/A	N/A
Both patient and partner are infected with HIV	44 600 000	261 260 000	28 140 000
Cost of Hepatitis B, Hepatitis C and HIV are $1 million	54 220 000	295 950 000	34 750 000

Figure 1 Decision Tree for Comparison of EPO alone versus No Intervention

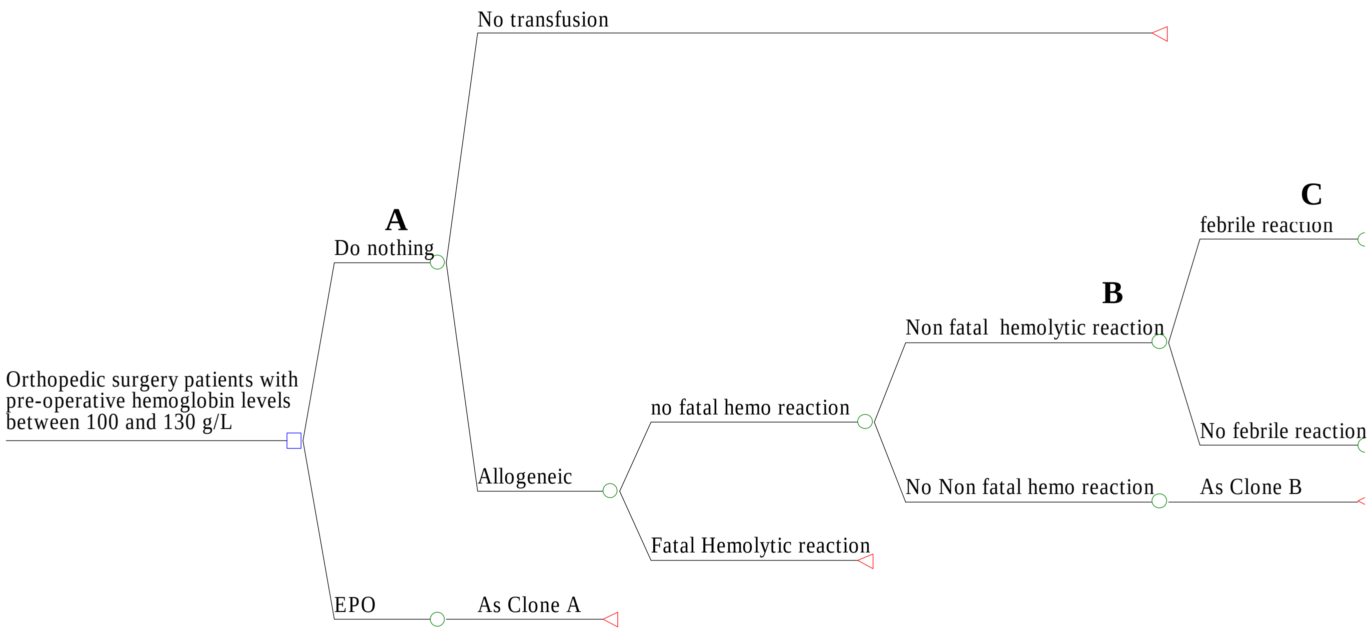
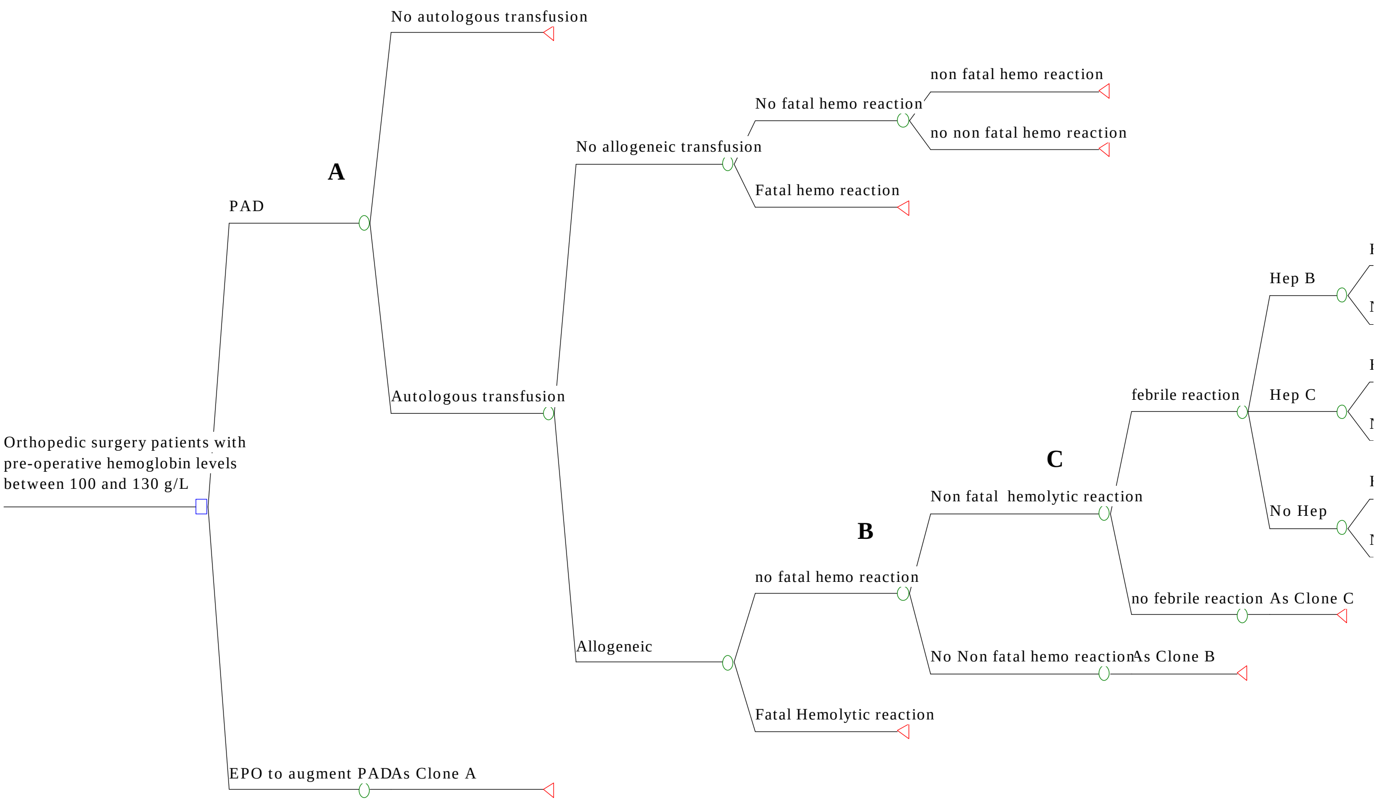


Figure 2 Decision Tree for Comparison of EPO to augment PAD versus PAD Alone : Orthopedic



APPENDIX 1: Systematic Review of Studies Detailing Quantity of Transfusions Received

Appendix 1a EPO vs. No intervention (Orthopedic surgery)

Study	Comparators	n	% patients exposed to allogeneic	# allogeneic units	Excluded/ Included
DeAndrade 1996	No intervention	96	22.9	N/S	Excluded
	EPO 1500IU/kg	95	10.5	N/S	
	EPO 4500IU/kg	100	11.0	N/S	
Faris 1996	No intervention	67	53.7	2.64	Included
	EPO 1500IU/kg	54	16.7	2.32	
	EPO 4500IU/kg	64	25.0	2.22	
COPES 1993	No intervention	78	43.6	2.61	Included
	EPO 2700IU/kg	53	30.2	2.32	
	EPO 4200IU/kg	77	23.4	2.22	
ALL studies n=3	*No intervention*	*241*	*38.2*	*2.63*	
	EPO	*443*	*18.1*	*2.26*	
INCLUDED n=2	*No intervention*	*145*	*48.3*	*2.63*	
	EPO	*248*	*23.8*	*2.26*	

N/S = Not stated

APPENDIX 1b - PAD vs. No Intervention

Study	Comparators	n	% patients exposed to allogeneic	# allog. units	# units pre-donated	# PAD units received	% patients exposed to autologous	Excluded/ Included
Orthopedic Studies								
Toy	PAD	189	14.8	2.1	2.0	N/S	93.1%	Included
1992	No intervention	60	60.0	1.7	0.0	0.0	0	
Elawad	PAD	15	13.3	3	N/S	N/S	100.0%	Included
1991	No intervention	15	100.0	2	0.0	0.0	0	
Other Studies								
Sandrelli	PAD	348	12.6	2.3	2.0	N/S	N/S	Excluded
1995	No intervention	344	45.9	2.3	0.0	N/S	N/S	
Guiratti	PAD	28	14.3	1.78	2.0	1.42	N/S	Excluded
1995	No intervention	29	100.0	1.24	0.0	0.0	N/S	
Kajikawa	PAD	21	23.8	N/S	2.0-6.0	N/S	N/S	Excluded
1994	No intervention	21	61.9	N/S	0.0	N/S	N/S	
O'Hara	PAD	73	32.9	1.3	2.0	1.9	N/S	Excluded
1994	No intervention	72	63.9	1.9	0.0	0.0	N/S	
Busch	PAD	239	28.0	N/S	2.0	N/S	N/S	Excluded
1993	No intervention	236	55.9	N/S	0.0	N/S	N/S	
Heiss	PAD	58	34.5	1.91	2.0	N/S	N/S	Excluded
1993	No intervention	62	59.7	1.25	0.0	N/S	N/S	
Yamada	PAD	37	5.4	1.2	2.0	1.59	N/S	Excluded
1992	No intervention	34	20.6	2.14	0.0	0.0	N/S	
van Papendrecht								
1991	PAD	131	58.8	1.83	2.0	N/S	N/S	Excluded
	No intervention	137	28.5	1.65	0.0	N/S	N/S	
Britton	PAD	104	20.2	0.6	4.1	3.3	N/S	Excluded
1989	No intervention	111	79.3	2.1	0.0	0.0	N/S	
Love	PAD	58	36.2	1.1	1.97	1.71	N/S	Excluded
1987	No intervention	58	62.1	2.05	0.0	0.0	N/S	
ALL studies (n=13)								
	PAD	*1341*	*23.9*	*1.40*	*2.22*	*2.16*	*97.7*	
	No intervention	*1179*	*53.9*	*1.51*	*0.00*	*0.00*	*N/S*	
ORTHO studies (n=2)								
	PAD	*204*	*14.7*	*2.16*	*N/S*	*N/S*	*N/S*	
	No intervention	*75*	*68.0*	*1.79*	*N/S*	*N/S*	*N/S*	

N/S = Not stated

APPENDIX 1c - EPO and PAD vs. PAD alone (Orthopedic Surgery)

Study	Comparators	n	% patients exposed to allogeneic	# allog. units	# units pre-donated	# PAD units received	% patients exposed autologous	Excluded/ Included
Price	PAD	87	31.0	2.2	3	N/S	94.0	Excluded
1996	EPO 3600IU/kg	86	19.8	2.6	4.5	N/S	98.0	
Biesma	PAD	45	35.6	1.97	2	1.8	89.0	Included
1994	EPO 3000IU/kg	50	10.0	4	2	1.96	46.0	
Goodnough	PAD	23	8.7	1.15	4.6	3.4	N/S	Included
1994	EPO 900IU/kg	24	8.3	4.8	5.2	4.0	N/S	
	EPO 1800IU/kg	26	3.8	5.2	5.5	3.5	N/S	
	EPO 3600IU/kg	18	16.7	2.4	5.6	2.9	N/S	
Schlaeppi	PAD	21	9.5	3.0	4	3.9	100	Included
1994	EPO 400IU/kg	19	0.0	0.0	4	3.4	100	
	EPO 800IU/kg	22	0.0	0.0	4	2.9	100	
Beris	PAD	52	5.8	4	3	2.60	100	Included
1993	EPO 2000IU/kg (approx.)	49	14.3	3	3	2.55	100	
Biesma	PAD	20	35.0	N/S	2	N/S	90.0	Excluded
1993	EPO 3000IU/kg	20	5.0	N/S	4	N/S	50.0	
Mercuriali	PAD	8	50.0	1.2	2.8	2.8	100.0	Included
1993	EPO 1800-3600IU/kg	36	25.0	0.4	4.5	4.1	100.0	
von Bormann								
1991	PAD	5	0.0	NA	4	2.4	N/S	Excluded
	EPO 1400IU/kg	5	0.0	NA	4	0.8	N/S	
Goodnough								
1989	PAD	24	8.3	2.4	4.1	3.8	83.0	Included
	EPO 3600IU/kg	23	4.4	2.3	5.4	3.6	70.0	
ALL studies (n=9)								
	PAD	*285*	*22.1*	*2.24*	*4.93*	*2.82*		
	EPO	*378*	*12.2*	*2.46*	*5.71*	*3.02*		
INCLUDED (n=6)								
	PAD	*173*	*16.8*	*2.11*	*3.22*	*2.83*		
	EPO	*267*	*10.5*	*2.46*	*3.99*	*3.08*		

N/S = Not stated

APPENDIX 1d - EPO and PAD vs. PAD alone (Cardiac Surgery)

Study	Comparators	n	% patients exposed to allogeneic	# allog. units	# units pre-donated	# PAD units received	% patients exposed to autologous	Excluded/ included Included
Walpoth 1995	No intervention	10	20.0	3.0	3.0	2.80	N/S	Included
	EPO 600 IU/kg	11	9.1	19.0	3.0	3.0	N/S	
	EPO 1200IU/kg	10	30.0	3.33	3.0	3.0	N/S	
Hayashi 1994	No intervention	28	35.7	6.0	2.0	2.0	100.0	Included
	EPO 12 000IU/kg	28	10.7	6.7	2.0	2.0	100.0	
	EPO 24 000 IU/kg	30	10.0	3.0	2.0	2.0	100.0	
Kulier 1993	No intervention	12	66.7	2.2	N/S	N/S	N/S	Excluded
	EPO 1600 IU/kg	12	8.3	0.3	4.0	N/S	N/S	
Schmoeckel 1993	No intervention	6	16.7	N/S	2.0	N/S	100.0	Excluded
	EPO 800IU/kg	9	44.4	N/S	2.0	N/S	100.0	
	EPO 1600 IU/kg	10	10.0	N/S	3.0	N/S	100.0	
	EPO 3200 IU/kg	8	12.5	N/S	4.0	N/S	100.0	
	EPO 6400 IU/kg	10	10.0	N/S	4.0	N/S	100.0	
Watanabe 1992	No intervention	14	28.6	2.9	4.0	N/S	100.0	Excluded
	EPO 1400 IU/kg	12	0.0	0	4.0	N/S	100.0	
	EPO 1200 IU/kg	14	0.0	0	4.0	N/S	100.0	
ALL studies (n=5)								
	No EPO	*70*	*35.7*	*3.77*	*2.62*	*2.21*		
	EPO	*154*	*11.7*	*3.10*	*2.86*	*2.27*		
INCLUDED (n=2)								
	No EPO	*38*	*31.6*	*5.5*	*2.26*	*2.21*		
	EPO	*79*	*12.7*	*5.8*	*2.27*	*2.27*		

N/S = Not stated

APPENDIX 2 Modeling of Transfusions Received

Modeling of EPO vs. PAD in Orthopedic Surgery

No published studies are available incorporating a head to head comparison of EPO vs. PAD. Thus, a synthetic comparison is required using data from the comparisons of EPO to no intervention and PAD to no intervention.

The transfusions received for the no intervention group varied between the comparisons with EPO alone and PAD alone. This is likely due to variety of factors including differences in patient characteristics, surgical expertise and transfusion thresholds. To facilitate a comparison we need to standardize the transfusions received based on the differences in the no intervention group.

Thus, we created the synthetic comparison as follows.

The proportion of PAD patients transfused and the transfusions received were taken direct from the comparison with no intervention.

    14.7% of patients received allogeneic blood
    2.16 allogeneic units per patient transfuse d

The transfusion requirements of patients receiving EPO relative to PAD was then estimated by adjusting the transfusions received in the no intervention arm of the PAD comparison with the effect of PAD on transfusions received.

Transfusions received in the no intervention group of the PAD versus no intervention comparison =

    68.0% of patients received allogeneic blood
    1.79 allogeneic units per patient transfused

Reduction in proportion of patients requiring blood with EPO	=50.7% (Table 1)
Reduction in allogeneic units per patient transfused with EPO	= 2.26/2.63
	= 0.859

Thus, the proportion of EPO patients transfused and the transfusions received for the synthetic comparison with PAD =

    33.6% of patients received allogeneic blood (68.0 x .493%)*
    1.55 allogeneic units per patient transfused (1.79 x .859)*

* Note calculations are subject to rounding.

Modeling of Transfusions Received Based on Ottawa Data

Data were obtained for 40 orthopedic surgery patients and 186 cardiac surgery patients who predonated blood. The quantity of transfusions received are as detailed for the PAD alone comparisons in Table 9 =

Number of autologous units donated =	2.5
Proportion of patients receiving no transfusions =	21.1%
Proportion of patients receiving autologous blood only =	71.0%
Mean number of autologous units received =	1.72
Proportion of patients receiving autologous and allogeneic blood =	7.9%
Mean number of autologous units received =	2.5
Mean number of allogeneic units rec eived =	2.22

For estimation of the transfusions received with no intervention, the data for PAD was adjusted based on the effects of PAD on the proportions transfused and the quantity of allogeneic blood received from the systematic review.

No intervention :

Proportion transfused:	7.9 (Table 9) * 68.0/14.7 (Table 8)	= 36.5
Units of allogeneic received:	2.22 (Table 9) * 1.79/2.16 (Table 8)	= 1.84

For estimation of the transfusions received with EPO alone, the data for no intervention was then adjusted based on the effects of EPO on the proportions transfused and the quantity of allogeneic blood received from the systematic review.

EPO:

Proportion transfused:	36.5 (Table 9) * 23.8/48.3 (Table 8)	= 18.0
Units of allogeneic received:	1.84 (Table 9) * 2.26/2.63 (Table 8)	= 1.58

For estimation of the transfusions received with EPO to augment PAD in orthopedic surgery, the data for PAD was adjusted based on the effects of EPO to augment PAD on the proportions transfused and the quantity of allogeneic blood received from the systematic review.

EPO to augment PAD to orthopedic surgery:

Proportion receiving allogeneic transfusions:		
	7.9 (Table 9) * 10.5/16.8 (Table 8)	= 4.9
Units of allogeneic received:	2.22 (Table 9) * 2.46/2.11 (Table 8)	= 2.58
Units of PAD received:	1.8 (Table 9) * 3.08/2.82 (Table 8)	= 1.96

For estimation of the transfusions received with EPO to augment PAD in cardiac surgery, the data for PAD in cardiac surgery was adjusted based on the effects of EPO to augment PAD on the proportions transfused and the quantity of allogeneic blood received from the systematic review.

EPO to augment PAD to cardiac surgery:

Proportion receiving allogeneic transfusions:		
	8.0 (Table 9) * 12.7/36.1 (Table 8)	= 2.8
Units of allogeneic received:	2.29 (Table 9) *5.8/5.5 (Table 8)	= 2.41
Units of PAD received:	1.93 (Table 9) * 2.27/2.21 (Table 8)	= 1.98

APPENDIX 3 Cost of Blood Products

Cost of Blood: Allogeneic

Study	Total Cost/unit	Included
Roberts 1996	$146	Collection, production, distribution, delivery, waste
Sonnenberg 1996	$78	N/S
Tretiak 1996	$210	Collection, production, distribution, delivery, waste
Etchason 1995	$234	Collection, production
Mah 1995	$134	Direct costs (not specified)
Monk 1995	$169	Collection, distribution
Healy 1994	$92	Direct costs (not specified)
Scott 1992	$410	N/S
Solomon 1988	$140 (for orthopedic) $321 (for CABG)	N/S

All costs converted to 1996 Canadian dollars

N/S = Not stated

Cost of Blood: PAD

Study	Total Cost/unit	Included
Roberts 1996	$134	Collection, distribution, waste
Sonnenberg 1996	$101	N/S
Tretiak 1996	$277	Collection, production, storage, distribution, waste
Etchason 1995	$276	Collection, production
Mah 1995	$154	Direct costs (not specified)
Monk 1995	$238	Collection, distribution
Healy 1994	$128	Direct costs (not specified)
Elawad 1991	$118	N/S
Solomon 1988	$289 (orthopedic)	N/S
	$415 (CABG)	N/S

All costs converted to 1996 Canadian dollars

N/S = Not stated

Search Strategy

Search strategy combined a detailed review of the literature in the ISPOT database with a MEDLINE search of English language studies. Studies were then reviewed to identify and subsequently abstract studies providing estimates of the costs of PAD and/or allogeneic blood.

MEDLINE Search Strategy

Cost of Blood (Allogeneic and Autologous)

1	blood transfusion/exp
2	blood/exp
3	predonated autologous blood.tw
4	predonated blood.tw
5	autologous blood.tw
6	blood transfusion.tw
7	allogeneic blood.tw
8	cost and cost analysis/exp
9	cost.tw
10	costs.tw
11	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7
12	8 OR 9 OR 10
13	11 AND 12

APPENDIX 4 Lifetime cost of Transfusion Illness

Study	Country	Lifetime cost	Comments
Hepatitis			
Dusheiko 1995	UK	$19 141 $15 621	Hepatitis B Hepatitis C
Wong 1995	USA	$45 570	Hepatitis B
Struve 1993	UK	$22 203	Hepatitis B
HIV			
Brettle 1997	UK	$100 558	Direct costs
Gold 1996	CAN	$68 394	Direct costs
Gable 1996	USA	$129 160	Direct costs
Petrou 1996	UK	$283 823	Total costs
Brettle 1994	UK	$196 042	Direct costs
Etchason 1995	USA	$165 836	Direct costs
Fortgang 1995	USA	$124 959	In-patient costs
Healy 1994	USA	$172 356	N/S
Birkmeyer 1993, 1994	USA	$279 499	N/S
Hellinger 1993	USA	$159 632	Direct costs
Andrulis 1992	USA	$133 685	Direct costs
Zowall 1992	CAN	$28 341	Direct costs
Andrews 1991	USA	$36 941	Direct costs
Whyte 1987	AUS	$22 232	In-patient costs

All costs converted to 1996 Canadian dollars and discounted at 5%.

N/S = Not stated

Search Strategy

Search strategy combined a detailed review of the literature in the ISPOT database with a MEDLINE search of English language studies. Studies were then reviewed to identify and subsequently abstract studies providing estimates of the costs associated with HIV and hepatitis and transfusion reactions.

MEDLINE Search Strategies:

HIV/AIDS and Hepatitis

1	acquired immunodeficiency syndrome/exp
2	acquired immunodeficiency syndrome.tw
3	HIV/exp
4	HIV infection/exp
5	HIV.tw
6	hepatitis/exp
7	hepatitis.tw
8	cost and cost analysis/exp
9	cost.tw
10	costs.tw
11	1 OR 2 OR 3 OR 4 OR 5
12	6 OR 7
13	8 OR 9 OR 10
14	11 AND 13
15	12 AND 13

Transfusion Reactions

1	blood transfusion/exp
2	blood/exp
3	infection/exp
4	blood.tw
5	hemolytic.tw
6	transfusion.tw
7	illness.tw
8	infection.tw
9	reaction.tw
10	cost and cost analysis/exp
11	cost.tw
12	costs.tw
13	2 OR 4 OR 5
14	3 OR 6 OR 7 OR 8 OR 9
15	13 AND 14
16	1 OR 15
17	10 OR 11 OR 12
18	16 AND 17

APPENDIX 5 Likelihood of Transfusion Related Illness

ILLNESS	STUDY	LIKELIHOOD
Hemolytic reaction	Walker 1987	1/6 000
	Birkmeyer 1993	1/10 000
	Linden 1992	1/19 000
Fatal hemolytic reaction	Walker 1987	1/100,000
	Birkmeyer 1993	1/500,000
	Linden 1992	1/600,000
Hepatitis B	US General Accounting Office 1997	1/63 000
	Schreiber 1996	16/1 000 000
	Krever 1995	3/10 000
	Etchason 1995	1/200 000
	Healy 1994	1/20 000
	Birkmeyer 1993	1/50 000
	Public Service Guidelines USA 1991	1/50 000
Hepatitis C	US General Accounting Office 1997	1/4 100
	Schreiber 1996	1/100 000
	Krever 1995	66/100 000
	Etchason 1995	3/10 000
	Healy 1994	3/10 000
	Birkmeyer 1993	33/100 000
	Donahue 1992	1/4 000
HIV	US General Accounting Office 1997	1/450 000
	Schreiber 1996	1/500 000
	Krever 1995	1/750 000
	Etchason 1995	6.7/1,000,000
	Lackritz 1994	1.5/1,000,000
	Healy 1994	4.4/1,000,000
	Birkmeyer 1993	1/100 000
	Nelson 1992	1/60,000
	Murphy 1992	1/500 000
Febrile reaction	Walker 1987	1/100

Search Strategy

Search strategy combined a detailed review of the literature in the ISPOT database with a MEDLINE search of English language studies. Studies were then reviewed to identify and subsequently abstract studies providing rates for risks of infections by HIV or hepatitis and transfusion reactions.

Medline Search Strategy

HIV/AIDS and Hepatitis

1	probability/exp
2	incidence/exp
3	likelihood.tw
4	probability.tw
5	incidence.tw
6	acquired immunodeficiency syndrome/exp
7	acquired immunodeficiency syndrome.tw
8	HIV/exp
9	HIV infection/exp
10	HIV.tw
11	hepatitis/exp
12	hepatitis.tw
13	1 OR 2 OR 3 OR 4 OR 5
14	6 OR 7 OR 8 OR 9 OR 10
15	11 OR 12
16	13 AND 14
17	13 AND 15

Transfusion Reactions

1	probability/exp
2	incidence/exp
3	likelihood.tw
4	probability.tw
5	incidence.tw
6	blood transfusion/exp
7	blood/exp
8	infection/exp
9	blood.tw
10	hemolytic.tw
11	transfusion.tw
12	illness.tw
13	infection.tw
14	reaction.tw
15	1 OR 2 OR 3 OR 4 OR 5
16	7 OR 9 OR 10
17	8 OR 11 OR 12 OR 13 OR 14
18	(16 AND 17) OR 6
19	15 AND 18