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Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model

L Davies, TJ Brown, S Haynes, K Payne, RA Elliott and C McCollum

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Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model

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Abstract

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Objectives: To compare patient outcomes, resource use and costs to the NHS and NHS Blood Transfusion Authority (BTA) associated with cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion.

Data sources: Electronic databases covering the period 1996–2004 for systematic reviews and 1994–2004 for economic evidence.

Review methods: Existing systematic reviews were updated with data from selected randomised controlled trials (RCTs) that involved adults scheduled for elective non-urgent surgery. Any resource use or cost data were extracted for potential use in populating an economic model. Relative risks or weighted mean difference of each outcome for each intervention were assessed, taking into account the number of RCTs included in each outcome and intervention and the presence of any heterogeneity. This allowed indirect comparison of the relative effectiveness of each intervention when the intervention is compared with allogeneic blood transfusion. A decision analytic model synthesised clinical and economic data from several sources, to estimate the relative cost-effectiveness of cell salvage for people undergoing elective surgery with moderate to major expected blood loss. The perspective of the NHS and patients and a time horizon of 1 month were used. The economic model was developed from reviews of effectiveness and cost-effectiveness and clinical experts. Secondary analysis explored the robustness of the results to changes in the timing and costs of cell salvage equipment, surgical procedure, use of transfusion protocols and time horizon of analysis.

Results: Overall, 668 studies were identified electronically for the update of the two systematic reviews. This included five RCTs, of which two were cell salvage and three preoperative autologous donation (PAD). Five published systematic reviews were identified for antifibrinolytics, fibrin sealants and restrictive transfusion triggers, PAD plus erythropoietin, erythropoietin alone and acute normovolaemic haemodilution (ANH). Twelve published studies reported full economic evaluations. All but two of the transfusion strategies significantly reduced exposure to allogeneic blood. The relative risk of exposure to allogeneic blood was 0.59 for the pooled trials of cell salvage (95% confidence interval: 0.48 to 0.73). This varied by the type and timing of cell salvage and type of surgical procedure. For cell salvage, the relative risk of allogeneic blood transfusion was higher in cardiac surgery than in orthopaedic surgery. Cell salvage had lower costs and slightly higher quality-adjusted life years compared with all of the alternative transfusion strategies except ANH. The likelihood that cell salvage is cost-effective compared with strategies other than ANH is over 50%. Most of the secondary analyses indicated similar results to the primary analysis. However, the primary and secondary analyses indicated that ANH may be more cost-effective than cell salvage.

Conclusions: The available evidence indicates that cell salvage may be a cost-effective method to reduce exposure to allogeneic blood transfusion. However, ANH may be more cost-effective than cell salvage. The results of this analysis are subject to the low quality and reliability of the data used and the use of indirect comparisons. This may affect the reliability and robustness of the clinical and economic results. There is a need for further research that includes adequately powered high-quality RCTs to compare

directly various blood transfusion strategies. These should include measures of health status, health-related quality of life and patient preferences for alternative transfusion strategies. Observational and tracking studies are needed to estimate reliably the incidence of adverse events and infections transmitted during blood transfusion and to identify the lifetime consequences of the serious hazards of transfusion on mortality, health status and health-related quality of life.

Contents

List of abbreviations vii

Executive summary ix

1 Introduction 1
Background 1
Aims and objectives 3

2 Methods: systematic review 5
Approach 5
Transfusion strategies evaluated 5
Update of the cell salvage and PAD systematic reviews 6
Search strategy 6
Review of the systematic reviews 8
Review of economic evaluations and cost studies 9

3 Results: systematic reviews of effectiveness 13
Updates of cell salvage and PAD reviews ... 13
Cell salvage update 14
PAD update 18
Review of systematic reviews 27
Summary 37

4 Results of the review of economic evaluations 39
Characteristics of the included economic evaluations 39
Quality assessment of the economic evaluations 44
Results of the economic evaluations 44
Summary 45

5 Methods: economic model 47
Approach 47
Decision analytic model 48
Variable estimation 54
Analysis of data 56

6 Data used as inputs to the economic model 59
Likelihood of events 59
Costs of events 63
Outcomes, utility and QALYs 71

7 Results of the economic model 73
Primary analysis 73
Secondary analyses 75
Impact of cell salvage on the NHS BTA 86

8 Discussion 91
Summary of the clinical evidence 91
Summary of the economic evidence 92
Summary of the results of the economic model 93
Strengths and weaknesses of the methodologies used 94
Strengths and weaknesses of the data 97
Comparison of the economic model with other studies 99
Limitations 99

9 Conclusions 103
Implications for healthcare 103
Recommendations for further research 104

Acknowledgements 107

References 109

Appendix 1 Search strategies for the update of the Cochrane systematic reviews of cell salvage and preoperative autologous donation 115

Appendix 2 Inclusion/exclusion screening form for the cell salvage and PAD systematic review update 119

Appendix 3 Quality assessment forms for the cell salvage and PAD systematic review update 121

Appendix 4 Data extraction form for the cell salvage and PAD systematic review update 123

Appendix 5 Inclusion/exclusion form for the review of systematic reviews 129

Appendix 6 Search strategy for the economic data 131

Appendix 7 Inclusion/exclusion form for the economic data 133

Appendix 8 Economic data extraction form 135

Appendix 9 Table of characteristics of original cell salvage and PAD systematic reviews 141

Appendix 10 Cell salvage meta-analyses .. 143

Appendix 11 PAD meta-analyses 165

Appendix 12 Table of included cost studies 171

Appendix 13 Table of included economic evaluations 197

Health Technology Assessment reports published to date 211

Health Technology Assessment Programme 225

List of abbreviations

AAA	abdominal aortic aneurysm
AF	antifibrinolytic
AIDS	acquired immunodeficiency syndrome
AIOD	aortoiliac occlusive disease
Allo	allogeneic
ANH	acute normovolaemic haemodilution
BRAT-2	Baylor rapid autotransfusion system-2
CABG	coronary artery bypass graft
CCA	cost-consequence analysis
CCOHTA	Canadian Coordinating Office for Health Technology Assessment
CEA	cost–effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CMA	cost-minimisation analysis
CPB	cardiopulmonary bypass
CS	cell salvage
CUA	cost–utility analysis
DEALE	declining exponential approximation of life expectancy
DVT	deep vein thrombosis
EACA	ε-aminocaproic acid
EPO	recombinant human erythropoietin (rHuEPO)
FS	fibrin sealant
HAART	highly active antiretroviral therapy
HAM	human-T lymphotrophic virus-I associated myelopathy
HAV	hepatitis A virus
Hb	haemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HTLV	human T-cell lymphotrophic virus
IBCT	incorrect blood component transfused
ICER	incremental cost-effectiveness ratio
INAHTA	International Network of Agencies of Health Technology Assessment
IOCS	intraoperative cell salvage
ISBT	International Society of Blood Transfusion
ISPOT	International Study of Perioperative Transfusion
ISTAHC	International Society of Technology Assessment in Health Care

continued

List of abbreviations *continued*

ITT	intention-to-treat
LVEF	left ventricular ejection fraction
MeSH	medical subject heading
MI	myocardial infarction
NHS BTA	National Health Service Blood Transfusion Authority
NHS EED	National Health Service Economic Evaluation Database
OR	odds ratio
PAD	preoperative autologous donation
POCS	postoperative cell salvage
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
RBC	red blood cell
RCT	randomised controlled trial
rHuEPO	recombinant human erythropoietin
SD	standard deviation
SHOT	Serious Hazards of Transfusion
SMUHT	South Manchester University Hospital Trust
THA	total hip arthroplasty
TKA	total knee arthroplasty
TRALI	transfusion-related acute lung injury
TXA	tranexamic acid
vCJD	variant Creutzfeldt–Jakob disease
WMD	weighted mean difference

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

Executive summary

Background

When severe haemorrhage occurs due to surgery, blood transfusion can be life saving. Elective surgery accounts for over 40% of requests for stored blood to the National Health Service Blood Transfusion Authority (NHS BTA) (previously the National Blood Service).

Alternatives to allogeneic transfusion (blood from an unrelated donor) include autologous transfusion using the patient's own blood, interventions to reduce surgical blood loss and interventions to minimise the use of perioperative allogeneic blood.

All blood transfusions are associated with serious adverse events. The cost of allogeneic blood has risen and the NHS BTA faces difficulties in meeting demand for blood products.

Objectives

The principal objectives were to:

1. Assess the effectiveness of alternative transfusion strategies in terms of the relative risk of exposure to allogeneic and autologous blood transfusion, postoperative complications, reoperation due to bleeding, adverse transfusion reactions and mortality and the mean length of stay. Two Cochrane systematic reviews of cell salvage (published/last updated 2003) and preoperative autologous donation (PAD) (published/last updated 2001) were updated; existing systematic reviews were reviewed [acute normovolaemic haemodilution (ANH), erythropoietin, antifibrinolytic drugs and fibrin sealants]. The updates were submitted to the Cochrane Library.
2. Obtain data on health-related quality of life and utilities and the relative cost and cost-effectiveness of the transfusion strategies. This included a review of economic evidence.
3. Use a decision analytic model to determine the likely cost-effectiveness of cell salvage.

Methods

Data sources

Searches were conducted for the period 2002–4 (cell salvage) and 2001–4 (PAD) to update the two Cochrane systematic reviews. Search strategies for the original Cochrane systematic reviews were adapted to identify new trials. Data for the updates were obtained from electronic searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, ISI Web of Science and International Network of Agencies of Health Technology Assessment (INAHTA). The searches for the review of systematic reviews covered the period 1996–2004, using the Cochrane Database of Systematic Reviews and MEDLINE. The review of economic evidence covered the period 1994–2004, using MEDLINE, EMBASE, Econlit, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects and the NHS Economic Evaluation Database (National Electronic Library for Health, Issue 3, 2004).

Study selection

Only randomised controlled trials (RCTs) undergoing elective non-urgent surgery were included for the update of existing systematic reviews. The review of systematic reviews only included reviews with explicit search and selection criteria. The patient population was adults undergoing elective non-urgent surgery. Included interventions were allogeneic transfusion; cell-salvage; PAD; ANH; antifibrinolytic drugs; fibrin sealants; and recombinant human erythropoietin (EPO). Economic and cost studies were only included if they reported resource use or cost for allogeneic blood transfusion or included interventions for adult patients undergoing major elective surgery.

Data extraction

Two reviewers independently abstracted data for the updates to the cell salvage and PAD systematic reviews. One reviewer extracted data about the focus, inclusion criteria and number and methodological quality of the included studies in each systematic review. The systematic reviews

were quality assessed using a form developed for the Critical Appraisal Skills Programme. Any resource use or cost data were extracted for potential use in populating an economic model.

Data synthesis

Data for the updated systematic reviews were added to the original meta-analyses from the two original systematic reviews. Differences in outcomes were combined across studies using relative risks or weighted mean differences in random effects meta-analyses. Results of the meta-analyses for each systematic review were extracted into tables. Relative risks or weighted mean difference of each outcome for each intervention were assessed, taking into account the number of RCTs included in each outcome and intervention and the presence of any heterogeneity. This allowed indirect comparison of the relative effectiveness of each intervention when the intervention is compared with allogeneic blood transfusion.

Economic model

A decision analytic model synthesised clinical and economic data from several sources, to estimate the relative cost-effectiveness of cell salvage for people undergoing elective surgery with moderate to major expected blood loss. The perspective of the NHS and patients and a time horizon of 1 month were used. The economic model was developed from reviews of effectiveness and cost-effectiveness and clinical experts. Secondary analysis explored the robustness of the results to changes in the timing and costs of cell salvage equipment, surgical procedure, use of transfusion protocols and time horizon of analysis.

Results

Overall, 668 studies were identified electronically for the update of the two systematic reviews. Five RCTs were included (two cell salvage, three PAD). Five published systematic reviews were identified for antifibrinolytics, fibrin sealants and restrictive transfusion triggers, PAD plus erythropoietin, erythropoietin alone and ANH. Twelve published studies reported full economic evaluations.

All but two of the transfusion strategies significantly reduced exposure to allogeneic blood. The relative risk of exposure to allogeneic blood was 0.59 for the pooled trials of cell salvage (95% CI 0.48 to 0.73). This varied by the type and timing of cell salvage and type of surgical procedure. For cell salvage, the relative risk of allogeneic blood transfusion was higher in cardiac surgery than in orthopaedic surgery.

Cell salvage had lower costs and slightly higher quality-adjusted life years compared with all of the alternative transfusion strategies except ANH. The likelihood that cell salvage is cost-effective compared with strategies other than ANH is over 50%. Most of the secondary analyses indicated similar results to the primary analysis. However, the primary and secondary analyses indicated that ANH may be more cost-effective than cell salvage.

Conclusions

Implications for healthcare

The available evidence indicates that cell salvage may be a cost-effective method to reduce exposure to allogeneic blood transfusion. However, ANH may be more cost-effective than cell salvage. The results of this analysis are subject to the low quality and reliability of the data used and the use of indirect comparisons. This may affect the reliability and robustness of the clinical and economic results.

Recommendations for research

There is a need for further research that includes:

1. Adequately powered high-quality RCTs to compare directly various blood transfusion strategies. These should include measures of health status, health-related quality of life and patient preferences for alternative transfusion strategies.
2. Observational and tracking studies to estimate reliably the incidence of adverse events and infections transmitted during blood transfusion.
3. Observational studies to identify the lifetime consequences of the serious hazards of transfusion on mortality, health status and health-related quality of life.

Chapter 1
Introduction

Background

Elective surgery accounts for over 40% of all requests for stored blood to the National Health Service Blood Transfusion Authority (NHS BTA) (previously known as the National Blood Service). Transfusion is life saving in severe haemorrhage due to surgery. The cost of providing allogeneic blood (blood from an unrelated donor) has increased dramatically[1] and the NHS BTA faces increasing difficulties and expense in meeting demand for blood products. An ageing population and the use of blood transfusion in a wider population mean that the demand for blood products will increase.[2,3] In the short term, it is estimated that the demand for blood will increase by 5% by 2008.[3] Over the long term, the demand for blood has been estimated to be 1.3 times higher than the supply of blood products by 2026.[2] A review of the NHS BTA by the National Audit Commission concluded that efficient use of such a scarce resource as blood was a crucial element of maintaining a balance between demand and supply.[4] More recently, there has been a decrease in the demand for blood. For example, the demand for red cells was projected to fall from 2,186,000 units in the financial year 2002–3 to 2,165,000 units in the financial year 2003–4.[5]

Allogeneic transfusion is associated with adverse events. The Serious Hazards of Transfusion (SHOT) scheme[6] collects data on the serious sequelae of transfusing allogeneic blood components. Participation in the scheme is voluntary, and covers both NHS and private hospitals in the UK. Participation by NHS hospitals was reported to be 85% in 2003.[6] Reported adverse events following allogeneic blood transfusion include the transmission of blood-borne viral infections such as hepatitis, HIV, human-T lymphotrophic virus (HTLV); transfusion reactions (ranging from minor febrile reactions to major haemolytic reactions); and serious bacterial infection causing pneumonia and sepsis. Other adverse events include transfusion-related acute lung injury (TRALI), post-transfusion purpura and transfusion-related graft versus host disease.[6] Allogeneic transfusion is also associated with immunosuppression that may influence postoperative infection rates and the prognosis for patients with cancer and transplant rejection.[7–11]

Increasing costs and blood shortages combined with the risk of transmitting infection through allogeneic blood products emphasise the need to assess the relative cost-effectiveness of alternative interventions to replace or minimise perioperative allogeneic blood products.

Alternatives to allogeneic blood transfusion include use of autologous blood (a person's own blood), methods to reduce blood loss and other methods to minimise the need for allogeneic blood. Autologous blood transfusion interventions include:

- Cell salvage (auto-transfusion), which includes a range of techniques that scavenge blood from operative or wound sites (intraoperatively and/or postoperatively) for re-infusion back into the patient during or after surgery as required.[12]
- Preoperative autologous donation (PAD), where blood is removed from the patient prior to operation and stored within the blood bank ready for re-infusion during or after surgery if required.[13]
- Acute normovolaemic haemodilution (ANH), where blood is removed from a patient, usually during induction of anaesthesia, replacing it with crystalloid or colloid fluid to maintain circulating volume and kept ready for re-infusion if necessary.[14]

Interventions that aim to minimise perioperative allogeneic blood products by reducing surgical blood loss include:

- antifibrinolytic drugs [aprotinin, tranexamic acid (TXA), ε-aminocaproic acid (EACA)]
- fibrin sealants (FSs).

Aprotinin is a non-specific, serine protease inhibitor, derived from bovine lung, with antifibrinolytic properties (bleeding prevention). It acts as an inhibitor of several serine proteases and also inhibits the contact phase activation of coagulation that both initiates coagulation and promotes fibrinolysis.[15] TXA and EACA are synthetic derivatives of the amino acid lysine that

act as effective inhibitors of fibrinolysis. TXA and EACA block the lysine binding sites on plasminogen molecules, inhibiting the formation of plasmin and inhibiting fibrinolysis.[16]

FSs are made from human plasma derived from either allogeneic blood or autologous blood. FSs are mainly comprised of fibrinogen (± factor XIII) and thrombin (plus calcium, usually in the form of calcium chloride). FSs mimic the final phase of the coagulation cascade and produce a semi-rigid clot.[17]

Other alternative strategies to minimise the use of perioperative allogeneic blood include:

- recombinant human erythropoietin (rHuEPO)
- restrictive transfusion thresholds or protocols.

Recombinant human erythropoietin (EPO) is a protein that increases the production of erythrocytes [red blood cells (RBCs)] in the body and can be administered before surgery to reduce the need for allogeneic blood transfusion.[18] Transfusion thresholds based on haemoglobin or erythrocyte volume fraction values can be used to determine a level when blood transfusion is indicated and decrease the use of allogeneic blood.[19]

Combinations of the techniques described above can be used. Examples are the use of cell salvage in conjunction with ANH[20] and augmenting PAD with EPO to increase red cell mass.[21]

In 2002, the UK Department of Health reaffirmed previous recommendations to the NHS to use autologous blood transfusion including cell salvage.[22] Recent guidelines and a national blood conservation strategy for the UK provide evidence-based frameworks to inform clinicians about the appropriate use of alternative blood transfusion strategies.[23,24] These identify transfusion strategies supported by evidence of effectiveness and set out the principles from which local policies and written procedures can be developed for the administration of blood products and management of transfused patients. However, the quality of evidence is varied and for some interventions, such as ANH, equivocal. There may also be organisational issues to ensure that blood-sparing strategies such as PAD and ANH do not compromise patient management and health.

A survey of surgeons in northwest England concluded that transfusion practice had changed little between 1990 and 1999, with only 24% of respondents using autologous blood transfusion in 1999.[25] Many of the respondents were keen to use autologous techniques. However, logistical obstacles were cited as the main reason for the low use of autologous techniques. These included the anticipated high cost of autologous techniques, staff-related problems and lack of facilities. A more recent survey of NHS Trusts found that the use of cell salvage had increased. However, the survey also confirmed that the use of autologous blood transfusion strategies was relatively low in the UK.[26] The results of the survey suggested that improved use of limited allogeneic blood supplies required the following: training of staff, development of hospital transfusion teams in NHS Trusts, development of protocols for the appropriate use of blood, provision of information to patients and expansion in the use of perioperative cell salvage. More recently, a pilot study of the introduction of cell salvage identified similar obstacles. Logistical obstacles to the introduction of cell salvage included lack of information about suppliers of equipment and disposables, and support to identify the equipment and disposables required. Finance for the purchase of cell salvage equipment was cited as an obstacle, as was a lack of trained staff to provide an adequate cell salvage service.[27]

Autologous transfusion strategies and alternative interventions to replace and/or minimise perioperative allogeneic blood products are not without risk of adverse events and often do not eliminate the need for allogeneic blood transfusion. It has been demonstrated that the availability of predonated autologous blood can encourage an increase in overall (autologous plus allogeneic) transfusion rate.[16] PAD can cause vasovagal reactions, anaemia and cardiac complications ranging from angina to cardiac arrest. Predonated autologous blood is still exposed to handling and storage risks such as transfusion mismatch and bacterial contamination, which can lead to a major transfusion reaction.[28] Cell salvage has been associated with adverse events such as air embolism, nephrotoxicity and coagulation abnormalities.[12,16] FSs made from allogeneic blood are associated with the potential risk of transfusion transmitted infection, and FSs made from autologous blood are susceptible to contamination during processing.[17] A recent overview of cell salvage, PAD and ANH reported that all three alternative transfusion strategies significantly reduced the likelihood of exposure to allogeneic blood but effectiveness was reduced when a transfusion protocol to guide transfusion

was used.[29] However, the authors noted that the evidence to support these transfusion strategies may be weak, owing to flawed study design and the poor methodological quality of the individual trials.[29] A number of systematic reviews have been conducted to compare allogeneic blood transfusion with autologous blood transfusion or interventions to minimise blood loss and/or reduce the need for allogeneic blood.[13,21,29–33] These found that most of the interventions reduced the need for allogeneic blood. However, the evidence to support these transfusion strategies was considered to be uncertain, owing to flawed study design and the poor methodological quality of trials. These systematic reviews are included in a review of clinical evidence in subsequent chapters of this report.

Interventions to minimise allogeneic blood transfusion may be associated with relatively higher costs. Cell salvage requires a trained member of staff, which may add to the costs of setting up and maintaining a cell salvage service. The use of cell salvage equipment to wash the salvaged blood will also affect cost. The evidence about cost-effectiveness is uncertain, with reported cost per quality-adjusted life-year (QALY) gained by cell salvage as high as US$120,000.[12] Other studies suggest that cell salvage is moderately more expensive than allogeneic blood or equivalent in cost.[20]

PAD and ANH require careful selection of patients according to medical condition, coexisting disease, estimated blood loss and preoperative haemoglobin (Hb) levels.[34] PAD is also associated with wastage rates of up to 55% of autologous blood units' collected.[35] These factors mean that evidence about the relative cost-effectiveness of PAD is uncertain. A US study concluded that PAD was not worth the cost compared with allogeneic transfusion.[36] However, a retrospective economic evaluation on a single US study indicated that PAD was both more effective, in terms of infection rate, and less expensive than allogeneic transfusion.[37]

EPO with supplementary iron and folate, used alone or with PAD, could reduce exposure to allogeneic blood.[21] However, economic evaluations suggest that this is associated with incremental costs per QALY gained of US$6–8 million.[38]

In 2002, a Health Service Circular recommended an assessment of the clinical and cost-effectiveness of alternatives to allogeneic blood transfusion.[22] To our knowledge, a single overview of the cost-effectiveness of all these interventions does not exist. This report investigates the cost-effectiveness of cell salvage, PAD, ANH, EPO, antifibrinolytics (AFs) and FSs to minimise perioperative allogeneic blood transfusion.

Aims and objectives

The overall aims of this review were to compare patient outcomes, resource use and cost to the NHS and NHS BTA associated with cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion. The patient population for the study, specified in the commissioning brief, was patients requiring major surgery where there is likely to be blood loss requiring replacement. Part of the remit of this study was to update the published Cochrane systematic reviews of cell salvage[30] and PAD[13] and review existing systematic reviews of ANH, EPO, AFs and FSs.

The principal objectives were:

1. To assess the effectiveness of alternative transfusion strategies on the proportion of patients exposed to allogeneic and autologous blood transfusion, postoperative complications, reoperation due to bleeding, adverse transfusion reactions, length of stay and mortality.
2. To obtain data on health-related quality of life (HRQoL) and utilities associated with the transfusion strategies.
3. To obtain data on the relative cost and cost-effectiveness of the transfusion strategies.
4. To synthesise the data in a decision analytic model to determine the relative cost-effectiveness and uncertainty associated with the data and model structure.
5. To identify the impact of different transfusion strategies on the demand for allogeneic blood and blood products, by surgical procedure and patient group.
6. To assess whether further primary research is necessary to guide national and local transfusion policies and practice.

The study assessed the interventions for all surgical procedures (as defined in the clinical trials of the alternative transfusion strategies) and for two types of elective (non-emergency) surgical procedure:

- orthopaedic (primary or revision joint replacement)

- cardiac [coronary artery bypass grafting (CABG) or valve replacement].

These two types of surgery were chosen by the project team and the expert panel because they are relatively common surgical procedures in the UK. A prospective observational study of blood transfusion found that surgery accounted for around half of the transfusions in surgical patients.[3] In addition, the majority of studies included in the literature and published systematic reviews were in patients undergoing elective cardiac or orthopaedic surgery, and these surgical procedures typically involve moderate to major blood loss.

Specific research questions to meet the aims and objectives of the study were:

1. Are there differences in effectiveness between cell salvage and the alternative transfusion strategies for the index inpatient admission?
2. Do differences in the effectiveness of cell salvage and alternative transfusion strategies result in differences in mortality, adverse events and health status and HRQoL for the index inpatient admission and at 6 and 12 months post-discharge?
3. Are there differences in resource use and costs between cell salvage and alternative transfusion strategies for the index inpatient admission and at 6 and 12 months post-discharge?
4. What is the impact of moving from allogeneic blood transfusion to cell salvage or alternative strategies to minimise allogeneic blood transfusion?

The index inpatient admission was defined as hospital admission when a patient had the primary operation of interest (referred to as the index inpatient admission throughout this report).

Chapter 2

Methods: systematic review

Approach

This evaluation used systematic review and economic modelling to address the research questions. The methods for the systematic review are described in this chapter. The systematic review included:

1. A systematic review of the clinical evidence:
   (a) An update of two existing Cochrane systematic reviews of cell salvage[30] (intra- and postoperative) and PAD.[13]
   (b) A review of systematic reviews of PAD plus EPO, EPO, ANH, AFs (aprotinin, TXA, EACA), FSs and restrictive transfusion thresholds. It was beyond the scope of the study to update these systematic reviews.
2. A systematic review of the economic evidence, including resource use and cost data and economic evaluations.

Transfusion strategies evaluated

In addition to cell salvage and PAD, the project team developed a list of potential transfusion strategies based on published literature and experience in surgery and/or transfusion. An expert panel judged the relevance of these on the following criteria:

1. The transfusion strategy could be assessed as a stand-alone transfusion technique (i.e. independent of one or more other included interventions and the surgical procedure).
2. The intervention was currently used in NHS practice or was a new intervention with the potential to change usual care in NHS practice.

In addition, the scope of the evaluation was constrained to using existing systematic reviews to assess the effectiveness of interventions. This meant that only transfusion strategies where a systematic review existed were included. This was for two reasons. First, the aim was to base the clinical review and economic model as far as possible on evidence derived from data collection methods designed to minimise bias and reduce the chance of errors due to small sample sizes. Second, a systematic search and review of all the clinical literature for each transfusion strategy were beyond the scope and resources of this project.

The nine transfusion strategies to minimise perioperative allogeneic blood transfusion that were included in the systematic review were:

1. cell salvage
2. PAD
3. PAD plus EPO
4. EPO
5. ANH
6. cell salvage plus ANH
7. AFs (aprotinin, TXA, EACA)
8. FSs
9. restrictive transfusion thresholds or protocols.

A number of transfusion strategies were excluded by the criteria specified above. These included: platelet-rich plasmapheresis; iron; patient (body) warmers; new surgical equipment (e.g. cut and coagulate at the same time); near-patient testing (e.g. Hb and thromboelastography); haemeostatic agents (recombinant factor VIIa); vitamin K (promotes coagulation factor synthesis); preoperative clinics to prepare patients for surgery and combinations such as cell salvage combined with ANH. The main reason for exclusion of these transfusion interventions was that no systematic review of evidence to support them was identified. Patient (body) warmers and near-patient testing were identified as interventions used for purposes other than minimising allogeneic blood transfusion. Total platelet-rich plasma harvest and vitamin K were excluded since they are not appropriate for all kinds of elective surgery with moderate to high blood loss. Recombinant factor VIIa was excluded because it is licensed in the UK for restricted use for people with haemophilia and it is not fully licensed for use in routine practice in UK in a general elective surgery population.

Cell salvage comprises intraoperative cell salvage and postoperative cell salvage, using washed or unwashed techniques. The primary analyses for the systematic review and economic model relate to cell salvage overall. Secondary analyses explored differences between intra- and postoperative cell salvage (timing) and washed

and unwashed cell salvage. The comparison between washed and unwashed cell salvage was included since many of the trials included in the review of clinical evidence used one or both of these techniques. In addition, the choice of technique may influence the relative cost-effectiveness of intraoperative compared with postoperative cell salvage. However, it should be noted that if unwashed cell salvage is used intraoperatively, either the patient or the collected blood needs to be anticoagulated (with either citrate or heparin). If it were not washed out, this anticoagulant would then be reinfused to the patient. In addition, the use of unwashed blood carries the potential risk of reinfusing a myriad of bioactive substances resulting from surgical trauma. For these reasons, unwashed cell salvage is not deemed appropriate in current practice. Even when the blood is defibrinated, as in the postoperative setting, there remain issues surrounding the quality and composition of the unwashed blood.

Update of the cell salvage and PAD systematic reviews

Where possible, the methodology of the original reviews was replicated to update the two Cochrane systematic reviews. Additional searches were conducted based on the search strategies and the inclusion/exclusion criteria developed for the original two Cochrane systematic reviews of cell salvage and preoperative autologous donation[13,30] to identify new trials published since these searches were originally conducted (Appendix 1). The original searches were conducted for the period January 1966 to July 2002 for the cell salvage review and the period January 1966 to January 2001 for the PAD review.

The updates were performed in collaboration with an author (Paul Carless) and review group coordinator (Katherine Kerr) of the original cell salvage and PAD systematic reviews. All literature searches were carried out by one author of this evaluation (TJB). Where no additional evidence of effectiveness of cell salvage and/or PAD was found for any of the included outcomes, data from the two previous systematic reviews were reported.

Search strategy

For the update of the cell salvage review the Cochrane Central Register of Controlled Trials (National Electronic Library for Health, Issue 3, 2004) was searched, as were MEDLINE (Ovid, 2002–January 2004), EMBASE (Ovid, 2002–January 2004) and ISI Web of Science (Ovid, 2002–January 2004). For the update of the PAD review the same databases were searched for the period 2001 to January 2004. The International Network of Agencies of Health Technology Assessment (INAHTA) was searched from January 2002 to February 2004. The International Society of Technology Assessment in Health Care (ISTAHC) has been disbanded since the original systematic reviews of cell salvage and PAD were carried out and replaced with the *International Journal of Technology Assessment in Healthcare*. This journal index linked to MEDLINE and so any relevant articles would have been picked up in the search of MEDLINE. Current Contents was searched by the authors of the original systematic reviews of cell salvage and PAD but could not be searched for this update owing to lack of access. It was for this reason that we searched the Web of Science, which holds similar types of journal. For both the updates all the searches were conducted in January 2004.

Slight amendments were made to the medical subject heading (MeSH) terms and text words of the original search strategies. For example, different spelling of text words was added to identify studies that hyphenated the words 'pre-operative' and 'pre-donation'. Appendix 1 provides further details of all amendments made to the original search strategies. The MEDLINE and EMBASE search strategies were adapted for use in the Cochrane Library and Web of Science and a very broad, simple search was carried out in INAHTA for cell salvage and PAD simultaneously. In MEDLINE and EMBASE, the International Study of Perioperative Transfusion (ISPOT) filter was used to identify blood transfusion trials, as it was in the original systematic reviews of cell salvage and PAD. The only amendment to the ISPOT filter was the addition of the English spelling of haemorrhag$.tw. A randomised controlled trial (RCT) filter for EMBASE was developed for the update of both reviews, based on the MEDLINE RCT filter using Ovid and the EMBASE RCT filter using Silverplatter, which can be found in the Cochrane Reviewers Handbook[39] and a search strategy developed by TJB previously for another HTA review.[40]

The original cell salvage and PAD systematic reviews were used to exclude studies picked up in the updated search due to a slight overlap of dates between the original and the updated search (January to July 2002 for the cell salvage review

and January 2002 for the PAD review). The electronic searches of the major databases were run in January 2004 and so only studies published before February 2004 were included. We excluded studies published after January 2004 that might have been identified during the course of the review to exclude any potential selection bias through including studies collected in a non-systematic fashion.

The results of the electronic searches for both updates were downloaded on to Reference Manager software and de-duplicated into one file. Reference lists of published reviews and the bibliographies of included studies were searched to identify any other potentially relevant studies. These were checked against the list of studies already assessed for inclusion and any new potentially relevant studies were collected. Owing to time constraints, only authors of studies where the inclusion was unclear were contacted for more information to ascertain if the study fitted our inclusion criteria. Extensive attempts were made to obtain translations of all potentially relevant articles written in languages other than English.

Inclusion criteria

To be included, the identified studies had to meet the following inclusion criteria:

- Be an RCT, where patients were the unit of randomisation. Full paper publications and abstracts were included.
- Only include adults (minimum age 18 years) scheduled for elective non-urgent surgery.
- Compare PAD with a control group who did not receive PAD or compare cell salvage with a control group who did not receive cell salvage.
- Patients could only have received additional interventions if patients in all study arms received that additional intervention (e.g. cell salvage plus PAD versus PAD would be included in the update of the cell salvage systematic review).
- Report one or more of the following primary outcomes: proportion/number of patients transfused with allogeneic and/or autologous blood; the volume of allogeneic and/or autologous blood transfused.

Secondary outcomes measured were reoperation for bleeding, adverse transfusion reactions, preoperative morbidity and Hb levels, postoperative complications [thrombosis, infection, renal failure, non-fatal myocardial infarction (MI)], length of hospital stay and mortality.

Data on volume of autologous blood wasted (not transfused back to the patient) were collected from the PAD studies for potential use in the economic model. Data on resource use (for example, length of hospital stay) and cost were extracted from cell salvage and PAD studies, where reported, for potential use in the economic analysis.

An inclusion/exclusion form was developed for the update and used to determine inclusion (Appendix 2). The titles and/or abstracts identified by the electronic searches were screened independently by two reviewers using the inclusion/exclusion criteria form, and potentially relevant references were copied to another file for collection of the full paper copy.

References were only rejected from this initial screen if the reviewer could determine that the study did not meet all of the inclusion criteria. When either or both of the reviewers were unclear whether the study should be included or excluded, the full paper copy of the reference was obtained for further evaluation.

Assessment for inclusion of the full paper copies of potentially relevant studies was carried out independently by the two reviewers. Any differences between reviewers' assessment of the studies were resolved by discussion and, when necessary, in consultation with the rest of the project team. Reviewers were not masked to the source and authors of the studies. Each study was coded with reasons for rejection in the Reference Manager software or the study was included. (See *Figure 1* for a flow chart of the selection of studies for the update of the cell salvage and PAD systematic reviews.)

Quality assessment

The quality of the studies included in the review was formally assessed using the same criteria as in the original systematic reviews. The original systematic reviews of cell salvage and PAD assessed the quality of included studies using quality assessment criteria from three sources: (i) quality assessment criteria by Schulz and colleagues[41] that are underpinned by evidence of association with treatment effects in controlled trials; (ii) a three-item quality assessment score proposed by Jadad and colleagues[42] and (iii) ranked allocation concealment according to the Cochrane criterion (grade A for adequate concealment, grade B for uncertain and grade C for inadequate concealment). Quality assessment of RCTs for the update was performed independently by two reviewers not masked to study authors. Any

differences between reviewers were resolved by discussion. Quality assessment of the RCTs included information on randomisation procedure, allocation concealment, blinding and losses to follow-up (Appendix 3).

The original systematic reviews were critically appraised using a form developed by the Critical Appraisal Skills Programme that was adapted from a quality assessment form designed by Oxman and colleagues.[43,44] Quality assessment of the systematic reviews was performed by one reviewer (TJB) not masked to study authors. Two initial screening questions assessed whether the systematic review asked a clearly focused question and included the right type of study. A further eight questions assessed the validity and generalisability of the results.

Data extraction

A data extraction form was developed and piloted (Appendix 4). Data describing participants, interventions and outcomes were independently abstracted by two reviewers. Any differences between reviewers' extraction results were resolved through discussion and, if necessary, through consultation with the rest of the project team. Participant demographics and baseline characteristics, details of the intervention (i.e. what, where, when and how the participants received cell salvage or PAD), the type of elective non-urgent surgery and the presence or absence of a transfusion protocol were all recorded where reported.

Data synthesis

All analyses were performed using Review Manager 4.1 software (MetaView 4.1). Data on the numbers of patients exposed to allogeneic blood and the numbers of patients in each treatment group were entered into Review Manager. Data were added to the original meta-analyses from the two Cochrane systematic reviews. When appropriate, differences in outcomes for each comparison were combined across studies using relative risks or weighted mean differences in random effects meta-analyses.

Relative risks (RRs) and 95% confidence intervals (CIs) for allogeneic blood transfusion in the intervention group compared with the control group were calculated for each trial using a random effects model.[45] A similar approach was adopted to examine the other outcomes of transfusion. The presence of heterogeneity of treatment effect was assessed using the Q statistic, which has an approximate χ^2 distribution with degrees of freedom equal to the number of studies minus one.[45] A p-value of ≤ 0.10 was used to define statistically significant heterogeneity.

The mean number of units of RBCs transfused to each group and the corresponding standard deviations (SDs) were also entered. Blood loss in millilitres was converted to units of blood by dividing by 300, to be consistent with the original systematic reviews. Weighted mean differences (WMDs) and 95% CIs were used to express the average reduction in the number of units of RBC administered to the intervention group, compared with the control. If the SD or the standard error of the mean were not reported for continuous data, the study was not included in the meta-analysis. Subgroup analyses were performed as in the original two systematic reviews, which assessed the effects of the type of surgery, use of transfusion protocols, the type and timing of cell salvage and the quality of the study. The latter analysis may help to identify the impact of more recent trials if they reflect lessons from previous experience and are of better quality than less recent trials.

Review of the systematic reviews

A separate review of systematic reviews was conducted to obtain data for the following transfusion strategies:

1. PAD plus EPO
2. EPO
3. ANH
4. cell salvage plus ANH
5. AFs (aprotinin, TXA, EACA)
6. FSs
7. restrictive transfusion thresholds.

Search strategy

The Cochrane Database of Systematic Reviews (National Electronic Library for Health, Issue 3, 2004) was searched using the search terms 'allogeneic next blood next transfusion', then '((cell next salvage) and (acute normovolaemic next haemodilution))'.

Where a systematic review was not identified in the Cochrane Database of Systematic Reviews, MEDLINE (OVID, 1996–August 2004) was also searched.

Inclusion criteria

To be included the identified studies had to meet the following inclusion criteria:

1. Be systematic reviews of RCTs and have defined explicit selection criteria.
2. Only include adults undergoing elective non-urgent surgery.
3. Compare one or more of the following interventions to a control group that did not receive the intervention:
   (a) PAD plus EPO
   (b) EPO
   (c) ANH
   (d) cell salvage plus ANH
   (e) AFs (aprotinin, TXA, EACA)
   (f) FSs
   (g) restrictive transfusion thresholds.
4. Report the proportion of patients transfused with allogeneic blood or report the volume of allogeneic blood transfused.

An inclusion/exclusion form was developed based upon the inclusion/exclusion form developed for the update of the cell salvage and PAD reviews, with changes in the inclusion criteria for study design (to include only systematic reviews not individual RCTs) and to include the interventions listed above (Appendix 5).The titles and/or abstracts identified by the electronic searches were screened by one reviewer (TJB) using the inclusion/exclusion criteria form, and potentially relevant references were obtained.

References were only rejected from this initial screen if the reviewer could determine that the study did not meet all the inclusion criteria. When the reviewer was unclear whether the systematic review should be included or excluded, the full paper copy was obtained for further evaluation. Assessment for inclusion of the full paper copies of potentially relevant systematic reviews were carried out by the same reviewer using the same inclusion/exclusion form and the reviewer was not masked to the source and authors of the studies.

Quality assessment

The systematic reviews were quality assessed using a form developed for the Critical Appraisal Skills Programme that was adapted from a quality assessment form designed by Oxman and colleagues.[43,44] Quality assessment of the systematic reviews was performed by one reviewer (TJB) not masked to study authors. Two initial screening questions assessed whether the systematic review asked a clearly focused question and included the right type of study. A further eight questions assessed the validity and generalisability of the results. Both the cell salvage and the PAD reviews that were updated and the other included systematic reviews were critically appraised using the same form to permit comparison.

Data extraction

A data extraction form was developed for the systematic reviews based on tables reported in the literature.[46] One reviewer (TJB) extracted data about the focus, inclusion criteria, number and methodological quality of the included studies in each systematic review. Inclusion criteria included details of study design, participants, intervention and outcomes.

Data synthesis

The results of the meta-analyses for each systematic review were extracted into three tables: number of patients transfused with allogeneic blood, average units of allogeneic blood transfused and adverse events. Results of the primary outcome (proportion of patients transfused with allogeneic blood) were also extracted according to type of surgery and presence or absence of transfusion protocol. RRs or the WMD of each outcome for each intervention could then be assessed, taking into account the number of included RCTs used in the estimation of each outcome and the presence of any heterogeneity. This also allows indirect comparison of the relative effectiveness of each intervention when the intervention is compared with allogeneic blood transfusion.

Review of economic evaluations and cost studies

The systematic review of economic evaluations was conducted for two purposes: to summarise the economic evidence about alternative transfusion strategies and to identify any good-quality cost data for potential use in the economic analysis.

Search strategy

The following databases were searched for economic evaluations (and resource use and cost data): MEDLINE (Ovid, 1994–April 2004), EMBASE (Ovid, 1994–April 2004), Econlit (Ovid WebSPIRS 5.03, 1991–March 2004), Cochrane Database of Systematic Reviews (National Electronic Library for Health, Issue 3, 2004), Database of Abstracts of Reviews of Effects (National Electronic Library for Health, Issue 3, 2004) and the NHS Economic Evaluation Database (NHS EED) (National Electronic Library for Health, Issue 3, 2004). The Health Economic Evaluations Database (Office of Health Economics) was not searched since it was felt that the

additional yield of relevant studies given the extensive search already carried out in the other databases did not justify the substantial extra cost of purchasing subscription. The search strategy for the economic evaluation, resource use and cost review combined the transfusion MeSH and text terms with the search terms used to identify economic studies for the NHS EED database (Appendix 6).

Reference lists of published systematic reviews of economic evaluations and the bibliographies of included studies were searched to identify any other potentially relevant studies. These were checked against the list of studies already assessed for inclusion and any new potentially relevant studies were collected. Studies published before 1994 were excluded unless they were subsequently referenced more than once in papers published after 1994. This was for two reasons. First, both transfusion practice and knowledge of the risks associated with allogeneic transfusion have changed over the last 10 years, and the incidence of adverse events and transfusion transmitted infections associated with allogeneic blood transfusion has declined. Second, the methodology for economic evaluations has become more rigorous and standardised in this time. These factors meant that evidence published more than 10 years ago was unlikely to be representative of the current risks, costs and benefits of alternative transfusion strategies. Owing to time constraints, authors of included studies were not contacted for further information, nor were attempts made to obtain translations of non-English papers.

In addition, any resource use data identified in the systematic reviews of effectiveness were extracted for the economic analysis. A number of measures used to assess the effectiveness of the transfusion interventions were also measures of resource use (e.g. frequency and volume of allogeneic and/or autologous blood transfused, length of inpatient hospital stay and dose regimen of drugs prescribed for the AF and EPO transfusion strategies).

Inclusion criteria

Studies reporting economic evaluations were included only if they were performed in adult patients undergoing major elective surgery and reported at least one resource use or cost associated with the control or intervention transfusion strategies, or a treatment intervention for any adverse event associated with blood transfusion. Data on longer term clinical outcomes, HRQoL, satisfaction, preferences or utility values for health states associated with blood transfusion were also collected where reported.

Economic evaluations were only included if they reported a full economic evaluation. A full economic evaluation was defined as a study that compared the costs and outcomes of two or more of the transfusion strategies included in this report. Economic evaluations based on primary data collection or systematic reviews were given preference. Economic evaluations that reported resource use and costs separately and in sufficient detail to extract costs and outcome data relevant to any of the included transfusion strategies were given preference. Only economic evaluations published since 1994 were included. Economic evaluations had to include only adult patients undergoing any of the following types of major elective surgery: primary and/or revision joint replacement (orthopaedics); CABG and/or valve replacement (cardiac).

Economic evaluations had to include at least two of the following interventions: intraoperative cell salvage, postoperative cell salvage, PAD, PAD plus EPO, EPO, ANH, AFs (aprotinin, TXA, EACA), FSs, restrictive transfusion thresholds, allogeneic blood.

Economic evaluations had to include one or more of the following; reoperation for bleeding; adverse transfusion reactions (incorrect blood component transfused, acute haemolytic transfusion reaction, delayed haemolytic transfusion reaction, transfusion-related acute lung injury, post-transfusion purpura, transfusion-related graft versus host disease, transfusion-transmitted infection); postoperative complications (thrombosis, infection, renal failure, non-fatal MI, stroke); mortality; patient-based outcomes such as HRQoL, satisfaction, preferences or utility values for health states.

In addition to the inclusion criteria above, all included papers were screened to determine the source of resource use and cost data, methods used to value resource use and patient benefits, methods of analysis and generalisability of results. Economic evaluations that used prospective data were regarded as higher quality than economic evaluations that relied on retrospective data, as were studies using data from RCTs rather than from non-randomised trials.

A screening form for inclusion/exclusion was developed and used for both the review of

resource use and cost studies and economic evaluations (Appendix 7). One reviewer (TJB) conducted the initial screen of titles and abstracts to exclude any studies that did not report resource use or costs related to blood transfusion. One reviewer (TJB) then screened all potentially included papers using the inclusion/exclusion form. The second reviewer (LD) independently screened any references where the first reviewer was unclear of inclusion. Differences between reviewers were resolved by discussion. Articles were only rejected on initial screen if the reviewer could determine from the title and abstract that the article did not meet the prespecified inclusion/exclusion criteria. If a title/abstract could not be rejected with certainty, the full text of the article was obtained for further evaluation.

Data extraction, quality assessment and data synthesis

Any resource use or cost data were extracted for potential use in populating the economic model. A description of each of the cost studies is provided in Appendix 12. The data extracted from resource use and cost studies that were not classed as economic evaluations were not synthesised as part of this review. If data from these studies were used in the economic model, they are reported in Chapter 6. Quality assessment of the economic evaluations was based on the critical appraisal criteria used by the NHS EED.[47] A data abstraction form was designed based on the criteria used to assess abstracts for the NHS EED[47] to extract data about participants, interventions, resource use, costs and outcomes (Appendix 8).

Chapter 3

Results: systematic reviews of effectiveness

Updates of cell salvage and PAD reviews

A flow chart of the selection of studies for the update of the cell salvage and PAD systematic reviews is shown in *Figure 1*.

Study flow

The electronic and bibliographic searches identified 668 potentially relevant titles and abstracts (*Figure 1*). A total of 568 of these were excluded on the basis of title and abstract and 100 full-text papers/abstracts were collected for more detailed evaluation. Five RCTs were eventually included, two in the update of the cell salvage review[48,49] and three in the update of the PAD review.[50–52] One of the cell salvage studies was published only in abstract form.[48] This was not located in the main electronic search but identified by searching for the same author of another trial identified in the electronic search where inclusion was unclear, and we attempted to contact the author for further details.

Excluded studies

Of the 100 potentially relevant RCTs, 95 were excluded because they were not an RCT (50), were not in adults (1) undergoing major elective non-urgent surgery (2), were not a relevant intervention (31), did not report any usable outcomes (2) or for other reasons (9). Other reasons were: excluded in the original PAD review for being either a duplicate report or a large number of participants excluded from the analysis, included in the original cell salvage review, referenced incorrectly and could not be located by the library.

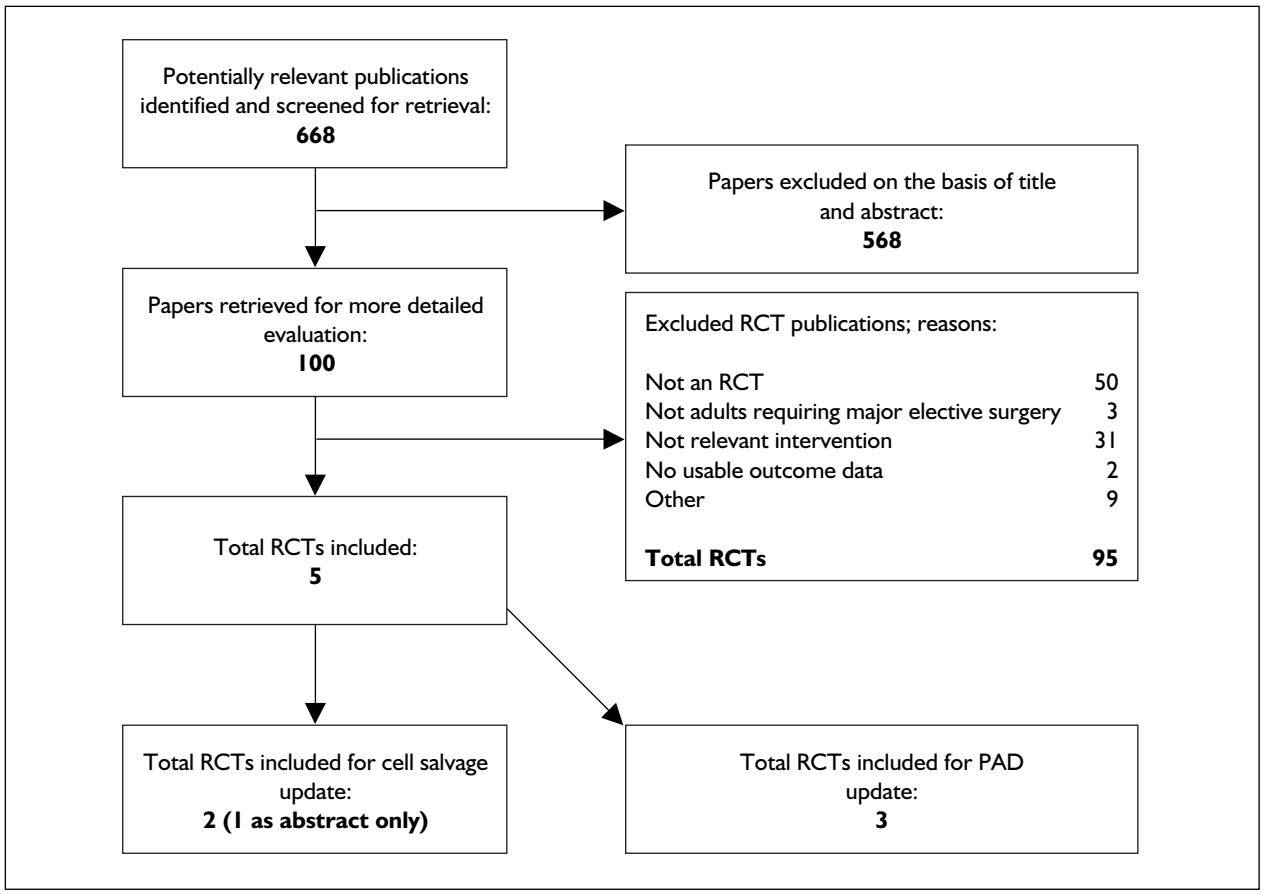

FIGURE 1 *Flow diagram for identifying RCTs for the update of the cell salvage and PAD systematic reviews*

Translation of potentially relevant papers

Eight potentially relevant studies were published in languages other than English (four Russian and one each Japanese, Chinese, Spanish and Czech). The reviewers contacted the Cochrane Review group coordinator of the original cell salvage and PAD systematic reviews, Katherine Kerr, who referred the Russian studies on to the Russian Cochrane centre and the Spanish study to a Spanish translator who generously screened these references on our behalf. All these studies were eventually excluded for not meeting all of the inclusion criteria.

Cell salvage update

Two RCTs were included in the update of the cell salvage systematic review and *Table 1* describes the characteristics of the two included studies.

Characteristics of new studies

Appendix 9 describes the characteristics of the original cell salvage systematic review. Two RCTs were included in this update, from one published paper and one abstract.[48,49] The studies included 125 participants randomised to the relevant study arms, with studies varying only slightly in size from 30 to 33 participants per arm. Both studies were single-centre, conducted in China and Russia and published in 2003. Both studies had the same primary objective: to assess whether cell salvage could reduce exposure to allogeneic blood transfusion.

Both studies were carried out in participants undergoing CABG. The mean age was 59 years in one study and was not stated in the other. There were more males than females in one study and not stated in the other. One study only included patients who bled less than 800 ml through draining tubes during first 8 hours postoperation; the other excluded patients with a bleeding time of more than 10 minutes (due to anticoagulant use), preoperative left ventricular ejection fraction less than 0.40 or diabetes, pulmonary or renal disease.

Both studies compared cell salvage with no cell salvage or allogeneic blood only. One study salvaged blood postoperatively and retransfused washed RBCs postoperatively. In the other study it was unclear if blood was salvaged both intraoperatively and postoperatively, and non-washed shed mediastinal blood retransfused postoperatively when considered necessary. Use of a transfusion threshold was reported in one study only and only with respect to autologous blood. It was unclear whether allogeneic blood was transfused routinely to the control group.

Reporting of relevant outcomes was scant; one study reported the number of patients exposed to allogeneic blood, volume of allogeneic blood transfused, blood loss, preoperative Hb; and the other study reported the number of patients exposed to allogeneic blood. The longest period of follow-up for a reported outcome was 7 days; no other adverse events were reported.

Complete assessment of the methodological quality of the study conducted by Naumenko and colleagues[48] could not be performed, as only a published abstract was available. The word 'randomisation' was reported in the trial but the method of randomisation was not reported. Allocation concealment, blinding and intention-to-treat (ITT) analysis were all unclear as they were not reported in the abstract. Using the Jadad quality assessment instrument,[42] the study by Zhao and colleagues[49] scored a total of 1 out of a possible 5, with the score of 1 given because the study reported that participants were 'divided at random' (but failed to provide any further details). Using the Cochrane grading system for allocation concealment, the trial scored B as the method of allocation concealment was not specified. Blinding was not reported. The study failed to report whether an ITT analysis had been performed but the same number of participants in each arm were assessed as were allocated.

Critical appraisal of the original systematic review of cell salvage

The systematic review (prior to update) asked a clearly focused question in terms of the population studied, intervention given and outcomes considered. The systematic review included a relevant type of study design to answer the review's question. The systematic review attempted to identify all relevant studies by conducting a thorough search of the literature. The systematic review formally quality appraised individual studies in duplicate using standardised forms and assessing inter-rater reliability. The review presented the results clearly and precisely using relative risk (RR) (random effects) with CIs and *p*-values and attempted to explain sources of significant heterogeneity. Fourteen of the 49 studies were conducted in the UK with the majority in cardiac and orthopaedic surgery, which supported generalisability to the UK setting where cell salvage is practised. Some evidence of

TABLE 1 *Characteristics of included studies for the cell salvage update*

Study identifier	Methods and validity	Participant characteristics	Intervention details	Outcome assessment
Naumenko, 2003[48] **Location:** one centre, hospital Russia **Abstract only** **Period of study:** prior to 2003 **Length of study:** not reported	**Method of randomisation** 'randomisation' **Allocation concealment:** unclear **Baseline comparability:** unclear, 'no significant difference between groups was detected at any stage of the study' **Participant blinding:** no **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** unclear	**Type of elective surgery:** CABG **Primary outcome of study:** to decrease allogeneic transfusion **Baseline risk factors:** no details **Age:** no details **Sex:** no details **Inclusion criteria:** patients with an uneventful postoperative period (discharge of less than 800 ml through draining tubes during first 8 hours postoperation **Exclusion criteria:** no details	**Comparison:** drainage discharge collected for 8 hours postoperatively and reinfused (b) vs no retransfusion of drainage discharge (a) **Type of cell salvage machine:** BRAT-2 Cell Saver **Timing of autologous blood collection/retransfusion:** drainage discharge collected for 8 hours postoperatively and erythrocytes reinfused postoperatively after washing (group B only) **Volume of autologous blood collected/retransfusion:** up to 800 ml collected, no other details **Use of transfusion threshold:** no details **Other active intervention given to both arms:** no details **Length of surgery:** no details **Aortic cross-clamp time:** no details	**Allocated:** (a) 33, (b) 32 **Assessed:** (a) 33, (b) 32 **Outcomes reported:** number exposed to allogeneic blood
Zhao, 2003[49] **Location:** one centre, Fuwai Hospital, Beijing, China **Period of study:** January to October 2000 **Length of study:** 7 days	**Method of randomisation:** 'divided at random' **Allocation concealment:** unclear (b) **Jadad score:** 1 out of 5 **Baseline comparability:** adequate **Participant blinding:** no **Assessor blinding:** unclear **Intention-to-treat:** unclear ***A priori* sample size:** no	**Type of elective surgery:** CABG **Primary outcome of study:** to evaluate if cell salvage reduced need for and volume of allogeneic blood transfusion **Baseline risk factors:** no details **Age:** (a) 59.2 (8.2); (b) 59.5 (8) **Sex:** M/F: (a) 27/3; (b) 26/4 **Inclusion criteria:** no details **Exclusion criteria:** bleeding time more than 10 minutes due to anticoagulant use; preoperative left ventricular ejection fraction <0.40; diabetes; pulmonary or renal disease	**Comparison:** shed mediastinal blood reinfused (b) vs banked allogeneic blood (a) **Type of cell salvage machine:** Beijing PerMed Biomedical Engineering Company **Timing of autologous blood collection/retransfusion:** non-washed shed mediastinal blood retransfused postoperatively after CABG [group (b) only]; mean 280 ml (155) autologous blood retransfused [group (b) only]; suction apparatus to make negative pressure 20 cm H_2O; up to 18 hours post-surgery **Volume of autologous blood collected/retransfusion:** shed blood not returned within 4 hours was discarded and a new bag attached **Use of transfusion threshold:** when more than 200 ml shed mediastinal blood collected within 4 hours the patients in group (b) received autologous blood if volume replacement was considered necessary **Other active intervention given to both arms:** extracorporeal blood routinely returned to all patients after CABG **Length of surgery:** (a) 121 minutes (58); (b) 121 minutes (26) **Aortic cross-clamp time:** (a) 76 minutes (33); (b) 74 minutes (15)	**Allocated:** (a) 30, (b) 30 **Assessed:** (a) 30, (b) 30 **Outcomes reported:** number exposed to allogeneic blood; volume of allogeneic blood transfused (ml); number exposed to autologous blood; volume of autologous blood transfused (ml); postoperative blood loss (median and range); preoperative haemoglobin

publication bias was found in the form of a missing population of small negative studies in funnel plots. The review did not consider cost-effectiveness and the reviewer could not tell if policy or practice should change as a result of the evidence. Use of washed cell salvage appears justified in orthopaedic patients.

Results of the cell salvage update

As only two studies (125 cardiac patients) were included in the update, very few data were added to the meta-analyses conducted in the original Cochrane systematic review. Paul Carless, co-author of the original cell salvage and PAD systematic reviews, provided the RevMan database containing the raw data and the meta-analyses plots. Data from the included studies obtained from the update were added to these meta-analyses and the results are reported in aggregate (i.e. the original data plus the data obtained from the update). The original systematic review analysed the data separately for all included studies, those studies that compared an active to a control intervention and those studies where both the intervention and control arms also received an additional active intervention. The same approach was used for this update. The results for all these comparisons are included in Appendix 10. The main objective of the update was to provide up-to-date evidence for the economic model. Therefore, only the active versus control comparison is shown in *Tables 2–4*. *Table 2* presents the RR of receiving a transfusion of allogeneic blood in patients receiving cell salvage compared with control. *Table 3* presents the WMD in units of allogeneic blood transfused in patients receiving cell salvage compared with control. *Table 4* presents the RR of having an adverse event in patients receiving cell salvage compared with control. Results in the tables in bold type indicate where data have been added as a result of the update of the systematic review. The results of the individual studies included in the update are not reported separately. The contribution of any additional data by these studies is identified and discussed in the light of what it adds to the original systematic reviews.

TABLE 2 *Meta-analysis and subgroup analysis results for the cell salvage update – number of patients transfused with allogeneic blood*[a]

Meta-analysis	No. of RCTs	No. of events/no. of participants in cell salvage	No. of events/no. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
Active vs control	**28**	**405/1035**	**677/1029**	**0.59**	**0.48 to 0.73**	**$p < 0.00001$ $I^2 = 90.6\%$**
Transfusion protocol	**24**	**349/841**	**551/833**	**0.63**	**0.51 to 0.77**	**$p < 0.00001$ $I^2 = 89.1\%$**
No transfusion protocol	**4**	**56/194**	**126/196**	**0.27**	**0.02 to 4.08**	**$p < 0.00001$ $I^2 = 95.8\%$**
Cardiac	**14**	**291/516**	**373/513**	**0.81**	**0.70 to 0.93**	**$p < 0.00001$ $I^2 = 78.9\%$**
Orthopaedic	11	74/128	239/421	0.35	0.24 to 0.52	$p = 0.0009$ $I^2 = 66.5\%$
Vascular	3	40/91	65/95	0.55	0.13 to 2.36	$p = 0.0003$ $I^2 = 87.9\%$
Washed	**14**	**168/550**	**324/560**	**0.53**	**0.39 to 0.72**	**$p < 0.00001$ $I^2 = 87.2\%$**
Unwashed	**13**	**236/425**	**318/409**	**0.73**	**0.58 to 0.91**	**$p < 0.00001$ $I^2 = 88.4$**
Intraoperative	5	74/191	113/191	0.61	0.39 to 0.95	$p = 0.01$ $I^2 = 68.9\%$
Postoperative	**18**	**287/738**	**473/724**	**0.60**	**0.45 to 0.79**	**$p < 0.00001$ $I^2 = 93.1\%$**
Intra- + postoperative	5	44/106	91/114	0.52	0.26 to 1.01	$p < 0.00001$ $I^2 = 90.8\%$

[a] Results in bold indicate where data have been added as a result of the update of the systematic review.

TABLE 3 *Meta-analysis and subgroup analysis results for the cell salvage update – units of allogeneic blood transfused*[a]

Meta-analysis	No. of RCTs	No. of participants in cell salvage	No. of participants in control	WMD (random effects)	95% CI	Heterogeneity *p*-value
Active vs control	**18**	**638**	**622**	**–0.90**	**–1.23 to –0.56**	**$p < 0.00001$ $I^2 = 79.9\%$**
Transfusion protocol	**15**	**486**	**483**	**–0.81**	**–1.16 to –0.46**	**$p < 0.00001$ $I^2 = 81.9\%$**
No transfusion protocol	3	152	139	–1.64	–2.96 to –0.33	$p = 0.05$ $I^2 = 66.7\%$
Cardiac	**11**	**442**	**424**	**–0.97**	**–1.40 to –0.55**	**$p < 0.00001$ $I^2 = 76.0\%$**
Orthopaedic	4	103	105	–1.13	–1.78 to –0.48	$p = 0.002$ $I^2 = 80.1\%$
Vascular	3	93	93	0.02	–0.34 to 0.38	$p = 0.42$ $I^2 = 0\%$

[a] Results in bold indicate where data have been added as a result of the update of the systematic review.

TABLE 4 *Meta-analysis and subgroup analysis results for the cell salvage update – adverse events and other outcomes*

Outcome	Meta-analysis	No. of RCTs	No. of events/no. of participants in cell salvage	No. of events/no. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
Mortality	All studies	15	13/614	11/598	1.22	0.55 to 2.70	$p = 0.78$ $I^2 = 0\%$
	Active vs control	11	13/417	8/394	1.53	0.65 to 3.61	$p = 0.86$ $I^2 = 0\%$
Reoperation for bleeding	All studies	14	22/563	20/556	1.00	0.55 to 1.81	$p = 0.87$ $I^2 = 0\%$
	Active vs control	8	13/302	10/290	1.08	0.47 to 2.48	$p = 0.65$ $I^2 = 0\%$
Any infection	All studies	13	25/721	34/669	0.74	0.44 to 1.25	$p = 0.49$ $I^2 = 0\%$
	Active vs control	9	24/420	31/406	0.75	0.41 to 1.37	$p = 0.37$ $I^2 = 0\%$
Wound complication	All studies	9	17/392	15/338	0.91	0.46 to 1.81	$p = 0.79$ $I^2 = 0\%$
	Active vs control	7	14/263	14/241	0.88	0.42 to 1.81	$p = 0.75$ $I^2 = 0\%$
Any thrombosis	All studies	7	9/264	6/233	1.46	0.56 to 3.83	$p = 0.95$ $I^2 = 0\%$
	Active vs control	6	9/189	6/190	1.46	0.56 to 3.83	$p = 0.95$ $I^2 = 0\%$
Stroke	All studies	4	3/247	5/249	0.65	0.17 to 2.50	$p = 0.76$ $I^2 = 0\%$
	Active vs control	3	2/149	3/149	0.73	0.14 to 3.72	$p = 0.57$ $I^2 = 0\%$
Non-fatal MI	All studies	9	16/411	22/420	0.76	0.40 to 1.43	$p = 0.68$ $I^2 = 0\%$
	Active vs control	5	10/223	19/225	0.58	0.28 to 1.19	$p = 0.88$ $I^2 = 0\%$
DVT	Active vs control	4	6/124	7/125	0.93	0.31 to 2.77	$p = 0.54$ $I^2 = 0\%$
Hospital length of stay	Active vs control	5	203	194	–1.28	–2.65 to 0.08	$p = 0.13$ $I^2 = 0\%$

DVT, deep vein thrombosis.

For a full description of the studies included in the original systematic reviews of cell salvage, for results of active versus active comparisons and outcomes where no extra data were added, readers are referred to the original publication.[30] Where data were added they had minimal impact on the results. Treatment effect reached significance with the addition of the study by Zhao and colleagues[49] for the number exposed to allogeneic blood in cardiac surgery (all studies) where participants received washed salvaged blood (RR 0.90, 95% CI 0.81 to 1.00 in original review to RR 0.87, 95% CI 0.78 to 0.97 after update). The study by Naumenko and colleagues[48] favoured control for exposure to allogeneic blood but the CIs were relatively wide and it did not impact on overall results. The quality of both new studies was poor which was similar to the quality of the studies in the original review.

Cell salvage reduced the RR of exposure to allogeneic blood by 41% (95% CI 27 to 52%) for active versus control studies. There was no significant reduction in exposure to allogeneic blood between cell salvage and control when a transfusion protocol was used in active versus control studies. Cell salvage significantly reduced the risk of exposure to allogeneic blood in cardiac and orthopaedic surgery, washed and unwashed, intraoperatively and postoperatively. When cell salvage was performed intra- plus postoperatively and when cell salvage was conducted in vascular surgery, there was no significant reduction in exposure to allogeneic blood in active versus control studies. In active versus control studies, cell salvage reduced the RR of exposure to allogeneic blood more in orthopaedic surgery than in cardiac surgery. Cell salvage was more effective in reducing the relative risk of exposure to allogeneic blood when the salvaged blood was washed rather than unwashed, in active versus control studies.

The use of cell salvage reduced the volume of RBCs transfused by a WMD of 0.90 units per patient (95% CI –1.23 to –0.56 units). Pooled estimates of effect were larger in those trials that did not report the use of transfusion protocols (WMD –1.64 units (95% CI –2.96 to –0.33) compared with those trials that reported the use of transfusion protocols (WMD –0.81 units: 95% CI –1.16 to –0.46) in active versus control studies.

Cell salvage did not appear to affect clinical outcomes adversely, but the data were insufficient to draw conclusions on the effect of cell salvage on important clinical events.

Figure 2 presents the forest plot of the meta-analysis of the RR of exposure to allogeneic blood in cell salvage compared with control for studies in which participants did not receive any other active co-intervention. Appendix 10 presents the Forest plots for all other outcomes where data were added to the Forest plots from the original Cochrane systematic review

Statistically significant heterogeneity was observed for virtually all of the meta-analyses examining the RR of receiving a transfusion of allogeneic blood in cell salvage compared with control. The observed variation in treatment effects was in both the size and direction of effect with RR point estimates for red cell transfusion exposure for the individual trials, ranging from 0.03 to 2.06 in active versus control studies. Of the 28 trials that provided data for the number of patients exposed to allogeneic red cell transfusion, four reported a negative effect of cell salvage with one of the effects in one of these trials being significant, and only 16 trials found that cell salvage statistically significantly reduced the probability of receiving a red cell transfusion.

Subgroup analyses by (i) the presence or absence of a transfusion protocol, (ii) cardiac or orthopaedic surgery, washed or unwashed salvaged blood, (iii) intraoperative or postoperative cell salvage and (iv) grade B or grade C studies (Appendix 10) did not explain this variation in treatment effect between studies. Statistically significant heterogeneity was observed in all of the subgroup analyses. Non-English studies were not heterogeneous with regard to this outcome (Appendix 10) but there were too few non-English studies to draw any conclusions.

The methodological quality of trials was poor with lack of blinding and allocation concealment. None of the trials were graded A for adequate concealment allocation, making it difficult to assess the impact of trial quality on treatment effects. It is unlikely that the addition of the two new studies would alter the conclusion of the original review that there was some evidence of publication bias in the form of a missing population of small negative studies.

PAD update

Three RCTs were included in the update of the PAD systematic review and *Table 5* describes the characteristics of the included studies.

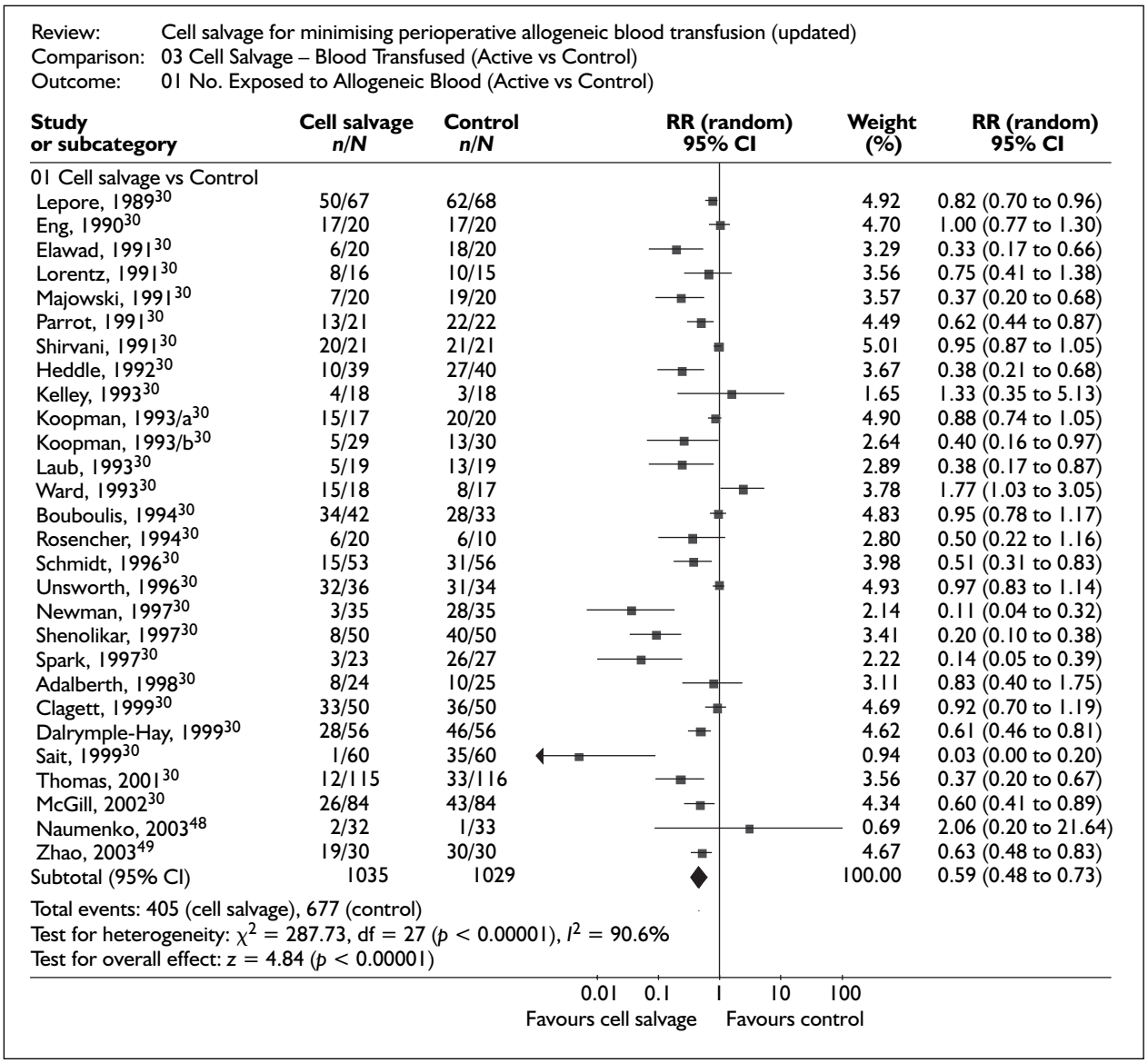

FIGURE 2 *Relative risk of exposure to allogeneic blood, cell salvage versus control (excluding studies with active co-intervention)*

Characteristics of new studies

Appendix 9 describes characteristics of the PAD systematic reviews. Three RCTs were included in this comparison.[50–52] A total of 320 participants were randomised to the relevant study arms, with studies varying in size from 20 to 80 participants per arm. All three studies were one-centre trials, with two studies conducted in the USA and one in Greece. The studies were published between 2001 and 2003 (one study was conducted between 1990 and 1995 but not published until 2001). The period of follow-up was 4 weeks in one study, 6 weeks in one study and not stated in one study. Only one study reported performing a sample size calculation to ensure that the study was sufficiently powered to detect any differences in outcomes between the comparisons. All three studies aimed to assess the effectiveness of PAD compared with no PAD, the efficacy of EPO alone and in combination with PAD, the efficacy of PAD in combination with EPO compared with PAD alone and a control group in reducing the need for allogeneic blood.

Two studies were carried out on participants undergoing joint arthroplasty (one for total hip arthroplasty and the other for a mixture of unilateral, bilateral, primary and revision hip and knee arthroplasty). One study was performed in patients undergoing maxillofacial surgery. One study, by Billote and colleagues,[51] was performed in patients with no co-morbidities where the patients were relatively healthy, young and predominantly male, with a higher Hb level as an

inclusion criterion. The study by Bezwada and colleagues[52] included patients with cardiovascular, renal and pulmonary risk factors at baseline.

The mean age of patients ranged from 58 to 65 years in two studies and from 18 to 45 years in the third. There were more males than females in one study and more females than males in two studies. Baseline comparability was similar with regard to age and sex but one study reported significantly higher haematocrit levels in the control group compared with the levels in the PAD group and the PAD plus EPO group combined. One study reported significantly lower Hb levels for the PAD group compared with the control group who did not receive PAD. One study reported significantly lower Hb levels for the EPO group compared with the EPO plus PAD group.

All three studies compared PAD with no PAD. One study gave EPO to both the active and control groups, and study participants undergoing revision and bilateral arthroplasty received intraoperative or intra- and postoperative cell salvage (there did not appear to be significant differences in the number of participants in each arm who received or did not receive cell salvage).[52]

Participants in one study predonated two units, one unit each time 1 week apart at least 2 weeks prior to surgery; participants in two studies predonated one or two units of blood depending on the type of surgery 1 week apart, at least 1 week prior to surgery in one study and not stated in the other study. Two studies retransfused autologous blood intraoperatively and one postoperatively. Participants in all included arms of all three studies received iron supplementation. None of the studies reported length of surgery.

Two of the studies reported using a transfusion threshold to guide the decision whether to transfuse a patient with autologous or allogeneic blood.[51,52] The study by Christopoulou and colleagues[50] did not report using a transfusion threshold to determine whether to transfuse with autologous or allogeneic blood. One of these studies used different transfusion thresholds for allogeneic and autologous transfusion. The outcomes reported that are relevant to this review update were: number of patients transfused with allogeneic blood, volume of allogeneic blood transfused, number of patients transfused with autologous blood, volume of autologous blood transfused, preoperative Hb, volume of autologous blood wasted and length of hospital stay. One study reported postoperative complications including wound haematomas, pulmonary embolus, mortality, stroke and deep vein thrombosis (DVT). However, these were not reported by intervention group, only in total. None of the studies reported any longer term outcomes.

Using the Jadad quality assessment instrument, two studies scored 1 and one study[51] scored 3 out of a possible 5. Both studies that scored 1 received the score of 1 because the study was described as randomised (but failed to provide any further details). The study by Billote and colleagues[51] scored 2 out of 2 for randomisation because it reported the method of randomisation that was judged as appropriate. Using the Cochrane grading system for allocation concealment, two studies scored B as the method of allocation concealment was not specified, and the study by Billote and colleagues[51] scored A as an adequate method to secure allocation concealment was reported.

Blinding was unclear in all three studies, but in one study only the operating surgeon was blinded only to whether the patient had received EPO and the participants received open-label treatment.[52] In the study by Billote and colleagues,[51] the decision to transfuse intraoperatively was made by the anaesthetist who was not involved in the study.

One study did not perform an ITT analysis as participants were excluded from the analysis by the authors[51] and in one study it was unclear whether an ITT analysis had been used. One study did analyse all the participants who were recruited and scored 1 out of 1 for the item relating to withdrawals.[52]

Critical appraisal of the original systematic review of PAD

The systematic review (prior to update) asked a clearly focused question in terms of the population studied, intervention given and outcomes considered. The review included a relevant type of study design to answer the review's question. The review attempted to identify all relevant studies by conducting a thorough search of the literature. The review formally quality appraised individual studies in duplicate using standardised forms and assessing inter-rater reliability. The review presented the results clearly and precisely using RR (random effects) with CIs and *p*-values and attempted to explain sources of significant heterogeneity. Only nine trials were included and

TABLE 5 *Characteristics of included studies for the PAD update*

Study identifier	Methods and validity	Participant characteristics	Intervention details	Outcome assessment
Christopoulou, 2001[50] **Location:** one centre, Evangelismos Hospital, University of Athens, Greece **Period of study:** 1990–5 **Length of study:** 4 weeks	**Method of randomisation:** 'consecutive patients randomly assigned' **Allocation concealment:** unclear **Baseline comparability:** inadequate; haematocrit and RBC levels of control group (a) were significantly higher than the totals of groups (b) and (c) **Participant blinding:** no **Assessor blinding:** unclear (B) **Jadad score:** 1 of 5 **Intention-to-treat:** Unclear ***A priori* sample size:** no	**Type of elective surgery:** maxillofacial operations **Primary outcome of study:** to determine the impact of PAD with and without EPO **Baseline risk factors:** haematocrit and RBC levels of control group (a) were significantly higher than group (b) **Age:** 18–45 years, no other details **Sex: M/F:** (a) 7/13, (b) 12/16 **Inclusion criteria:** orthognathic surgery, reconstruction after trauma or removal of tumours, removal of benign tumours or malformations; anticipated need for blood not to exceed 4 units; completion of donor form; haematological testing donor–recipient to be carried out **Exclusion criteria:** Hb >11 g/dl; haematocrit <11 g/dl or 34%; anaemia; <10 years of age and >65 years of age; active malignant tumour; coronary disease; recent MI; arterial hypertension (systolic blood pressure >180 mmHg, diastolic blood pressure >100 mmHg); pregnancy; AIDS; diabetes; active infection for which treatment being given	**Comparison:** PAD (b) vs autologous blood (a) **Timing of autologous blood collection/retransfusion:** blood donated at least 1 week before operation, time between donations was 1 week, retransfused intraoperatively [group (b) only] **Volume of autologous blood collected/retransfused:** 24 patients in group (b) predonated 1 unit each, 4 patients in group (b) predonated 2 units (bimaxillary osteotomies) **Use of transfusion threshold:** no details **Other active intervention given to both arms:** all patients had 150 mg ferrous sulfate daily by mouth preoperatively until 1 week post-operatively **Length of surgery:** no details **Other:** third arm received preoperative autologous donation plus EPO; not analysed for this review update	**Allocated:** (a) 20, (b) 28 **Assessed:** (a) 20, (b) 28 **Outcomes reported:** number of patients exposed to allogeneic blood, number of patients exposed to autologous blood, preoperative Hb [group (a) data obtained from figures only, no SD]

continued

TABLE 5 *Characteristics of included studies for the PAD update (cont'd)*

Study identifier	Methods and validity	Participant characteristics	Intervention details	Outcome assessment
Billote, 2002[51] **Location:** one centre, Northwestern Memorial Hospital, Northwestern University Medical School, Illinois, USA **Period of study:** not stated **Length of study:** 6 weeks	**Method of randomisation:** randomly allocated, computer-generated randomisation scheme (Analysis Tool Pack, Microsoft Excel) and use of sealed enveloped **Allocation concealment:** adequate; (a) sequential sealed enveloped by an independent research nurse **Jadad score:** 3 of 5 **Baseline comparability:** Hb levels on admission were significantly lower for group (b) (PAD) compared with group (a) (control); **Participant blinding:** unclear **Assessor blinding:** unclear **Intention-to-treat:** No ***A priori* sample size:** Yes	**Type of elective surgery:** elective total hip replacement **Primary outcome of study:** to determine the effectiveness of PAD in decreasing the need for allogeneic transfusion amongst patients potentially eligible to undergo PAD **Baseline risk factors:** no significant medical co-morbidities **Age (mean ± SD):** (a) 61 ± 14, (b) 58 ± 11 **Sex: M/F:** (a) 35/19, (b) 26/16 **Inclusion criteria:** baseline Hb at least 120 g/l (finger-prick); **Exclusion criteria:** severe or unstable cardiac disease; uncontrolled hypertension; symptomatic carotid or vertebral artery stenosis; a bleeding diathesis or bacteraemia	**Comparison:** PAD (b) vs no PAD (a) **Timing of autologous blood collection/retransfusion:** whole blood donated 1/week with last unit no later than 2 weeks prior to surgery, retransfused postoperatively (1 patient had retransfusion intraoperatively) [group (b) only] **Volume of autologous blood collected/retransfused:** 2 units, maximum 1 unit (approximately 500 g) at each time; 2 patients in group (b) only predonated 1 unit each **Use of transfusion threshold:** need for intraoperative blood transfusion decided by independent anaesthetist using standardised protocol and identical thresholds for autologous and allogeneic, autologous blood transfused before allogeneic if available; postoperative decision to transfuse made by orthopaedic surgeon (one of whom was an author of the study), **Other active intervention given to both arms:** all patients received thromboprophylaxis on first postoperative day continued for 1 month; 325 mg ferrous sulfate orally two times daily after 1st donation in group (b) and 10 days prior to surgery in group (a) **Length of surgery:** no details	**Allocated:** 112 recruited **Assessed:** (a) 54, (b) 42 **Outcomes reported:** number of patients transfused with allogeneic blood, number of patients transfused with autologous blood, volume of autologous blood transfused (no SD), preoperative Hb, blood loss (ml), autologous blood wastage (no SD), length of hospital stay (no SD)

continued

TABLE 5 *Characteristics of included studies for the PAD update (cont'd)*

Study identifier	Methods and validity	Participant characteristics	Intervention details	Outcome assessment
Bezwada, 2003[52] **Location:** one centre, Pennsylvania Hospital, Pennsylvania, USA **Period of study:** not stated **Length of study:** not reported	**Method of randomisation**: prospective, randomised, open-label, parallel-group, first consecutive 240 patients who presented were randomly assigned **Allocation concealment:** unclear (B) **Jadad score:** 1 of 5 **Baseline comparability:** adequate except for Hb levels were significantly lower in group (a) (EPO) compared with group (b) (PAD + EPO) **Participant blinding:** no, open-label **Assessor blinding:** unclear but states only operating surgeon was blinded regarding whether patient had received EPO **Intention-to-treat:** yes ***A priori* sample size:** unclear	**Type of elective surgery:** total joint arthroplasty, 59% revision or bilateral **Primary outcome of study:** to evaluate the efficacy of EPO in combination with and compared with PAD for reducing allogeneic blood requirements **Baseline risk factors:** Cardiovascular (a) 36/80, (b) 25/80; renal (a) 5/80, (b) 4/80; pulmonary (a) 12/80, (b) 7/80 **Age (mean + range):** (a) 65 (48–79), (b) 61 (55–81) **Sex: M/F:** (a) 27/53, (b) 35/45 **Inclusion criteria:** more than 21 years of age; scheduled to undergo total joint arthroplasty; initial Hb ≤140 g/l; willingness to participate in PAD programme; women had to be postmenopausal, sterile or taking oral contraceptives; **Exclusion criteria:** pregnancy; clinically relevant uncontrolled systemic disease or abnormal laboratory values; primary haematological disease; seizure disease; uncontrolled hypertension; recent gastrointestinal or intracranial haemorrhage; iron deficiency	**Comparison:** PAD plus EPO (b) vs allogeneic blood plus EPO (a) **Timing of autologous blood collection/retransfusion:** retransfusion performed intraoperatively [group (b)] **Volume of autologous blood collected/retransfusion:** 2 units for bilateral or revision arthroplasty and 1 unit for primary unilateral arthroplasty; all group (b) received oral supplement of 325 mg iron sulfate 3 times daily, **EPO:** [group (a) only] 600 IU/kg subcutaneously in a four-dose regimen, 21, 14, 7 and 1 day before surgery; single dose 100 mg intravenous iron dextran with initial dose of EPO followed by oral supplementation with 325 mg iron sulfate twice daily **Use of transfusion threshold:** indications for perioperative blood transfusion were Hb ≤ 80 g/l and/or persistent tachycardia or hypotension requiring large volumes of crystalloid; postoperative clinical symptoms; **Other active intervention given to both arms:** for all patients: warfarin prophylaxis; all patients having revision total hip arthroplasty had intraoperative cell salvage [14/80 in group (a) and 14/80 in group (b)]; intraoperative and immediate postoperative cell salvage performed for all patients having revision total knee arthroplasty [14/80 in group (a) and 10/80 in group (b)]; and bilateral total knee and total hip arthroplasty [23/80 group (a) and 23/80 group (b)] **Length of surgery:** no details **Other:** third arm received preoperative autologous donation only; not analysed for this review update	**Allocated:** (a) 80, (b) 80, (c) 80 **Assessed:** (a) 80, (b) 80, (c) 80 **Outcomes reported:** number of patients transfused with allogeneic blood, volume of allogeneic blood transfused (no SDs), volume of autologous blood transfused (no SDs), preoperative Hb (range not SD), volume of autologous blood wasted (no SD), (wound haematomas, pulmonary embolus, mortality, stroke, DVT; no groups stated)

none were conducted in the UK, where PAD is not standard practice, which limits the generalisability of the results.

The authors noted that there were concerns about publication owing to the number of small trials found. The small number of trials meant that it was not feasible to evaluate this further. The review did not consider cost-effectiveness and the reviewer could not tell if policy or practice should change as a result of the evidence.

Results of the included studies for the PAD update

As only three studies (196 orthopaedic and 48 oral surgery patients) were included in the update, very few data were added to the meta-analyses conducted in the original Cochrane systematic review. Appendix 11 presents all the PAD results. *Table 6* presents the RR of receiving a transfusion of allogeneic blood, allogeneic and/or autologous blood, any thrombosis and any infection in patients receiving PAD compared with control. *Table 7* presents the WMD in preoperative Hb levels in patients receiving PAD compared with control.

Overall, PAD reduced the risk of allogeneic blood transfusion by a relative 64% (RR 0.36, 95% CI 0.25 to 0.51). PAD significantly reduced the RR of exposure to allogeneic blood for all studies, with and without a transfusion protocol, in orthopaedic, oncology and one oral surgery trial. The pooled RR of exposure to allogeneic blood

TABLE 6 *Meta-analysis and subgroup analysis results for the PAD update*[a]

Outcome	Meta-analysis	No. of RCTs	No. of events/no. of participants in cell salvage	No. of events/no. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
No. of patients transfused with allogeneic blood	**All studies**	**11**	**149/716**	**375/707**	**0.36**	**0.25 to 0.51**	**$p = 0.0005$ $I^2 = 69.6\%$**
	Transfusion protocol	**7**	**138/585**	**299/611**	**0.48**	**0.38 to 0.60**	**$p = 0.18$ $I^2 = 34.3\%$**
	No transfusion protocol	**4**	**11/121**	**76/96**	**0.12**	**0.04 to 0.33**	**$p = 0.08$ $I^2 = 56.2\%$**
	Orthopaedic	**5**	**21/221**	**75/204**	**0.21**	**0.11 to 0.43**	**$p = 0.07$ $I^2 = 56.9\%$**
	Oncology	5	128/467	280/483	0.49	0.38 to 0.63	$p = 0.15$ $I^2 = 41.3\%$
	Oral	**1**	**0/28**	**20/20**	**0.02**	**0.00 to 0.28**	**NA**
No. of patients transfused with allogeneic/ autologous blood	**All studies**	**9**	**496/620**	**343/612**	**1.33**	**1.10 to 1.61**	**$p < 0.00001$ $I^2 = 80.6\%$**
	Transfusion protocol	**5**	**384/499**	**267/516**	**1.48**	**1.16 to 1.89**	**$p = 0.001$ $I^2 = 78.2\%$**
	No transfusion protocol	**4**	**112/121**	**76/96**	**1.10**	**0.95 to 1.29**	**$p = 0.26$ $I^2 = 24.8\%$**
	Orthopaedic	**3**	**105/125**	**43/109**	**1.78**	**0.61 to 5.20**	**$p < 0.00001$ $I^2 = 97.2\%$**
	Oncology	5	363/467	280/483	1.38	1.20 to 1.58	$p = 0.13$ $I^2 = 44.5\%$
Any thrombosis	All studies	3	6/140	3/110	0.82	0.21 to 3.13	$p = 0.53$ $I^2 = 0\%$
Any infection	All studies	3	74/309	81/312	0.70	0.34 to 1.43	$p = 0.07$ $I^2 = 61.9\%$

NA, not applicable.
[a] Results in bold indicate where data have been added as a result of the update of the systematic review.

TABLE 7 *Meta-analysis and subgroup analysis results for the PAD update*[a]

Outcome	Meta-analysis	No. of included RCTs	No. of participants in cell salvage	No. of participants in control	WMD (random effects)	95% CI	Heterogeneity *p*-value
Preoperative Hb levels (g/dl)	**All studies**	**5**	**267**	**267**	**–1.16**	**–1.60 to –0.73**	**$p = 0.004$ $I^2 = 73.9\%$**

[a] Results in bold indicate where data have been added as a result of the update of the systematic review.

transfusion for patients in orthopaedic surgery randomised to PAD was 0.21 (95% CI 0.11 to 0.43). The RR reduction ranged from 52% (95% CI 40 to 62%) with a transfusion protocol to 88% (95% CI 67 to 96%) without a transfusion protocol. The risk of receiving any transfusion was actually increased (allogeneic and/or autologous) in those randomised to PAD compared with control (RR 1.33, 95% CI 1.10 to 1.61).

The data on adverse events were insufficient to draw conclusions of the effect of PAD on important clinical events. In individual studies the numbers of adverse events were small, with no significant difference in any thrombosis or any infection between the PAD and control groups. Preoperative Hb levels were significantly reduced in PAD patients (WMD –1.16; 95% CI –1.60 to –0.73).

Figure 3 presents the Forest plot of the meta-analysis of the RR of exposure to allogeneic blood in PAD compared with control. *Figure 4* presents the Forest plot of the meta-analysis of the RR of exposure to any type of blood (allogeneic and/or autologous) in PAD compared with control. Appendix 11 presents the Forest plots for all other outcomes where data were added to the Forest plots from the original Cochrane systematic review.

For a full description of the studies included in the original systematic review of PAD, for Forest plots of outcomes where no extra data were added, readers are referred to the original publication.[13]

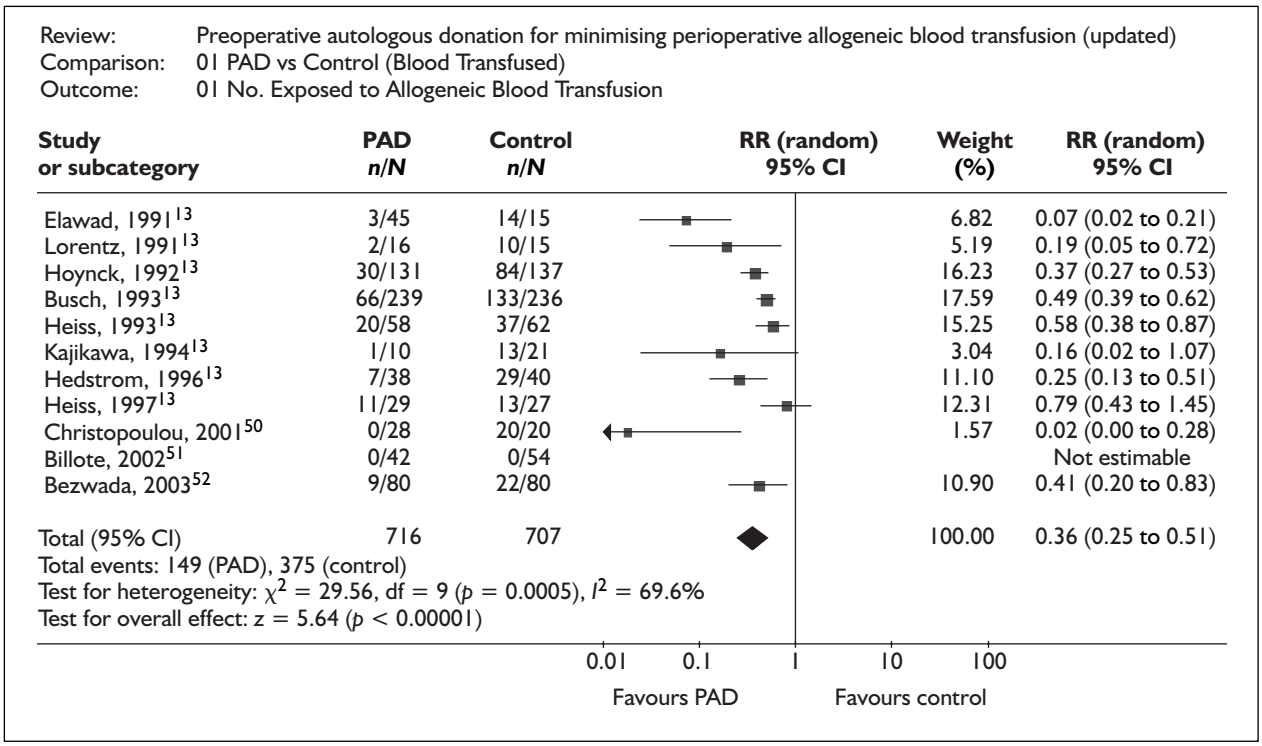

FIGURE 3 *Relative risk of exposure to allogeneic blood, PAD versus control*

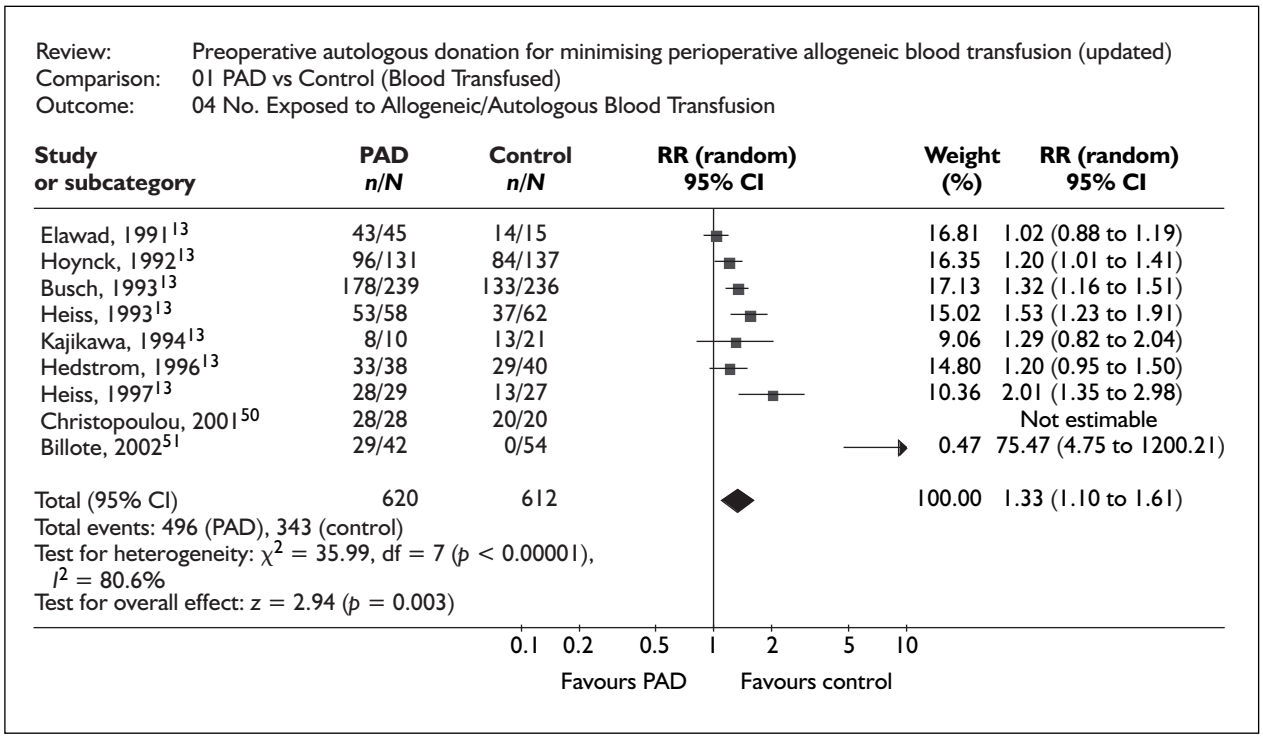

FIGURE 4 *Relative risk of exposure to allogeneic and/or autologous blood, PAD versus control*

It should be noted that in the study by Bezwada and colleagues,[52] participants in both arms also received EPO and some also received cell salvage. The study by Christopoulou and colleagues[50] was the only study to have been identified so far in oral and maxillofacial surgery. Therefore, the additional studies found in the update vary considerably in terms of participant characteristics and study interventions. The study by Billote and colleagues[51] increased the RR of exposure to allogeneic and/or autologous blood in orthopaedic patients but the overall RR failed to reach significance.

The quality of the new studies was poor, which is similar to the quality of the studies in the original review, although the study by Billote and colleagues[51] scored 3 out of a possible 5 using the Jadad instrument,[42] and this was the highest aggregate score of all nine included studies following the update.

Statistically significant heterogeneity was observed in the meta-analyses that examined the RR of receiving a transfusion of allogeneic blood in PAD, compared with control. The variation was in terms of the size, not the direction, of effect with RR point estimates for red cell transfusion exposure for the individual trials ranging from 0.02 to 0.79. Eight of the 11 studies demonstrated that PAD significantly reduced the probability of exposure to allogeneic blood transfusion and none of the 11 studies had a negative effect (in favour of control). Subgroup analyses by the presence or absence of a transfusion protocol and the type of surgery appeared partly to explain this variation in treatment effect between studies. There was no significant heterogeneity in studies that reported using a transfusion protocol and in cancer surgery with regard to this outcome. The additional studies found in the update varied considerably in terms of participant characteristics and study interventions. This might explain why heterogeneity became significant with the addition of the study by Bezwada and colleagues[52] with regard to exposure to allogeneic blood in orthopaedic patients. It also may explain why heterogeneity became significant with the addition of the study by Christopoulou and colleagues[50] with regards to exposure to allogeneic blood without a transfusion protocol.

The methodological quality of the trials was poor, trials were unblinded and allocation concealment was not described in the majority of studies. The addition of three small trials to the original review meant that it was not possible to evaluate publication bias formally. This means that the concerns about publication bias raised in the original review still stand.[13]

Review of systematic reviews

Cochrane systematic reviews were identified for AFs, FSs and restrictive transfusion triggers.[31–33] One published paper assessing PAD plus EPO and EPO alone[21] was found by searching the bibliographies of the included Cochrane reviews. One published paper[29] provided an overview of cell salvage, PAD and ANH describing the systematic reviews of cell salvage and PAD that were published in the Cochrane Library[13,30] and updated for this report. The systematic review of ANH published in the same paper was included in this review of systematic reviews. No systematic review of cell salvage combined with ANH was found. A new comprehensive literature search and systematic review of combined cell salvage and ANH was outside the scope of this study. The combined approach of cell salvage and ANH was therefore excluded from the review of clinical evidence and the primary economic analysis.

Table 8 describes the characteristics of the included systematic reviews.

Characteristics of the systematic reviews

Five additional systematic reviews were included, three of which were published as Cochrane systematic reviews and assessed the effectiveness of AFs, FSs and transfusion thresholds for minimising perioperative allogeneic blood transfusion.[31–33] One published paper reported a systematic review of two interventions, one of EPO alone and one of EPO combined with PAD to reduce exposure to allogeneic blood.[21] Another published paper included a systematic review of ANH.[29] All included reviews were published between 1998 and 2003. The searches for the reviews were conducted for the following periods:

- ANH: 1966 to July 2002
- transfusion thresholds: 1966 to November 2004
- FS: 1966 to July 2002
- AFs 1966 to May 1998
- EPO: 1985 to January 1997.

Four systematic reviews only included RCTs with a concurrent control group and one (ANH) included RCTs and observational cohort studies and assessed outcomes from each trial design separately.

The number of RCTs included in each systematic review that reported on the primary outcome were 5 (EPO alone), 7 (FSs), 9 (transfusion thresholds), 16 (EPO plus PAD), 25 (ANH) and 83 (AFs). Of the three AFs reviewed, there were four included trials of EACA, 18 trials of TXA and 61 trials of aprotinin that reported the primary outcome. The number of included participants in each review were 208 (EACA), 388 (FSs, that reported on primary outcome), 929 (EPO alone), 1049 (PAD plus EPO), 1295 (ANH), 1342 (TXA), 1780 (restrictive transfusion thresholds) and 7027 (aprotinin).

All the systematic reviews used either the Jadad criteria[42] or the Schulz criteria,[41] or both, for assessing the quality of the individual studies. All the Cochrane systematic reviews used the Cochrane criteria for assessing allocation concealment[39] and assessed the reliability of the quality assessment between reviewers using the kappa score. Most of the reviews included studies ranging in quality with most being unblinded and having inadequate or unclear allocation concealment. The review of AFs, which contained the largest number of trials (89), included 30 trials with adequate allocation concealment and 54 studies that were double blind.

Three reviews (ANH, AFs, FSs) only included adult participants undergoing elective surgery, two reviews only included adults undergoing elective cardiac and orthopaedic surgery and assessed the outcomes separately by type of surgery (EPO plus PAD, EPO alone). One review (transfusion thresholds) included surgical and medical adults and/or children. This review did not identify any relevant studies in children but did include three (of 10) studies in the context of acute blood loss and/or trauma and two studies in critical care units with elderly patients. Of the reviews that reported the information, the mean age of trial participants ranged from 45 to 76 years and the ratio of males to females was >2:1. The majority of included studies were in cardiac and orthopaedic surgery.

It was not explicitly stated in most of the reviews but other interventions were included if both the intervention and the control group were equally exposed to the extra intervention. This meant that, for example, all participants in a trial comparing FSs with no FSs (control) might have also received cell salvage. The systematic review of AFs also compared head-to-head trials of aprotinin, TXA and EACA (data not considered here). With the exception of the AF review, all the other reviews excluded head-to-head trials.

The primary outcomes of all the systematic reviews were the proportion of patients receiving allogeneic blood transfusion and the volume of

TABLE 8 *Characteristics of included systematic reviews*

Author	Focus	Inclusion criteria	Methodological quality of included studies	No. of included studies
Laupacis and Fergusson, 1998[21]	**Effectiveness of EPO given with or without PAD**, for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	**Study design:** randomised trials, excluded if clinician could have been aware of treatment allocation, also excluded if randomised postoperatively **Participants:** adults undergoing cardiac or orthopaedic elective surgery **Intervention:** EPO with or without PAD vs placebo or open-label controls **Primary outcomes:** proportion of patients receiving at least 1 unit allogeneic RBC. Other outcomes: mean volume allogeneic blood transfused, adverse events **Period:** 1985 – January 1997	Jadad criteria (out of possible score of 5): 5 trials = 1, 5 trials = 2, 6 trials = 3, 2 trials = 4, 2 trials = 5	16 RCTs assessed EPO to augment PAD (11 orthopaedic, 825 participants and 5 cardiac, 224 participants); 5 RCTs assessed EPO alone (3 orthopaedic, 684 participants and 2 cardiac, 245 participants)
Carless *et al.*, 2004[29]	**Effectiveness of ANH** for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	**Study design:** randomised controlled parallel group trials or observational cohort studies with concurrent or non-concurrent control groups (RCTs assessed separately from cohorts) **Participants:** adults (18 years or older) undergoing elective surgery **Intervention:** ANH vs no ANH (trials with a combination of active comparisons were included if both the intervention and the control groups were equally exposed to the active treatment) **Primary outcomes:** number of patients having allogeneic RBC transfusions. Amount of allogeneic blood transfused **Other outcomes:** adverse events, length of stay **Period:** 1966–July 2002	Schulz criteria; 96% of trials unblinded, allocation concealment inadequate in 100% of trials, method of randomisation inadequate in 92% of trials (κ = 0.78–1.0)	30 RCTs met the inclusion criteria (12 cardiac, 7 orthopaedic, 11 miscellaneous), 1295 patients, 704 randomised to ANH, average size of trial 41 patients, mean age 56 years, male to female ratio 2.3:1

continued

TABLE 8 *Characteristics of included systematic reviews (cont'd)*

Author	Focus	Inclusion criteria	Methodological quality of included studies	No. of included studies
Henry *et al.*, 1999[31]	**Effectiveness of AFs** (aprotinin, TXA, EACA) for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	**Study design:** RCTs with a concurrent control group **Participants:** adults (over 18 years) undergoing elective or non-urgent surgery, trials were included if participants aged less than 18 years were enrolled but the type of surgery was predominantly carried out in adult patients **Intervention:** AFs: aprotinin, TXA and EACA. **Primary outcomes:** proportion of patients 'at risk' transfused with allogeneic blood, autologous blood or both Amounts of allogeneic and autologous blood transfused **Other outcomes:** reoperation due to bleeding, mortality, postoperative complications (non-fatal MI, stroke, DVT, pulmonary embolism, any thrombosis, renal failure) **Period:** 1966–May 1998	Schulz criteria (out of a possible score of 7): 5 trials scored 7; 7 scored 6; 21 scored 5; 18 scored 4; 8 scored 3; 18 scored 2; 5 scored 1; and 1 scored 0. Jadad quality assessment instrument (out of a possible score of 5): 3 scored 5; 27 scored 4; 27 scored 3; 8 scored 2; and 18 scored 1. Cochrane criterion: allocation concealment was adequate (grade A) in 30 trials, inadequate (grade C) in 11, and not clearly described (grade B) in 48 trials. 54 (65.06%) were assessed to be double blind, 6 (7.23%) trials indicated double blinding but the method of blinding was unclear and 23 (27.7%) trials were assessed not to be double blind. 65 of 83 trials scored 0 out of 2 (Schulz criterion) for method of randomisation 43 trials reported no exclusions, or used ITT analysis. In 32 trials, where exclusions were reported, these exclusions were judged unlikely to cause bias. In 8 trials, exclusions were either judged to be excessive and likely to cause bias, or were not reported (κ = 0.71–0.97 for all the above items)	89 included RCTs (74 cardiac, 8 orthopaedic, 3 orthotopic liver transplantation, 3 vascular surgery, 1 liver resection). Average age 44.9–76.0 years, ratio of males to females 2.7:1 (intervention) and 2.5:1 (control). Trials that reported on primary outcome: 61 trials of aprotinin (7027 participants) 18 trials of TXA (1,342 participants). 4 trials of EACA (208 participants)

continued

TABLE 8 *Characteristics of included systematic reviews (cont'd)*

Author	Focus	Inclusion criteria	Methodological quality of included studies	No. of included studies
Carless *et al.*, 2003[32]	**Effectiveness of FSs**, for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	**Study design:** RCTs with a concurrent control group **Participants:** adults (over 18 years) undergoing elective or non-urgent surgery **Intervention:** FS applied to the wound surface in either liquid or aerosolised form (trials that studied bandages or pads impregnated with lyophilised FS components were excluded) **Primary outcomes:** number of patients exposed to allogeneic red cell transfusion, volume of blood transfused, blood loss **Other outcomes:** reoperation for bleeding, any infection, wound infection, haematoma formation, stroke, wound dehiscence, mortality, length of hospital stay. **Period:** 1966–July 2002	Cochrane criterion for grading allocation concealment: 1 trial = grade A, 2 trials = grade C, 8 trials = grade B. Schulz criteria (out of a possible score of 7): 82% trials scored ≤ 3 out of 7. Blinding of outcomes assessment was not described or not reported for 10 of the 11 trials. 8 trials reported no exclusions or used ITT analysis, 2 trials reported exclusions that were judged unlikely to cause bias and 1 trial did not report exclusions although there appeared to be some loss to follow-up. Kappa scores ranged from 0.62 to 1.0, being lowest in the case of the items measuring blinding (0.62) and allocation concealment (0.79)	7 RCTs, 388 patients, reported data on perioperative exposure to allogeneic RBC transfusion
Hill *et al.*, 2000[33]	**To compare clinical outcomes in patients randomised to restrictive versus liberal transfusion thresholds (triggers)**, to evaluate whether red cell transfusions can be withheld in some circumstances without harming patients	**Study design:** RCTs with a concurrent control group **Participants:** surgical and medical adults and/or children (neonates excluded) (average age varied from 47 to 80 years in actual trials included) **Intervention:** trials were included if the comparison groups were assigned on the basis of a clear transfusion 'trigger' or 'threshold', described as an Hb or haematocrit level (with or without a specified level of haemodynamic instability) which had to be reached before a red cell transfusion was administered. Control group patients were required to be either transfused allogeneic and/or autologous RBCs at higher Hb or haematocrit levels (transfusion threshold) than the intervention	Trials span a publication period of 40 years; the methodology and reporting of early studies reflect the less rigorous standards of the time. Schulz criteria (out of a possible score of 7): 1 trial scored 5, 2 scored 4, 5 scored 3 and 2 scored 2. Cochrane criteria: 5 trials used inadequate allocation concealment (grade C), in 4 trials allocation concealment was not clearly described (grade B), 1 trial had adequate allocation concealment (grade A). Double blinding was not reported in any of the 10 trials assessed for methodological quality. Method of randomisation was inadequate or not reported in 6 trials. 8 trials reported no exclusions, used survival analysis with all included subjects or used	Ten trials were identified that reported outcomes for a total of 1780 patients; 5 trials in cardiac, orthopaedic or vascular surgery, 3 in context of acute blood loss and/or trauma, 2 trials in critical care units

continued

TABLE 8 *Characteristics of included systematic reviews (cont'd)*

Author	Focus	Inclusion criteria	Methodological quality of included studies	No. of included studies
		group or transfused in accordance with current transfusion practices, which may not have included a well-defined transfusion threshold, but involved liberal rather than restrictive transfusion practices. **Primary outcomes:** the proportion of patients 'at risk', transfused with allogeneic and/or autologous RBCs, the amounts of allogeneic and/or autologous blood transfused. Other outcomes: morbidity (non-fatal MI, cardiac events, pulmonary oedema, stroke, thromboembolism, renal failure, infection, haemorrhage, mental confusion), mortality, haematocrit levels (postoperative/discharge) and length of hospital stay **Period:** 1966–December 2000	ITT analysis. In 1 trial, exclusions were reported but deemed unlikely to cause bias. In 1 trial, exclusions were deemed excessive and likely to cause bias (κ = 0.84–1.0)	

allogeneic blood transfusion received. The systematic review of restrictive transfusion thresholds assessed the proportion of participants who received allogeneic blood and/or autologous blood with the primary outcome being proportion of participants receiving any blood transfusion. Out of 10 included trials, two used PAD and only used autologous blood when transfusion was indicated. Other outcomes included reoperation for bleeding, mortality, non-fatal MI, stroke, thrombosis, infection, renal failure and length of hospital stay.

These differences in interventions between and within the included systematic reviews should be noted when interpreting the results.

Quality assessment of the systematic reviews

The systematic reviews were quality assessed using a form developed for the Critical Appraisal Skills Programme that was adapted from Oxman and colleagues.[43] All five systematic reviews asked a clearly focused question in terms of the population studied, intervention given and outcomes considered. All the reviews included the relevant type of study design to answer the review's question. All five of the systematic reviews attempted to identify all relevant studies by conducting a thorough search of the literature. All five of the systematic reviews formally quality appraised individual studies in duplicate using standardised forms and assessing inter-rater reliability. Four of the reviews pooled data and attempted to explain sources of significant heterogeneity.

The review of restrictive transfusion thresholds included studies conducted in a variety of settings with a mix of patient type (intensive care, acute trauma and elective surgery) and, given this variability, the reviewer (TJB) was not sure whether the data should have been combined. All five of the systematic reviews presented the results clearly and precisely, with the majority using RR (random effects). The review of EPO expressed results in random effects odds ratios (ORs). All reviews reported CIs and *p*-values.

The reviewer could not tell whether the results could be applied to the UK and the population that mainly requires transfusion in the UK in four of the reviews, and one review had limited generalisability to the UK (restrictive transfusion thresholds). The review of EPO did not explicitly report any details of the countries in which the studies had been conducted although the review was restricted to cardiac and orthopaedic surgery. Six of the 30 ANH trials were published in languages other than English and 11 were conducted in various types of surgery not including cardiac and orthopaedic. There were also twice as many males to females in the ANH trials. ANH is not standard practice in all surgical settings in the UK; therefore, generalisability of the trial results to the UK surgical setting is unclear. In the AF review only seven of the 89 trials were conducted in the UK and 74 of the trials were conducted in cardiac surgery. Therefore, results from AFs may not be generalisable outside the setting of cardiac surgery. Only one of 14 included trials of fibrin sealant was conducted in the UK, with large variation in the type of surgical setting and type of FS used. This may affect generalisability to UK surgical setting and the type of FS used in UK practice. The results of restrictive transfusion thresholds were limited in its generalisability to the UK elective surgical setting. Five of the 10 trials were in trauma or critical care, and the ages of patients also varied considerably, as did the transfusion thresholds used, with studies published over a time span of 40 years.

Some of the systematic reviews considered funnel plot analysis to explore the issue of publication bias (NB this is only an indication regarding publication bias). The reviews of FSs and restrictive transfusion thresholds[32,33] identified too few and small trials that made funnel plot analysis implausible. Some evidence of publication bias was found in the form of a 'missing' population of small negative studies in funnel plots for aprotinin in the AF review.[31] For this case, simulations of the data indicated that the effect of publication bias may have been to overestimate the true treatment effect of aprotinin. Two of the systematic reviews did not report analyses to explore publication bias.[21,29]

None of the five systematic reviews considered the cost-effectiveness of the transfusion strategies. The reviewer could not tell whether policy or practice should change as a result of the evidence contained in any of the five included systematic reviews.

Results of the systematic reviews

Table 9 presents the RR of receiving a transfusion of allogeneic blood for the included interventions compared with control, *Table 10* the WMD in units of allogeneic blood for the included interventions compared with control and *Table 11* the results for adverse events for the included interventions compared with control. The outcomes in the

systematic review of EPO, both alone and to augment PAD, were given as ORs (random effects), so one reviewer (TJB) entered individual study data into Review Manager in order to obtain RRs (random effects) to allow comparison with the outcome data from the other systematic reviews (all given as RR). The reviews of ANH, AFs and FSs reported the number of patients transfused with allogeneic blood. The review of EPO, both alone and to augment PAD, reported this outcome by type of surgery and did not attempt to pool the data. The review of restrictive transfusion thresholds only reported the number of patients transfused with allogeneic and/or autologous blood and so is considered separately as a different outcome.

TABLE 9 *Meta-analysis results for the transfusion strategies – number of patients transfused with allogeneic blood*

Outcome	Intervention	No. of RCTs	RR (random effects)	95% CI
All studies	Cell salvage	28	0.59[a]	0.48 to 0.73
	PAD	11	0.36[a]	0.25 to 0.51
	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	25	0.69[a]	0.56 to 0.84
	Aprotinin	61	0.70[a]	0.64 to 0.76
	TXA	18	0.66[a]	0.54 to 0.81
	EACA	4	0.48[a]	0.19 to 1.19
	FSs	7	0.46	0.32 to 0.68
Orthopaedic	Cell salvage	11	0.35[a]	0.24 to 0.52
	PAD	5	0.21[a]	0.11 to 0.43
	PAD + EPO	11	0.56	0.43 to 0.74
	EPO	3	0.49	0.38 to 0.64
	ANH	6	0.79	0.60 to 1.06
	Aprotinin	ND	ND	ND
	TXA	ND	ND	ND
	EACA	ND	ND	ND
	FSs	2	0.50	0.31 to 0.83
Cardiac	Cell salvage	14	0.81[a]	0.70 to 0.93
	PAD	ND	ND	ND
	PAD + EPO	5	0.36	0.15 to 0.88
	EPO	2	0.40	0.13 to 1.22
	ANH	10	0.77	0.57 to 1.04
	Aprotinin	55	0.69[a]	0.63 to 0.76
	TXA	15	0.71[a]	0.57 to 0.88
	EACA	ND	ND	ND
	FSs	ND	ND	ND
Transfusion protocol	Cell salvage	24	0.63[a]	0.51 to 0.77
	PAD	7	0.48[a]	0.38 to 0.60
	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	16	0.81	0.65 to 1.00
	Aprotinin	51	0.68[a]	0.61 to 0.74
	TXA	16	0.62[a]	0.51 to 0.75
	EACA	ND	ND	ND
	FSs	2	0.32	0.14 to 0.71
No transfusion protocol	Cell salvage	4	0.27[a]	0.02 to 4.08
	PAD	4	0.12[a]	0.04 to 0.33
	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	9	0.53	0.36 to 0.76
	Aprotinin	11	0.77	0.62 to 0.96
	TXA	2	1.13	0.82 to 1.55
	EACA	ND	ND	ND
	FSs	5	0.50	0.31 to 0.83

ND, no data.
[a] Statistically significant heterogeneity ($p > 0.1$).

TABLE 10 *Meta-analysis results for the transfusion strategies – units of allogeneic blood transfused*

Intervention	No. of RCTs	WMD (random effects)	95% CI
CS	18	–0.90	–1.23 to –0.56
PAD	ND	ND	ND
PAD + EPO	ND	ND	ND
EPO	ND	ND	ND
ANH	17	–1.9	–2.7 to –1.1
Aprotinin	25	–1.08	–1.47 to –0.69
TXA	5	–1.03	–1.39 to –0.67
EACA	ND	ND	ND
FS	4	–0.56	–0.84 to –0.29

ND, no data.

The use of a restrictive transfusion threshold reduced exposure to any blood transfusion by a relative 42% (95% CI 29 to 53%) compared with control. ANH, AP, TXA and FSs reduced the frequency of allogeneic transfusions with intervention effect sizes ranging from a relative 30% (95% CI 24 to 36%) with aprotinin to 54% (95% CI 32 to 68%) with FSs. Heterogeneity was significant for ANH and all three antifibrinolytics. EACA resulted in a statistically non-significant reduction in exposure to allogeneic blood (RR 0.48, 95% CI 0.19 to 1.19) and there were only four trials and 208 participants included in this outcome.

There was significant heterogeneity in effect amongst trials of ANH and AFs regarding transfusion with allogeneic blood. When studies of ANH were subgrouped by type of surgery and by the presence or absence of a transfusion protocol, heterogeneity disappeared. In this case, the effect sizes were non-significant. The exception was when ANH was used without a transfusion protocol. When studies of aprotinin and TXA were subgrouped by orthopaedic surgery and the presence of a transfusion protocol, heterogeneity was still present and only disappeared in studies of aprotinin and TXA where a transfusion protocol had not been used. Four reviews (PAD, PAD plus EPO, ANH, FSs) reported the number of participants who underwent orthopaedic surgery and were exposed to allogeneic blood. PAD, PAD plus EPO and FSs reduced the frequency of allogeneic transfusions in orthopaedic surgery with intervention effect sizes ranging from a relative 44% (95% CI 26 to 57%) with PAD plus EPO compared to control, to 51% (95% CI 36 to 62%) with EPO alone compared with control (only three studies). ANH resulted in a statistically non-significant reduction in exposure to allogeneic blood in orthopaedic surgery (RR 0.79, 95% CI 0.60 to 1.06).

Four reviews (PAD, PAD plus EPO, ANH, AFs) reported the number of participants who underwent cardiac surgery and were exposed to allogeneic blood. PAD plus EPO, aprotinin and TXA reduced the frequency of allogeneic transfusions in cardiac surgery with intervention effect sizes ranging from a relative 29% (95% CI 12 to 43%) with TXA compared with control to 64% (95% CI 12 to 85%) with PAD plus EPO compared with control. Significant heterogeneity was present among TXA and aprotinin studies. ANH reached non-significance within the CIs (RR 0.81, 95% CI 0.65 to 1.00). EPO alone and ANH failed to reduce significantly exposure to allogeneic blood in cardiac patients compared with control.

Three reviews (ANH, AFs and FSs) reported the number of participants exposed to allogeneic blood when a threshold protocol was present and was absent. ANH, aprotinin, TXA and FSs reduced the frequency of allogeneic transfusions when a threshold protocol was used, with intervention effect sizes ranging from a relative 32% (95% CI 26 to 39%) with aprotinin to 68% (95% CI 29 to 86%) with FSs. Significant heterogeneity was present for both AFs (aprotinin and TXA).

When a transfusion threshold protocol was not used, TXA failed to reduce exposure to allogeneic blood significantly. ANH, aprotinin and FSs reduced the frequency of allogeneic transfusions without the use of a threshold protocol, with intervention effect sizes ranging from a relative 23% (95% CI 4 to 38%) with aprotinin to 50% (95% CI 17 to 69%) with FSs. FSs were the most effective relative to the other strategies in reducing exposure to allogeneic blood, but this effect was

reduced when a transfusion threshold protocol was used.

Both the AF reviews (aprotinin and TXA) reported the mean volume of allogeneic blood transfused only in those patients who received a transfusion. The ANH and FS reviews reported the volume of allogeneic blood transfused divided by the number of participants in the group (including those who did not receive an allogeneic transfusion). The review of restrictive transfusion thresholds reported both ways of obtaining the average volume of allogeneic blood transfused (reported in the table as an average only in participants who received allogeneic blood). These differences should be considered when comparing the results of this outcome by the various strategies.

Only four of the systematic reviews reported the average units of allogeneic blood transfused. The use of FSs was associated with the least average difference in the amount of allogeneic blood transfused (WMD –0.56, 95% CI –0.84 to –0.29) and ANH was associated with the greatest average difference in the amount (WMD –1.9, 95% CI –2.7 to –1.1). It should be noted that the outcome for FSs was based on only four studies. Aprotinin and TXA were associated with a similar WMD of exposure to allogeneic blood (WMD –1.08, 95% CI –1.47 to –0.69 and WMD –1.03, 95% CI –1.39 to –0.67, respectively).

The review of restrictive transfusion thresholds only reported the average volume of allogeneic and/or autologous blood transfused and so is considered separately as a different outcome. The use of restrictive transfusion thresholds reduced the average volume of any type of blood by a relative 0.93 units (95% CI –1.50 to –0.36).

Few studies reported adverse events for PAD plus EPO and EPO alone and there were not enough data to pool and so the events were described. It should be noted that very few of the included studies in any of the systematic reviews were sufficiently powered to detect clinical outcomes.

One cardiac study of EPO alone reported overall mortality within 2 months of surgery: 7/126 (EPO) versus 0/56 (placebo).[53] One other cardiac study of EPO alone reported overall mortality: 4/38 (EPO) versus 4/38 (placebo).[54] All the other included strategies reported pooled data for mortality and none of the strategies significantly reduced the relative risk of mortality compared with control. For the mortality outcome in the review of restrictive transfusion thresholds, the meta-analysis was dominated by one large trial of 838 critically ill patients.

Only ANH and the AF review reported reoperation for bleeding and only aprotinin significantly reduced the RR of reoperation for bleeding by 60% (95% CI 34 to 75%). ANH, FSs and restrictive transfusion thresholds reported pooled data for any infection and none significantly reduced the RR. Only the FS review reported data for wound complication and failed to reduce significantly the RR compared with control.

ANH, AFs and restrictive transfusion thresholds pooled data on any thrombosis and only ANH significantly reduced the RR of developing any thrombosis by 56% (95% CI 7 to 79%). Only the AF review reported pooled data for DVT and neither aprotinin nor TXA significantly reduced the RR compared with control. One orthopaedic EPO study reported a 12.3% (EPO) versus 6.4% (placebo) frequency of postoperative DVT.[55]

AFs, FSs and restrictive transfusion thresholds reported pooled data on stroke and none significantly reduce the RR compared with control. ANH, AFs and restrictive transfusion thresholds pooled data on non-fatal MI and none significantly reduced the RR compared with control. One cardiac study of EPO alone reported non-fatal MIs: 0/38 (EPO) versus 1/38 (placebo).[54]

One orthopaedic study of EPO alone reported aggregate frequency of MI, angina, DVT, superficial phlebitis or peripheral vascular thrombosis: 4% (EPO) versus 9% (placebo).[56] One cardiac study of EPO alone reported all fatal and non-fatal vascular and thrombotic events: 23% EPO versus 29% placebo.[53]

Aprotinin, TXA and restrictive transfusion thresholds reported pooled data on renal failure or dysfunction and none significantly reduce the RR compared with control. The aprotinin and TXA reviews reported pooled data for pulmonary embolism and neither significantly reduced the RR compared with control.

ANH, FSs and restrictive transfusion thresholds reported mean length of stay. The greatest difference in length of hospital stay was with the use of FSs, which was associated with a reduction of 0.89 days (95% CI –2.51 to 0.73 days) compared with control. The use of ANH was associated with an increase of 0.21 days (95% CI –1.26 to 1.68 days) compared with control.

TABLE 11 *Meta-analysis results for the transfusion strategies – adverse events and other outcomes*

Outcome	Intervention	No. of RCTs	RR (random effects)	95% CI
Mortality	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	8	1.16	0.19 to 7.15
	Aprotinin	28	0.87	0.63 to 1.19
	TXA	11	0.43	0.15 to 1.18
	EACA	4	1.66	0.46 to 6.01
	FSs	4	0.66	0.18 to 2.38
	Restrictive transfusion threshold	7	0.80	0.63 to 1.02
Reoperation for bleeding	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	7	1.59	0.20 to 12.53
	Aprotinin	29	0.40	0.25 to 0.66
	TXA	9	0.72	0.29 to 1.79
	EACA	5	0.32	0.07 to 1.39
	FSs	ND	ND	ND
	Restrictive transfusion threshold	ND	ND	ND
Any infection	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	2	4.94	0.61 to 40.19
	Aprotinin	ND	ND	ND
	TXA	ND	ND	ND
	EACA	ND	ND	ND
	FSs	4	0.91	0.37 to 2.25
	Restrictive transfusion threshold	1	1.70	0.41 to 7.02
Wound complication	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	ND	ND	ND
	Aprotinin	ND	ND	ND
	TXA	ND	ND	ND
	EACA	ND	ND	ND
	FSs	2	0.31	0.09 to 1.08
	Restrictive transfusion threshold	ND	ND	ND
Any thrombosis	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	3	0.44	0.21 to 0.93
	Aprotinin	15	0.64	0.31 to 1.31
	TXA	12	0.98	0.49 to 1.94
	EACA	2	0.20	0.01 to 4.14
	FSs	ND	ND	ND
	Restrictive transfusion threshold	1	3.00	0.13 to 71.61
Stroke	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	ND	ND	ND
	Aprotinin	8	0.43	0.16 to 1.19
	TXA	6	2.27	0.65 to 7.99
	EACA	4	0.26	0.03 to 2.36
	FSs	2	0.37	0.02 to 7.99
	Restrictive transfusion threshold	2	0.96	0.10 to 8.96
Non-fatal MI	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	3	3.43	0.15 to 79.74
	Aprotinin	25	0.97	0.69 to 1.36
	TXA	8	0.69	0.21 to 2.29
	EACA	3	0.90	0.30 to 2.76
	FSs	ND	ND	ND
	Restrictive transfusion threshold	5	0.44	0.17 to 1.15

continued

TABLE 11 *Meta-analysis results for the transfusion strategies – adverse events and other outcomes (cont'd)*

Outcome	Intervention	No. of RCTs	RR (random effects)	95% CI
DVT	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	ND	ND	ND
	Aprotinin	5	0.54	0.14 to 2.12
	TXA	5	0.84	0.30 to 2.30
	EACA	ND	ND	ND
	FSs	ND	ND	ND
	Restrictive transfusion threshold	ND	ND	ND
Renal failure/dysfunction	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	ND	ND	ND
	Aprotinin	13	1.19	0.79 to 1.79
	TXA	2	0.87	0.08 to 9.78
	EACA	ND	ND	ND
	FSs	ND	ND	ND
	Restrictive transfusion threshold	1	1.63	0.54 to 4.90
Pulmonary embolism	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	ND	ND	ND
	Aprotinin	1	1.88	0.17 to 20.21
	TXA	5	0.32	0.07 to 1.56
	EACA	ND	ND	ND
	FSs	ND	ND	ND
	Restrictive transfusion threshold	ND	ND	ND
Length hospital of stay	PAD + EPO	ND	ND	ND
	EPO	ND	ND	ND
	ANH	3	0.21 = WMD	–1.26 to 1.68
	Aprotinin	ND	ND	ND
	TXA	ND	ND	ND
	EACA	ND	ND	ND
	FSs	2	–0.89 = WMD	–2.51 to 0.73
	Restrictive transfusion threshold	5	–0.29 = WMD	–0.90 to 0.32

ND, no data.

Summary

All the RR data (random effects) and CIs for each intervention (all the included systematic reviews plus the updated cell salvage and PAD systematic reviews) for the primary outcome (transfusion with allogeneic blood) are presented graphically in *Figure 5* to allow comparison of the effectiveness of each intervention to minimise allogeneic blood transfusion.

The point estimates on each line indicate the weighted mean RR. An RR of 1.0 suggests that there was no difference between the intervention and control groups, an RR of <1.0 suggests that fewer patients in the intervention group were exposed to allogeneic blood transfusion and an RR of >1.0 suggests that more patients in the intervention group were exposed to allogeneic blood transfusion compared with the control group. The lines running through the point estimates are the 95% CIs; when a line touches or crosses over 1.0 this demonstrates that the point estimate was not statistically significant.

Therefore, the nearer the point estimate is to zero, the more the RR is reduced (and the greater is the effect). The smaller the CI, the more precise is the estimate of effect.

All interventions significantly reduced exposure to allogeneic blood compared with control, with the exception of EACA and EPO in cardiac surgery:

- Cell salvage reduced the RR of exposure to allogeneic blood by 41% (95% CI 27 to 52%) for active versus control studies.
- PAD reduced the RR of exposure to allogeneic blood transfusion by 64% (RR 0.36: 95% CI 0.25 to 0.51).

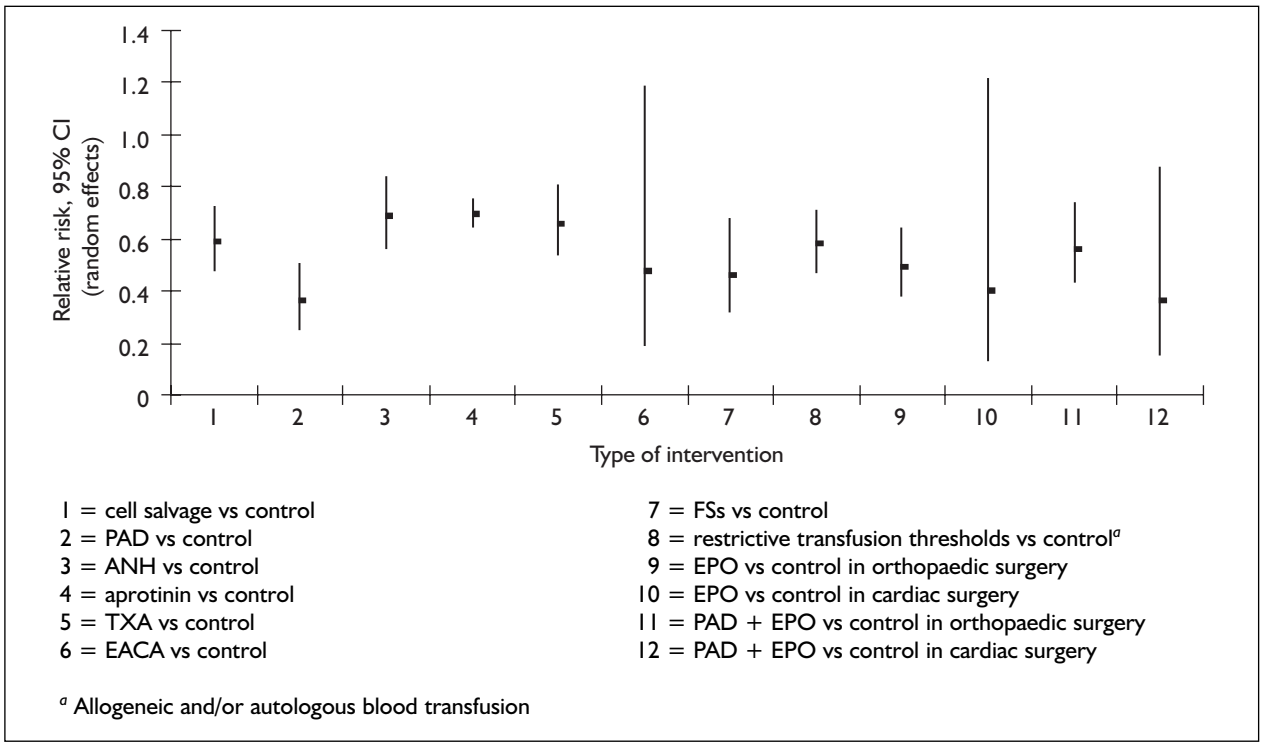

FIGURE 5 *Effect of intervention strategies on transfusion of allogeneic blood*

- ANH reduced the RR of exposure to allogeneic blood by 31% (95% CI 16 to 44%).
- Aprotinin reduced the RR of exposure to allogeneic transfusion by 30% (95% CI 24 to 36%).
- TXA reduced the RR of exposure to allogeneic blood by 34% (95% CI 19 to 46%).
- EACA resulted in a statistically non-significant reduction in exposure to allogeneic blood (RR 0.48, 95% CI 0.19 to 1.19). FSs reduced the RR of exposure to allogeneic transfusion by 54% (95% CI 32 to 68%).
- The use of a restrictive transfusion threshold reduced exposure to any blood transfusion by a relative 42% (95% CI 29 to 53%) compared with control.
- EPO alone reduced exposure to allogeneic blood by a relative 51% (95% CI 36 to 62%) in orthopaedic surgery and did not significantly reduce exposure to allogeneic blood in cardiac surgery (RR 0.40, 95% CI 0.13 to 1.22).
- PAD plus EPO reduced exposure to allogeneic blood transfusion by a relative 44% (95% CI 26 to 57%) in orthopaedic surgery and 64% (95% CI 12 to 85%) in cardiac surgery.

The majority of the trials included in the reviews examined the alternative transfusion strategies in elective surgery with expected moderate to high blood loss, particularly cardiac and orthopaedic surgery. This limits the extent to which the results can be generalised to surgical procedures with lower expected blood loss or emergency surgery. However, a recent prospective observational study of blood transfusion in the north of England indicates that cardiac and orthopaedic surgery accounts for around half of the transfusions in surgical patients.[3] In addition, the majority of trials were conducted outside the UK. It was not possible to assess the extent to which the results are applicable to practice in the UK in many of the studies.

Chapter 4

Results of the review of economic evaluations

Characteristics of the included economic evaluations

Twelve papers[36–38,57–65] were considered to be full economic evaluations that met all of the inclusion criteria. *Tables 12–14* summarise the main characteristics of each full economic evaluation and a more detailed description is provided in Appendix 13.

These economic evaluations synthesised costs and benefits where appropriate. One of these economic evaluations[61] was an update of another included economic evaluation.[60] One group conducted two of the economic evaluations.[64,65]

Country of origin

The studies were published between 1993 and 2002 and originated from the USA (seven), Canada (two), Italy (one) and France (one). None of the included evaluations were conducted in the UK.

Perspective

The perspective of the study was not clearly stated in the reports of some of the economic evaluations. Where the perspective was not clearly stated, the perspective implied by the data reported was used. Five studies used a societal perspective and five used a healthcare provider perspective. One study used a third-party payer perspective. None of the studies included indirect costs.

Source of funding

One of the studies was funded by a pharmaceutical company (Ortho Biotec); five studies were funded by various national institutes and training grants, including the National Library of Medicine and the National Institutes of Health (one), Robert Wood Johnson Clinical Scholars Programme and the Transfusion Medicine Academic Award from National Heart, Lung and Blood Institute (NHLBI) (one), American Association of Blood Banks and a career development award from the National Library of Medicine (one) and Canadian Coordinating Office for Health Technology Assessment (two); five studies did not report the source of funding.

Type of elective surgery

Four studies focused on elective cardiac surgery (mainly CABG) and seven studies focused on elective orthopaedic surgery (mainly total hip replacement). Many of the studies combined clinical data from a range of sources and it was not always possible to ascertain if these patient groups had similar characteristics.

Comparators

Six studies (two cardiac and four orthopaedic) compared PAD donation with allogeneic blood transfusion only. Two studies compared cell salvage with allogeneic blood transfusion only, in cardiac and orthopaedic surgery, of which one study used postoperative washed salvaged blood and one study used postoperative unwashed salvaged blood. Two studies compared EPO with allogeneic blood only (one in cardiac and one in orthopaedic surgery). Three studies compared EPO combined with PAD to PAD alone in orthopaedic (two studies) and cardiac (one study) surgery. One study compared EPO combined with PAD with allogeneic blood alone. (There are more comparators than studies because some studies looked at multiple comparisons.)

Type of economic evaluation

Five studies conducted a cost–utility analysis (CUA) and reported cost per QALY saved. Two studies used a decision tree model to synthesise the cost and QALY data and three studies used a Markov model. No study reported a primary economic evaluation. All are secondary economic evaluations and synthesised clinical and cost data from a variety of sources. Four studies conducted cost-effectiveness analyses (CEAs) using the following incremental cost-effectiveness ratios (ICERs): cost-per-life-year-gained (three studies), and preventing one hepatitis C virus (HCV) infection (one study). Two CEAs did not combine the costs and benefits since they demonstrated that PAD (one study) or cell salvage (one study) was the dominant strategy compared with allogeneic blood alone and were associated with greater risk reduction and less cost.

TABLE 12 *Table of economic evaluations – PAD versus allogeneic blood*

Study, year, country, perspective	Funded	Elective surgery	Comparators	Type	Results	Conclusion
Pre-autologous donation (PAD) vs allogeneic						
Birkmeyer, 1993;[58] USA, societal	Training grant from National Library of Medicine and the National Institutes of Health	CABG	PAD vs allogeneic	CUA Markov model	Cost per QALY saved of PAD compared with no donation: $508,000 (2 units collected), $621,000 (3 units), $752,000 (4 units), $909,000 (5 units)	PAD in CABG patients is not cost-effective, producing small health benefits at high societal costs
Healy, 1994,[59] USA, societal	Not stated	Primary hip arthroplasty	PAD vs allogeneic	CEA	Net saving PAD = $725 Incremental life-years gained PAD = 0.0008 (when postoperative infection is removed from model = 0.0005). Dominant factor is postoperative bacterial infection on length of stay and costs (marginal cost per life-year PAD = $181,400). PAD is more costly than allogeneic transfusion at $201 per day, at 0.17 days saved and when likelihood of transfusing blood is less than 0.10	PAD results in net cost savings compared with allogeneic blood over wide range of complication rates, patients ages and transfusion requirements
Etchason, 1995,[36] USA, societal	Robert Wood Johnson Clinical Scholars Program, Transfusion Medicine Academic Award from NHLBI	Total hip replacement CABG	PAD vs allogeneic	CUA decision analytic model	Incremental cost per QALY saved: Total hip replacement = $235,000 CABG = $494,000	Increased safety of using PAD is limited and may not justify the increased cost
Blumberg, 1996,[37] USA, hospital	Ortho Biotech Inc., RW Johnson Pharmaceutical Research Institute	Total hip replacement	PAD vs allogeneic	CEA	Cost and benefits not combined since autologous transfusion was the dominant strategy. Rate of infection or suspected infection was 3% (n = 1) for the autologous group and 32% (n = 16) for the allogeneic group (p = 0.0029) Incremental cost per unit allogeneic blood = $1043. Repeated analysis using figures for units donated and average percentage of autologous units transfused per patient for total hip arthroplasty and CABG from Etchason study (included in this table): cost-effectiveness per QALY was $1190 for total hip replacement, $1470 for CABG	PAD was the dominant strategy

continued

TABLE 12 *Table of economic evaluations – PAD versus allogeneic blood (cont'd)*

Study, year, country, perspective	Funded	Elective surgery	Comparators	Type	Results	Conclusion
Sonnenberg, 1999,[60] USA, third-party payer	American Association of Blood Banks and career development award from National Library of Medicine	Total hip replacement	PAD vs allogeneic	CUA Markov cohort simulation model	Cost-effectiveness of PAD is $2470 per QALY If assumed no increased risk of infection with allogeneic blood, then cost-effectiveness of autologous transfusion = $2,545,000 per QALY	Until more definitive data are available on the magnitude and costs of the risk of bacterial infection, the cost-effectiveness of PAD is still open to debate
Marchetti, 2000,[38] Italy, healthcare provider	Not stated	CABG	PAD vs allogeneic	CUA decision analytic model	Incremental cost per QALY: PAD alone = $1,784,946	PAD alone was not more cost-effective than a do-nothing strategy
Sonnenberg, 2002,[62] USA, third-party payer	American Association of Blood Banks and career development award from National Library of Medicine	Total hip replacement	PAD vs allogeneic	CUA Markov cohort simulation model	Cost-effectiveness of PAD is $2750 per QALY If assumed no increased risk of infection with allogeneic blood, then cost-effectiveness of autologous transfusion = $2,545,000 per QALY Repeated analysis using figures for units donated and average percentage of autologous units transfused per patient for total hip arthroplasty and CABG from Etchason study (included in this table): cost-effectiveness per QALY was $2580 for total hip replacement, $532 for CABG	Modifications to previously published CUA did not materially change results or conclusions. A modest increase in risk of bacterial infection following allogeneic transfusion would result in improved outcomes for PAD at a cost-effectiveness that compares favourably with well-accepted health interventions

TABLE 13 *Table of economic evaluations – cell salvage versus allogeneic*

Study, year, country, perspective	Funded by	Surgery	Comparators	Type	Results	Conclusion
Cell salvage vs allogeneic						
Kilgore, 1998,[63] USA, healthcare provider	Not stated	CABG, valve replacement or repair, cardiac transplantation	Unwashed postoperative filtered shed mediastinal chest tube drainage vs allogeneic	CEA	Costs and benefits not combined as cell salvage was associated with risk reduction and cost saving Reduction in need for allogeneic blood transfusion by using cell salvage estimated to be 54% Cost saving due to the use of postoperative cell salvage = $55 per case	Use of cell salvage has the potential to reduce significantly the costs and risks associated with allogeneic blood after cardiac operations
Jackson, 2000,[62] USA, societal	Not stated	Total joint arthroplasty	Postoperative washed RBC salvage vs allogeneic	CEA	ICER of postoperative cell salvage = $5.7 million per QALY (increased to $6.7 million per QALY at 5% discount rate) RBC salvage would only be cost neutral and save healthcare resources if cost less than $73 per device, and only cost neutral when returned volume exceeded 200 ml	Post-arthroplasty RBC salvage was not as cost-effective as other medical interventions

TABLE 14 *Table of economic evaluations – EPO*

Study, year, country, perspective	Funded by	Surgery	Comparators	Type	Results	Conclusion
EPO vs allogeneic						
Coyle, 1999,[64] Canada, healthcare provider	CCOHTA	Orthopaedic	EPO vs allogeneic	CEA	Incremental cost per life-year gained for EPO compared with no intervention = Can$66 million	Use of EPO to reduce perioperative allogeneic transfusions in orthopaedic surgery was not cost-effective
Marchetti, 2000,[38] Italy, healthcare provider	Not stated	CABG	EPO vs allogeneic	CUA decision analytic model	Incremental cost per QALY, EPO alone relative to a no-drug strategy = US$7,767,441	EPO alone was not more cost-effective than a do-nothing strategy
EPO plus PAD vs PAD						
Coyle, 1999,[64] Canada, healthcare provider	CCOHTA	Orthopaedic	EPO plus PAD vs PAD	CEA	Incremental cost per life-year gained for EPO to augment PAD = Can$329 million	Use of EPO to reduce perioperative allogeneic transfusions in orthopaedic surgery was not cost-effective
Woronoff-Lemsi, 1999,[57] France, societal	Not stated	Total hip replacement	PAD plus EPO vs PAD plus placebo	CEA	EPO as an adjunct to PAD produced an incremental cost of preventing one HCV infection = US$880 million	It was not cost-effective to add EPO to preoperative blood donation
Coyle, 2000,[65] Canada, healthcare provider	CCOHTA	Cardiac surgery	EPO to augment PAD vs PAD alone	CEA decision analytic model	Incremental cost per life-year gained for EPO to augment PAD = Can$44.6 million. EPO may be cost-effective if it leads to a reduction in average length of stay by more than 3 days per patient	EPO to reduce perioperative allogeneic transfusion in cardiac surgery is not cost-effective
EPO plus PAD vs allogeneic						
Marchetti, 2000,[38] Italy, healthcare provider	Not stated	CABG	EPO plus PAD vs allogeneic	CUA decision analytic model	Incremental cost per QALY relative to a no-drug strategy: EPO plus PAD = US$5,739,726	EPO plus PAD was not more cost-effective than a do-nothing strategy

CCOHTA, Canadian Coordinating Office for Health Technology Assessment.

Sources of clinical data

Two economic evaluations did not report performing a literature review. One of these evaluations used two cohort studies performed by the author, and the other evaluation used five previously published studies.

Nine economic evaluations reported conducting a literature review to obtain data on clinical effectiveness, but three of these gave no further information. Clinical data associated with transfusion strategies was obtained from a meta-analysis of a systematic review of the literature (one study), at least 14 trials including a meta-analysis of six RCTs from a previously published systematic review (one study), at least 20 references including RCTs, meta-analyses, longitudinal, observational and cost-effectiveness data (one study), published CEA, cohort and RCT data (one study), a published Markov model, three cohorts and a large multi-centred study (one study) and two studies and an RCT (one study). One evaluation used author assumptions, one used expert opinion and two used patients' records.

Sources of resource use and cost data

Resource use associated with transfusion strategies was obtained from hospital and patient charges (one study), hospital databases (four studies), literature review (four studies), cost studies (four studies), pharmacy list prices (two studies), drug cost to the hospital (one study), wholesale drug price list (one study), published Markov models (one study), hospital survey data (one study), hospital audit data (one study), official blood tariffs (one study), CEAs (one study), patients' records (one study), local Medicare cost data (one study) and hospital acquisition costs and audit of patient bills (one study). The majority of economic evaluations used a combination of sources to obtain resource use and cost data, mainly from hospital databases supplemented by literature review.

Quality assessment of the economic evaluations

Overall, the quality of the economic evaluations was poor. The perspective was not always explicitly stated, making it difficult to judge whether all relevant costs and outcomes had been assessed. None of the evaluations included indirect costs. In some case there was no justification for the alternative intervention. Although allogeneic blood is the standard practice in the UK and so makes the comparison relevant to this review, seven of the evaluations were conducted in the USA where PAD is offered as standard practice.

Few important clinical outcomes were considered. The time horizon was often unclear and there was a lack of justification for the time horizon used when it was reported. The majority of the studies were inadequately powered for the economic variables and clinical variables in the trial-based evaluations; it was unclear if this was also the case for model-based evaluations.

Six evaluations discounted costs and benefits and one discounted only costs; the remaining studies either failed to report discounting or did not discount owing to the short timeframe of the study. Ten studies performed sensitivity analysis to evaluate uncertainty in the results, which could not be assessed by statistical analysis, such as the range of costs used. Only one study used bootstrapping to assess clinical effectiveness data. In two studies the price year was not stated and most studies failed to report the methods used to adjust price data for inflation; only one study reported a currency conversion.

Results of the economic evaluations

PAD versus the allogeneic blood transfusion strategy

Six economic evaluations compared PAD with allogeneic blood. Three studies indicated that PAD was not cost-effective. Of these, one study reported that PAD in CABG patients was not cost-effective, producing small health benefits at high societal costs.[58] One study reported that the increased safety of using PAD was limited and may not justify the increased cost.[36] Another study reported that PAD alone was not more cost-effective than a do-nothing strategy.[38]

In contrast, three of the six studies indicated that PAD was cost-effective. Of these, one study reported that PAD resulted in net cost savings compared with allogeneic blood.[59] One study used rate of infection or suspected infection as the primary outcome of a cost-effectiveness analysis and reported that PAD was the dominant strategy compared with allogeneic blood.[37] One CUA demonstrated that if there were only a modest increase in the risk of bacterial infection following allogeneic transfusion, PAD would result in improved outcomes at a cost-effectiveness that compares favourably to well-accepted health

interventions.[60] Modifications to a previously published CUA indicated a similar result.[36,61]

Sonnenberg[61] conducted a repeat analysis using figures for PAD units donated and average percentage of PAD units transfused per patient for total hip arthroplasty (THA) and CABG from the study by Etchason and colleagues.[36] This repeated analysis resulted in a cost per QALY of US$2580 for THA and US$532 for CABG, thereby making PAD appear cost-effective compared with allogeneic blood when risk of infection was considered.[61] Until more definitive data are available on the magnitude and costs of the risk of bacteria infection, the cost-effectiveness of PAD is still debatable.

Cell salvage versus the allogeneic blood transfusion strategy

Two studies compared cell salvage with allogeneic blood. One study reported that the use of cell salvage blood had the potential to reduce significantly the costs and risks associated with transfusing allogeneic blood after cardiac operations.[63] One study reported that post-arthroplasty RBC salvage in orthopaedic surgery was not cost-effective.[62]

EPO versus the allogeneic blood transfusion strategy

Two studies reported the use of EPO alone compared with allogeneic blood. One study reported that the use of EPO to reduce perioperative allogeneic transfusions in orthopaedic surgery was not cost-effective.[64] EPO alone was not more cost-effective than a do-nothing strategy in cardiac surgery.[38]

EPO to augment PAD versus PAD

Three studies reported the use of EPO to augment PAD compared with PAD alone to reduce perioperative allogeneic blood transfusions. Two studies reported that the use of EPO combined with PAD was not cost-effective compared with using PAD alone in orthopaedic surgery.[57,64] Another study reported that EPO combined with PAD to reduce perioperative allogeneic blood transfusion in cardiac surgery was not cost-effective compared with PAD alone.[65]

EPO plus PAD versus the allogeneic blood transfusion strategy

One study reported the use of EPO plus PAD versus allogeneic blood only and reported that EPO plus PAD was not more cost-effective than a do-nothing strategy.[38]

Summary

In general, EPO does not appear to be a cost-effective method of minimising allogeneic blood transfusion, whereas cell salvage may have the potential to reduce risks and cost in the cardiac setting. Evidence regarding the cost-effectiveness of PAD varied considerably and PAD may be cost-effective when postoperative complications such as infection are considered.

Owing to the lack of relevant primary economic evaluations, comparing the various transfusion strategies, in a UK context, it is not possible to draw definitive conclusions about the cost-effectiveness of all the alternative transfusion strategies to reduce allogeneic blood transfusion in elective surgery. Full economic evaluations that compared the costs and outcomes of two or more interventions for ANH, AFs, FSs or restrictive transfusion thresholds were not identified in this search. Overall, the data from the studies in the economic literature review were not judged relevant to the UK setting and were not included in the economic model unless stated otherwise.

Chapter 5

Methods: economic model

Approach

A decision analytic model was developed to synthesise clinical and economic data from a number of sources. The model was used to estimate the relative cost-effectiveness of cell salvage when compared with the routine strategy of allogeneic blood transfusion and alternative methods of minimising perioperative allogeneic blood transfusion. The patient population used for the analysis was constrained to those undergoing elective surgical procedures for the primary analysis. For the secondary analyses, the patient populations used were those undergoing elective surgery associated with moderate to major blood loss as represented by elective non-urgent cardiac surgery (e.g. CABG and valve replacement) and elective non-urgent orthopaedic surgery (e.g. joint replacement and revision of joint replacements). These procedures were not defined explicitly for the analysis but based on the data extracted for these procedures in the systematic reviews discussed in Chapter 3.

The comparators chosen and rationale for inclusion are described in Chapter 1. However, the economic model excluded restrictive transfusion thresholds or transfusion protocols from the primary analysis. The decision to exclude this transfusion strategy was based on the practical constraints of the availability of data. As noted in Chapter 3, the systematic review of restrictive transfusion thresholds was based on a substantial number of studies and patients in critical care or undergoing emergency surgery. It was decided that this was not relevant to the patient populations for the analysis, or consistent with the data for the other transfusion strategies. The use of transfusion protocols was explored in the secondary analyses.

The analysis used the perspective of the NHS and the National Blood Service (the key funders and providers of transfusion services for perioperative blood transfusion) and patients. These comprise the key components of a societal perspective. The time horizon used for the primary analysis was 1 month post-transfusion. This limited time horizon was specified for a number of reasons. First, the evidence about the relative long-term benefits (in terms of survival and health status) of transfusion alternatives is based on secondary data analysis and modelling studies, rather than primary data. As the review of economic studies above indicates, the evidence about long-term benefits is limited and uncertain. Previous economic studies indicate that transfusion-transmitted viral infections such as hepatitis and HIV have a limited impact on the relative long-term costs and benefits of alternative transfusion strategies.[60,61] This is because the probabilities of transfusion-transmitted viral infection in the study settings used were extremely low. Second, adverse events with higher probabilities of occurrence and short-term impacts, such as bacterial infection, are more likely to affect the relative cost-effectiveness of alternative transfusion strategies.[60,61] Thirdly, there is a range of adverse events, such as stroke, that may affect the long-term cost-effectiveness of the alternative transfusion strategies. However, it is not clear whether these are due to the type and effectiveness of the surgical technique, the transfusion process or the type of blood (autologous or allogeneic) transfused. In addition, the rates of these adverse events were not consistently recorded in the clinical trials of autologous and allogeneic transfusion strategies. This means that any apparent differences in the rates between alternative transfusion strategies may be confounded by small sample sizes, the type of surgery and transfusion and surgical practice in the settings evaluated. Finally, the average age of elective surgery patients at risk of moderate to high blood loss is between 60 and 70 years.[3] The median survival of surgical patients having a transfusion has been estimated at 6.5 years.[66] This means that the life expectancy of patients undergoing surgery and having a blood transfusion may be lower than the life expectancy associated with transfusion transmitted infections. For example quality-adjusted life expectancy following HIV infection treated with highly active antiretroviral therapy (HAART) is over 10 years.[67]

However, to explore the potential long-term impact of these events, longer time horizons of 1, 10 and 30 years were tested in secondary analyses. The time horizon of 1 year was chosen to reflect the extent of short-term adverse events. The time horizon of 30 years is based on the predicted life

expectancy of a 50-year-old member of the general population. The time horizon of 10 years is based on the predicted life expectancy of a 70-year-old member of the general population. The age groups were derived to reflect the range of ages of first, all patients having surgery, and second, the average age of patients having total joint replacement (Hospital Episode Statistics). The age range includes the average age of all patients (61–63 years) having blood transfusion in England.[3,66]

Decision analytic model

The structure of the decision analytic model was initially developed from the literature reviews of effectiveness and economic evaluations of alternative strategies for blood transfusion described in Chapters 3 and 4. The accuracy of the model in predicting the probability of events, average length of stay and units of autologous/allogeneic blood transfused was tested against the data reported in the systematic reviews used for the study.

The range of events and outcomes included in the model of the alternative transfusion strategies was supplemented by a review of the serious hazards of transfusion published by the Serious Hazards of Transfusion (SHOT) Steering Group for the UK[6,68,69] and discussions with experts in transfusion, anaesthetics and surgery. These sources indicated a range of events associated with blood transfusion that could have an impact on mortality and morbidity, resource use and costs. The range of events included in the model was constrained to those for which data were available on the rate or likelihood of occurrence from either the systematic reviews of published effectiveness literature or were reported in the SHOT Annual reports.[6,68,69] This meant that the analysis was restricted to serious events associated with blood transfusion. A number of events were excluded that may have an impact on both resource and costs and overall quality of life. These include some of the possible transfusion-transmitted infections (syphilis, *Trypanosoma cruzi*, cytomegalovirus), which may bias the analysis in favour of strategies that are associated with higher rates of allogeneic blood transfusion. The fact that these infections are not reported in either the SHOT Annual Reports or systematic reviews does not necessarily mean that the incidence of the infections was zero. However, it is likely that available tests and rigorous screening of donors mean that the incidence of these infections in the UK blood transfusion system is very low. In addition, a number of other events were excluded. These include transfusion-related complications (gastrointestinal symptoms, hypersensitivity, phlebitis, platelet refractoriness, air embolism) and complications where the cause could be surgical or transfusion related (e.g. multi-organ failure, bacterial infection due to immunosuppression).

Figures 6–10 illustrate a simplified version of the decision analytic model. Square boxes represent decision nodes, where there is a choice to be made between strategies. Circles represent chance nodes, where there are a number of subsequent events that could happen; each event is assigned a probability that it will occur. Triangles represent terminal nodes, to signify the last stage in the model. *Figure 6* starts with the choice of transfusion strategies considered in the model. Whichever strategy is chosen, there is a chance that the patient will sustain sufficient blood loss to necessitate a blood transfusion. It is assumed that the tree pathways for strategies to minimise blood loss or the need for a blood transfusion (fibrin sealants, antifibrinolytics, EPO) and those that rely on transfusion of allogeneic blood (allogeneic blood) will be identical. However, the probability of needing a blood transfusion will differ between these strategies. If one of the autologous blood strategies is chosen and a transfusion is required, then the patient may have autologous blood only or both autologous and allogeneic blood. The pathway of possible events is assumed to be identical, but the probability of events occurring is assumed to differ if the patient has autologous blood only. If the patient has both autologous and allogeneic blood, then the probabilities of subsequent events are assumed to be equal to those if only allogeneic blood is transfused.

Whether or not a transfusion is required, there is a chance that the patient will die or survive the perioperative period, index admission and longer term follow-up. If a transfusion is given, there is a chance that the patient may have complications that are related to the transfusion or surgery, complications related to transfusion only or no transfusion-related complications (*Figure 7*). The range of complications included in the model is illustrated in *Figure 7*. If the patient is given the incorrect blood component, they may die, suffer major morbidity or have no ill effects from reactions (e.g. coagulopathy) to the incorrect blood component. If the patient has a haemolytic transfusion reaction, this may be acute or delayed. Following each of these complications, the patient

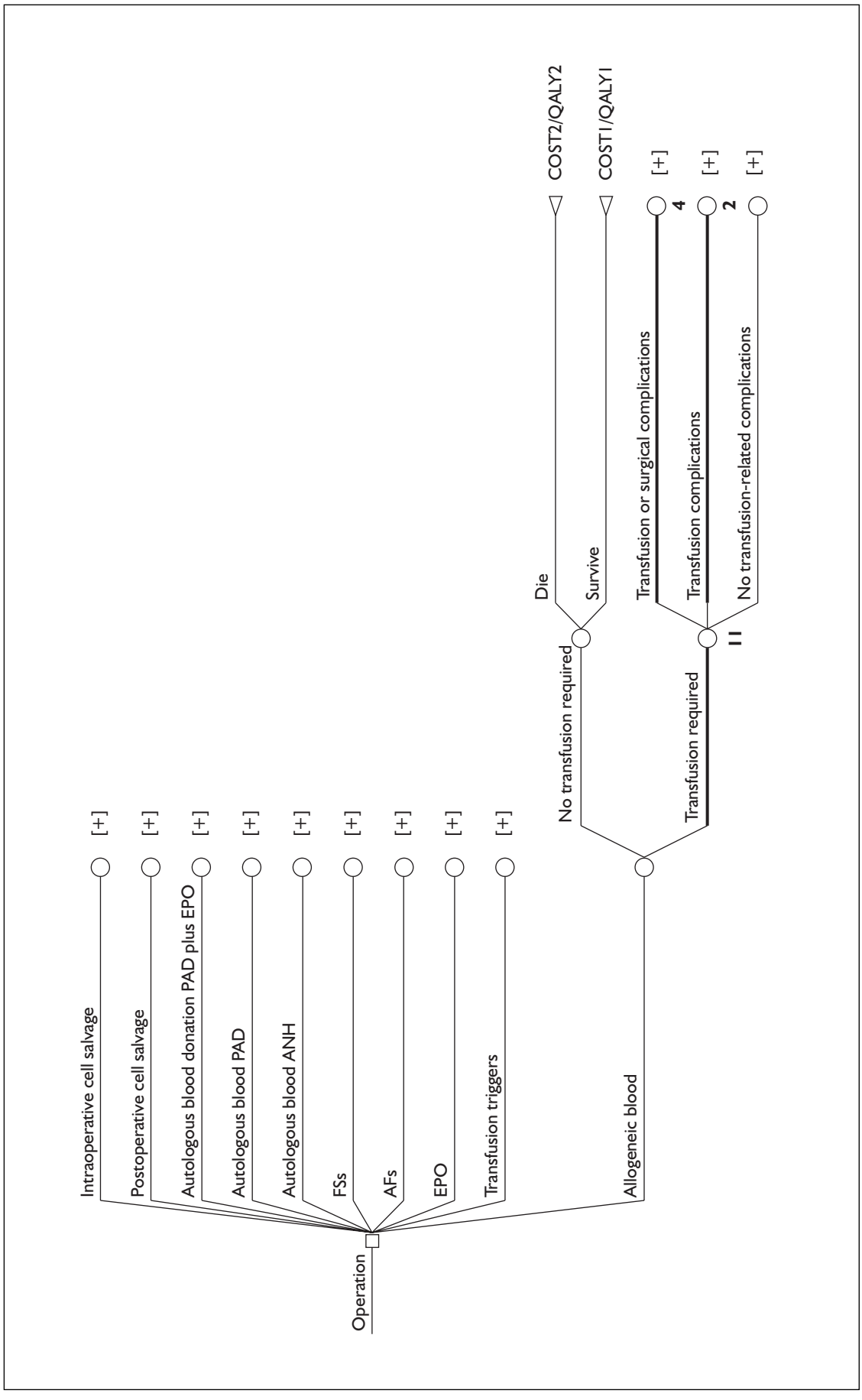

FIGURE 6 *Simplified decision tree: allogeneic blood 1*

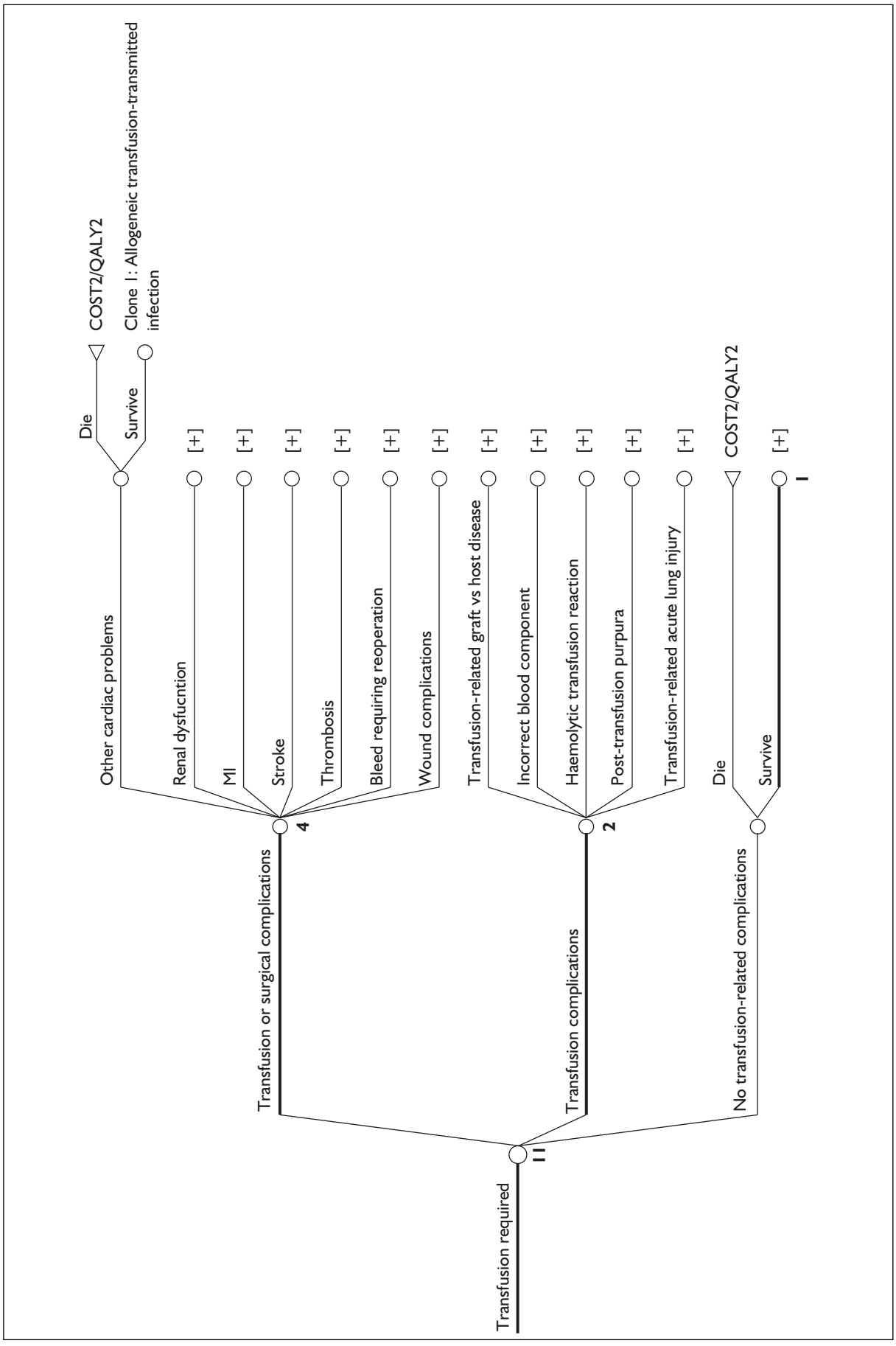

FIGURE 7 *Simplified decision tree: allogeneic blood 2*

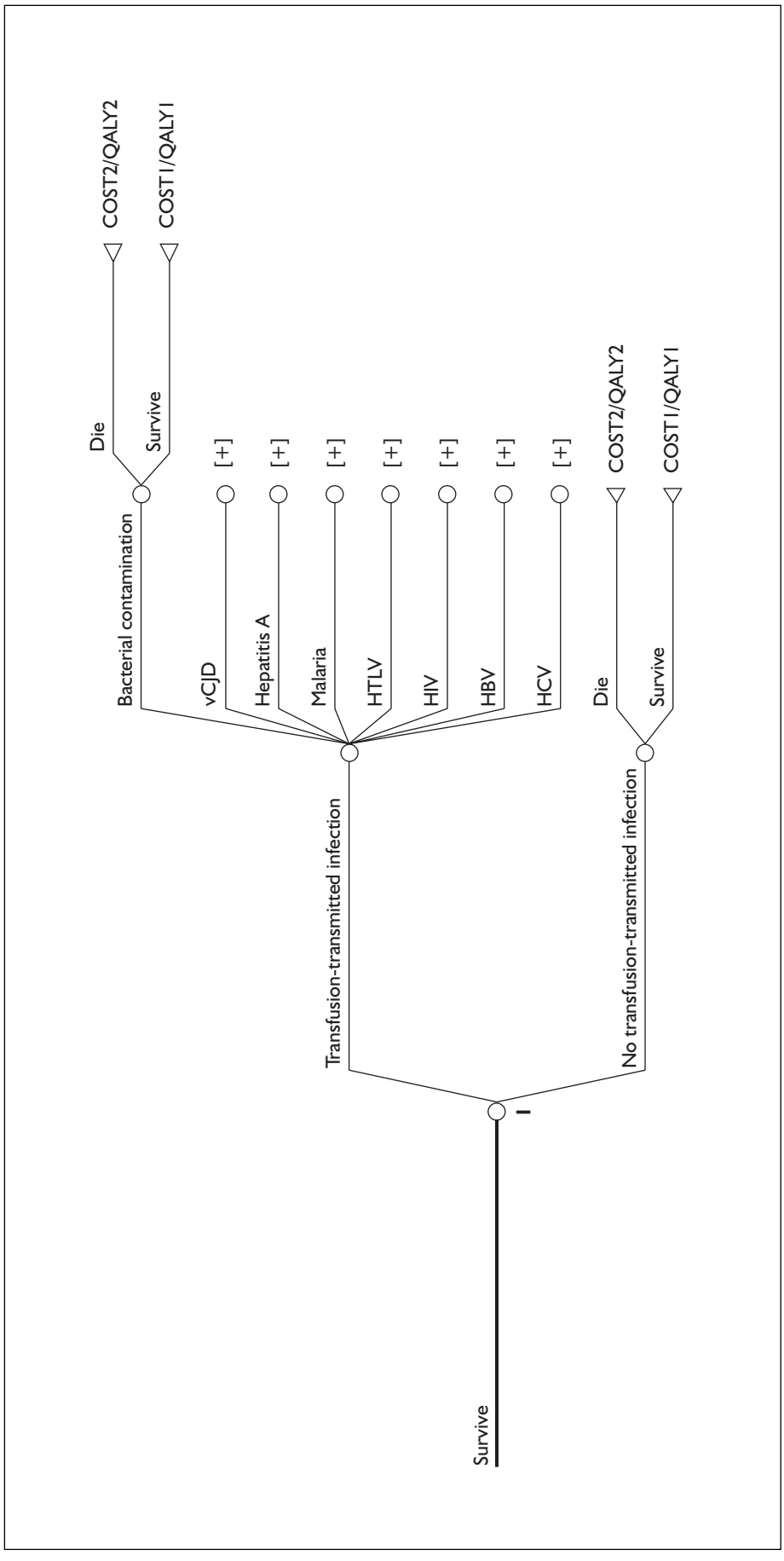

FIGURE 8 *Simplified decision tree: allogeneic blood 3. HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T-cell lymphotrophic virus; vCJD, variant Creutzfeldt–Jakob disease.*

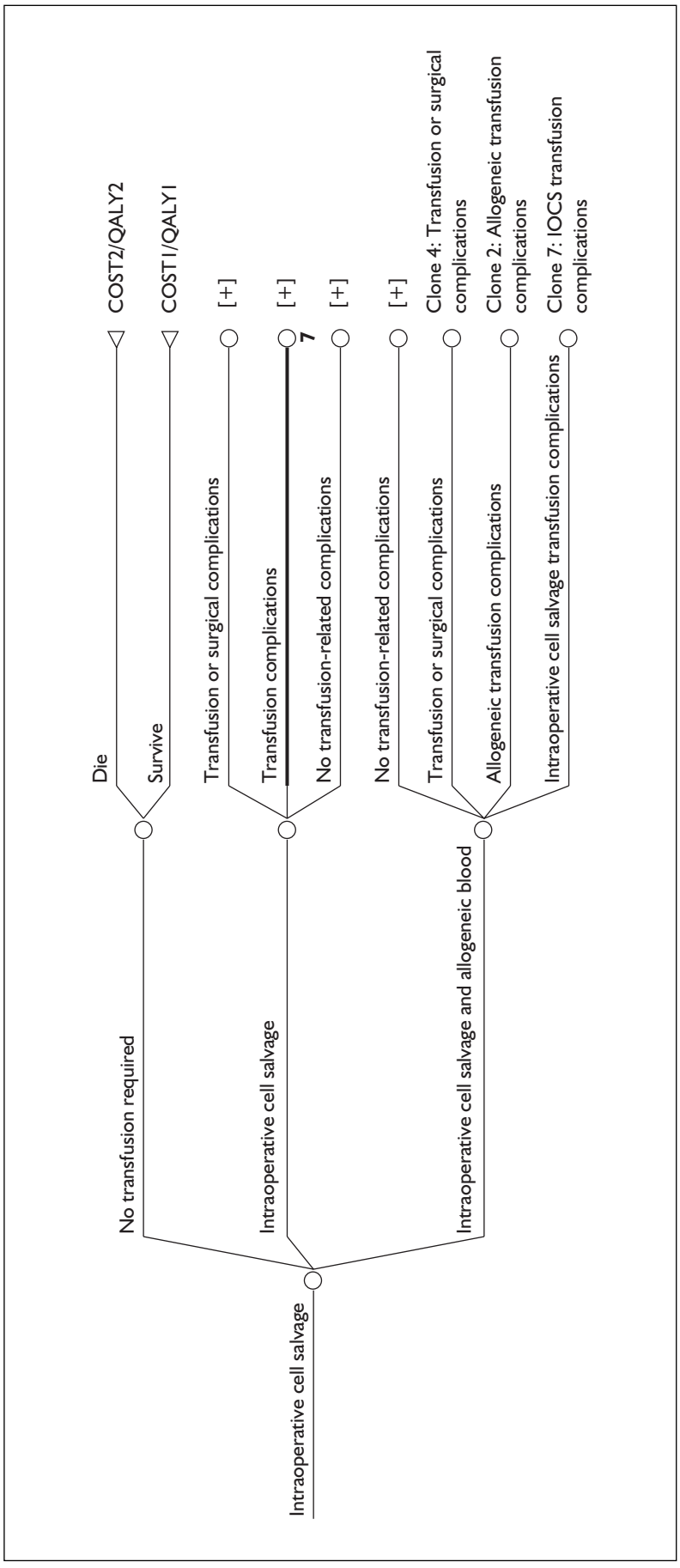

FIGURE 9 *Simplified decision tree: autologous blood 1*

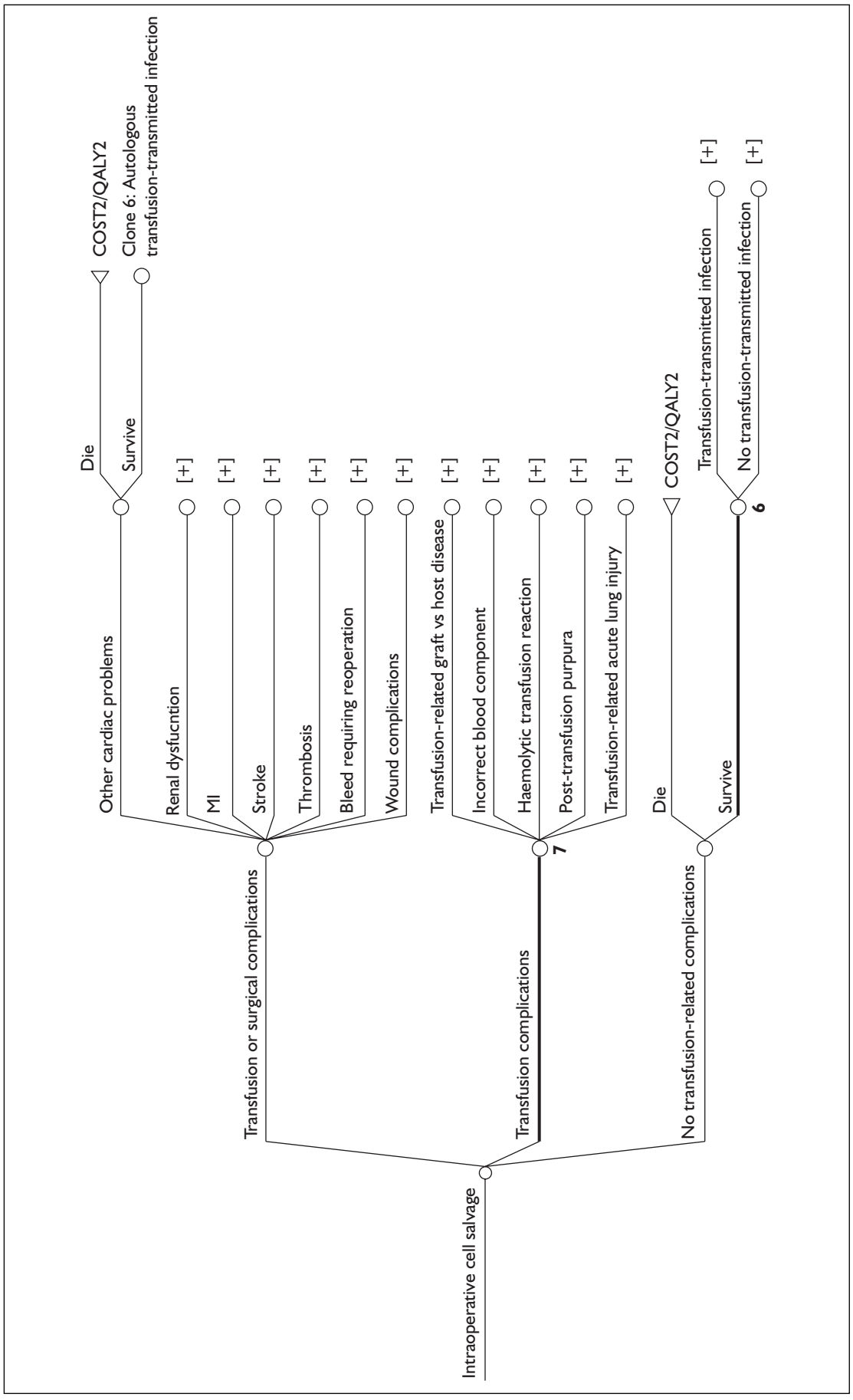

FIGURE 10 *Simplified decision tree: autologous blood 2*

will either die or survive within the timeframe of the analysis. If they survive the perioperative stage, then they have a chance of developing one of the transfusion-transmitted infections shown in *Figure 8*. *Figures 9* and *10* illustrate the pathways for autologous blood transfusion strategies.

Variable estimation

The decision model required three categories of data: the likelihood of events occurring, the resource use and costs of those events and the outcomes associated with those events. The overall approach and sources of data used for variable estimation for each of these categories are described below. Estimation of each variable used in the model was to some extent determined by the data available. The method of estimation and source of data for individual variables are described in more detail in Chapter 6.

Likelihood of events

Likelihood of transfusion

The probability of an allogeneic transfusion for patients, in the allogeneic blood-only transfusion strategy, was estimated as the absolute risk (number of events divided by number of patients in the sample) of an allogeneic blood transfusion. This was calculated from pooling the data from the control arms of the trials included in the systematic reviews reported in Chapter 3. The probability estimates for the allogeneic blood transfusion strategy were derived by pooling data from trials where a transfusion protocol was specified and those where a transfusion protocol was not specified.

For some of the trials included in the systematic reviews the control arm (allogeneic blood) also allowed the use of strategies to minimise perioperative blood transfusion. For this study, these were classed as active comparators and excluded from the set of trials used to estimate the probability of an allogeneic blood transfusion, for both the allogeneic blood transfusion strategy and alternative blood transfusion strategies. These studies were identified from the descriptions of the trials in each systematic review.

The likelihood of needing an allogeneic blood transfusion, for each of the alternative blood transfusion strategies to minimise the use of perioperative allogeneic blood, was estimated as the probability of a transfusion with the allogeneic transfusion strategy minus the weighted risk difference (95% CI) between the active strategy (i.e. cell salvage, PAD, PAD plus EPO, ANH, FSs, AFs or EPO) and the control (allogeneic blood). The risk difference was estimated from the data reported in the systematic reviews of the alternative transfusion strategies using the DerSimonian and Laird method for combining trials.[70] There were insufficient studies to estimate directly the risk difference between cell salvage and each of the alternative transfusion strategies. Therefore, it was assumed that applying the risk difference between each strategy and the control (allogeneic blood) would approximate the actual risk difference if cell salvage were tested directly against one of the other alternative strategies. The distribution used was a triangular distribution, with the mean risk difference used as the best estimate and the 95% CI used to specify the minimum and maximum risk difference. In the model, this distribution gave the best prediction of the mean risk difference estimated in the systematic reviews. Other distributions gave a biased estimate of the mean risk difference. Applying the derived minimum and maximum estimates to the probability of allogeneic blood transfusion replicated the total range of probability values for allogeneic blood transfusion, for each comparator.

Likelihood of adverse events

The likelihood of mortality for the index admission was estimated as the risk of mortality with the allogeneic blood transfusion strategy and the risk difference between the allogeneic transfusion strategy and the alternative transfusion strategies, as described above for exposure to allogeneic blood transfusion. These estimates of mortality were applied to patients having no transfusion, transfusion but no adverse events and transfusion plus adverse events due to transfusion or surgery.

The probability of all other adverse events was estimated as

$$\frac{\text{number of people with event}}{\text{number of people in sample}}$$

The data to estimate these probabilities were derived from the systematic reviews identified in Chapter 3, whenever possible. If the events were not reported in the systematic review, then the original papers used in the systematic review, the economic evaluations and the SHOT Annual reports[6,68,69] were searched for relevant data.

Probability distributions

Each estimate of likelihood, or probability, was assigned a distribution for the PSA. For the

probability of allogeneic blood transfusion in the allogeneic blood transfusion comparison (with and without restrictive transfusion protocol), the distribution was specified directly using the data from the trials, using the event rate from each of the included trials, weighted by the size of the trial (table distribution). The distribution for the risk difference of an allogeneic transfusion between the blood minimisation strategies and the allogeneic blood strategy was estimated using a triangular distribution, with the mean risk difference used as the best estimate and the 95% CI used to specify the minimum and maximum risk difference. The distributions for all other probabilities were estimated directly from the data using weighted estimates of the occurrence of events if there were more than three trials to include in the distribution. If there were insufficient data to estimate a table distribution, triangular distributions or beta distributions were used according to the number of estimates and availability of data about sample size.

Resource use and costs

The costs of healthcare resources used as inputs to provide transfusion, surgical management and follow-up and treatment of complications occurring with the timeframe of the analysis were estimated. The costs of the transfusion and index hospital admission were estimated as the product of resource use and unit costs for each transfusion and subsequent events prior to discharge, including the capital costs of hospital equipment for each of the transfusion strategies.

To estimate the costs of the transfusion and index admission, primary data were used to estimate the quantity and unit cost of hospital-based and Blood Service resources used for alternative transfusion strategies from South Manchester University Hospital Trust (SMUHT), the Manchester Blood Transfusion Service and the National Blood Transfusion Service. The resource use and cost data included additional inpatient stay or outpatient visits, additional time in the operating theatre suite, quantity and type of blood products used, staff time, facilities and equipment for collection, storage, quality control, patient testing and transport of blood products, selection and testing of patients to determine suitability for alternative transfusion strategies, administration of blood products and supportive pharmacological therapy. It was expected that there would be few data available from published literature and databases to estimate the costs of hospital-based resources for the primary operation and transfusion. Therefore, these data were estimated from local audit, finance, hospital and operating theatre activity data in SMUHT. These data were supplemented where necessary with data from the systematic reviews of the transfusion strategies, original studies and the economic evaluation and cost studies reviewed. In addition, Department of Health databases, Hospital Episode Statistics, Reference Costs and Health Related Resource Groups[71,72] were reviewed for data relevant to the resource use and/or costs associated with transfusion and transfusion-related events. Wherever possible, these additional sources of data were also used to generate ranges of resource use and unit costs for the probabilistic sensitivity analysis (PSA).

For each cost item, data on resource use and unit costs were extracted from the reviewed literature and databases. Where more than one estimate for each cost item was obtained, the range of values found were used to generate a distribution for the PSA. The unit costs of blood products for transfusion were derived from the 2003–4 national price list from the National Blood Service,[5] which is based on one delivery per weekday and augmented with local NHS Trust data to estimate the cost of *ad hoc* deliveries.

The distribution for each variable included the minimum, mean or median and maximum values found. Where possible, a mean value and measure of variance (e.g. SD or 95% CI) was defined and used to derive a distribution. If this information was not available, minimum and maximum estimates of cost were used to estimate a triangular distribution for the PSA. The distributions were estimated for resource use and total costs only.

Outcomes, utility values and QALYs

For the primary analysis, the final outcomes of lives gained, lives with no adverse events and QALYs are described. The outcome of lives gained does not take into account any differences in the HRQoL gained. The range of adverse events found in developing the structure of the model and the systematic review suggests that this may bias an analysis if the rate of adverse events differs between the transfusion strategies. The outcome of lives gained with no adverse events takes into account differences in the rates of adverse events, but assigns an equal weight to the range of adverse events. This implicitly assumes that the impact of each adverse event on HRQoL and morbidity is equal. If this assumption is not valid, then the analysis may be biased. QALYs are a method to weight gains in survival by both the occurrence of adverse events and the impact of

those events on health status and HRQoL. QALYs are used extensively in economic evaluations to value outcomes, and are incorporated into the evaluations considered by the National Institute for Health and Clinical Excellence. For these reasons, QALYS were used in the estimation of ICERs for both the primary and secondary analyses. ICERs are estimated as the cost per QALY gained. The data to estimate mortality and utility values were extracted from the systematic reviews, economic evaluations of transfusion strategies, the serious hazards of transfusion reports[6,68,69] and health survey data for the UK.[73]

Analysis of data

Monte Carlo simulation was used to generate the PSA and estimate the mean expected costs and outcomes, and statistical measures of expected variance (2.5th to 97.5th percentiles) around the mean. The PSA allows estimation of the probability that uncertainty and variation in the data used affect the model values (absolute and relative costs and outcomes). It also indicates the extent to which each input variable affects the model results. For this analysis, each variable was assigned a base case or average value and a distribution of possible values. Any deterministic parameters in the model were assigned distributions derived from minimum, mean and maximum values. The PSA sums the results of multiple analyses (iterations). Each iteration samples values for the variables at random from the specified distributions. The sampling method used was Monte Carlo, expected value. The simulation software was TreeAGe Pro plus Healthcare module.

ICERs were calculated as: (expected cost of A – expected cost of B)/(expected outcome A – expected outcome B). Statistical measures of variance around the ICERs were not calculated, since standard methods of analysis do not allow this to be calculated in any meaningful way. No predefined target ceiling ratio (i.e. the maximum that a decision-maker is willing to pay for a unit of effect) for cost-effectiveness was chosen. This was because there is no evidence on what a single target ceiling ratio should be. A range of ceiling ratios were used from decision-makers being willing to pay £0 to gain one QALY to decision-makers being willing to pay £30,000 to gain one QALY.

Cost-effectiveness acceptability curves (CEACs) were plotted and used as a method of summarising the uncertainty around the generated cost-effectiveness ratios. CEACs plot the probability that an intervention is cost-effective against the value of a ceiling ratio (i.e. the maximum a decision-maker is willing to pay for a unit of effect). To estimate the CEAC of cell salvage, simulations are treated as positive or negative results.

Positive results were defined as cases when

- Both the incremental cost and incremental QALY estimate for cell salvage are higher than that of the comparator.
- Both the incremental cost and incremental QALY of cell salvage are lower than that of the comparator.
- The incremental cost of cell salvage is lower and the incremental QALY is higher than that of the comparator.

Negative outcomes were defined as cases when the incremental cost of cell salvage was higher than that of the comparator and the incremental QALY was lower.

The CEAC estimates the probability that cell salvage is cost-effective. This is done by first bootstrapping the estimates of cost per QALY (ICER) from the PSA. The proportion of bootstrapped estimates where the cost per QALY is lower than the ceiling ratio is calculated out of the total number of bootstrapped estimates of the ICER. This is repeated for each of the ceiling ratios (in this case the ceiling ratios were: £0 to £30,000 per QALY gained, in increments of £1000). The probability that cell salvage is cost-effective is then estimated as the proportion of bootstrapped estimates of the ICER that are lower than each ceiling ratio. These estimates are plotted graphically against each of the ceiling ratios to derive a CEAC.

Net benefit statistics were estimated by revaluing the bootstrapped estimates of QALYs, using the ceiling ratios or willingness to pay to gain one unit of outcome used for the CEAC analysis (i.e. £0 to £30,000 per QALY gained, in increments of £1000). For each willingness to pay threshold, the net benefit (*NB*) is estimated as

$$NB = E \times WTP - C$$

where E = the incremental QALY gained by an intervention, WTP = willingness to pay to gain 1 QALY, and C = the incremental cost of the intervention.

The CEAC summarises the information at each value of willingness to pay to gain a QALY. The net benefit statistic gives an estimate of the monetary value of a QALY or other measure of effectiveness.

Primary analysis

The primary analysis estimated the risks, costs and outcomes of the alternative transfusion strategies for 30 days from surgery, including the index admission. The evidence about the relative long-term benefits (in terms of survival and health status) of transfusion alternatives is limited and uncertain. It is also likely to be confounded by type and effectiveness of surgical technique. In addition, the use of a timeframe longer than 1 year for the analysis, with a high level of uncertainty about these outcomes of treatment, would mask the costs, outcomes and uncertainty resulting from the use of the alternative transfusion techniques. The impact of 1-, 10- and 30-year costs and outcomes associated with key adverse events such as infection was explored in the secondary analyses.

Secondary analysis

Secondary analysis was used to explore whether the relative cost-effectiveness of cell salvage was affected by the following factors:

1. timing of cell salvage (intraoperative versus postoperative) and technique (washed versus unwashed)
2. cost of cell salvage (equipment and activity levels per year)
3. surgical procedure (cardiac, orthopaedic)
4. use of transfusion protocol for allogeneic blood transfusion
5. long-term impact of adverse events on QALYs (time horizon of analysis).

The primary outcome for the secondary analyses was the QALY.

Impact of increasing the use of cell salvage on the National Blood Service

The model estimated the expected volume of blood with an allogeneic blood transfusion strategy and expected reductions in the volume of blood used and the associated costs and outcomes if cell salvage was used as a strategy to minimise the use of allogeneic blood. The analysis explored different levels of surgical activity for elective procedures. In addition, the analysis explored different levels of use of cell salvage.

Chapter 6

Data used as inputs to the economic model

Likelihood of events

Table 15 summarises the probability of receiving an allogeneic blood transfusion for the allogeneic blood comparison (with and without restrictive transfusion protocol). *Table 15* also presents the estimated risk differences for the alternative strategies to minimise allogeneic blood transfusion when compared with allogeneic blood only. Where possible, risk differences were calculated for all surgical procedures, cardiac procedures and orthopaedic procedures. However, there were insufficient data for all the alternatives to estimate risk differences for the cardiac or orthopaedic procedures. In these cases it was assumed that the risk difference for specific procedures was adequately represented by the risk difference for all procedures.

Table 16 shows the probability of transfusion with autologous blood for the autologous blood transfusion strategies. These data include autologous transfusions for patients who received autologous blood only and autologous transfusions for patients who received both autologous and allogeneic blood transfusions. For the model, the probability of autologous transfusion only was estimated as the probability of autologous blood transfusion from *Table 16* minus the probability of both autologous and allogeneic blood transfusion

TABLE 15 *Probability of transfusion with allogeneic blood*

	All procedures	**Cardiac procedures**	**Orthopaedic procedures**
	Mean (range) probability	**Mean (range) probability**	**Mean (range) probability**
AB[a]	0.66 (0–1)[a]	0.50 (0–1)[a]	0.45 (0–0.98)[a]
TP[a]	0.61 (0–1)[a]	0.61 (0–1)[a]	0.48 (0–1)[a]
	Mean (95% CI) risk difference	**Mean (95% CI) risk difference**	**Mean (95% CI) risk difference**
All CS[b]	–0.26 (–0.36 to –0.16)	–0.14 (–0.23 to –0.05)	–0.42 (–0.57 to -0.28)
IOCS[b]	–0.24 (–0.45 to –0.03)	–0.28 (–0.48 to –0.07)	–0.24 (–0.45 to –0.03)[i]
POCS[b]	–0.24 (–0.37 to –0.12)	–0.10 (–0.20 to –0.01)	–0.45 (–0.62 to –0.27)
CS washed[b]	–0.29 (–0.44 to –0.15)	–0.22 (–0.39 to –0.05)	–0.38 (–0.61 to –0.14)
CS unwashed[b]	–0.21 (–0.35 to –0.07)	–0.09 (–0.20 to –0.02)	–0.44 (–0.67 to –0.20)
PAD[c]	–0.42 (–0.68 to –0.17)	–0.42 (–0.68 to –0.17)[i]	–0.42 (–0.88 to 0.04)
PAD + EPO[d]	–0.14 (–0.21 to –0.08)	–0.12 (–0.31 to 0.07)	–0.079 (–0.14 to –0.02)
ANH[e]	–0.21 (–0.25 to –0.16)	–0.21 (–0.25 to –0.16)	–0.14 (–0.32 to –0.03)
AFs[f]	–0.20 (–0.26 to –0.015)	–0.20 (–0.23 to –0.16)[i]	–0.20 (–0.34 to –0.06)
FSs[g]	–0.19 (–0.29 to –0.09)	–0.19 (–0.29 to –0.09)[i]	–0.27 (–0.50 to –0.03)
EPO[h]	–0.23 (–0.33 to –0.12)	–0.29 (–0.53 to –0.05)	–0.20 (–0.32 to –0.07)

AB, allogeneic blood no restrictive transfusion protocol; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.

[a] Estimates of allogeneic transfusion (with and without restrictive transfusion protocol) derived from pooling the control arms reported in the updated systematic reviews of CS and PAD and the published systematic reviews of the remaining interventions[13,21,29–33] and Chapter 3.

[b] Estimates derived from updated systematic review of CS[30] and Chapter 3.

[c] Estimates derived from updated systematic review of PAD[13] and Chapter 3.

[d] Estimates derived from published systematic review of PAD plus EPO, risk difference PAD plus EPO versus PAD.[21]

[e] Estimates derived from published systematic review of ANH.[29]

[f] Estimates derived from published systematic review of AFs.[31]

[g] Estimates derived from published systematic review of FSs.[32]

[h] Estimates derived from published systematic review of EPO.[21]

[i] If there was insufficient information to estimate surgical procedure specific risk differences, these were assumed to equal the risk differences for all surgical procedures.

TABLE 16 *Probability of transfusion with autologous blood*

	Mean (range) probability		
	All procedures	**Cardiac procedures**	**Orthopaedic procedures**
All CS	0.64 (0.21–0.84)	0.64 (0.21–0.84)	0.64 (0.21–0.84)
IOCS[a]	0.64 (0.21–0.84)	0.64 (0.21–0.84)	0.64 (0.21–0.84)
POCS[a]	0.64 (0.21–0.84)	0.64 (0.21–0.84)	0.64 (0.21–0.84)
CS washed[a]	0.64 (0.21–0.84)	0.64 (0.21–0.84)	0.64 (0.21–0.84)
CS unwashed[a]	0.64 (0.21–0.84)	0.64 (0.21–0.84)	0.64 (0.21–0.84)
PAD[b]	0.66 (0.47–1.00)	0.66 (0.47–1.00)	0.67 (0.51–0.89)
PAD + EPO[c]	0.68 (0.36–1.00)	0.68 (0.36–1.00)	0.68 (0.36–1.00)
ANH[d]	0.92 (0.24–1.00)	0.92 (0.24–1.00)	0.92 (0.24–1.00)

CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Estimates derived from updated systematic review of CS[30] and Chapter 3.
[b] Estimates derived from updated systematic review of PAD[13] and Chapter 3.
[c] Estimates derived from published systematic review of PAD plus EPO, risk difference PAD plus EPO vs PAD.[21]
[d] Estimates derived from published systematic review of ANH.[29]

TABLE 17 *Probability of events related to transfusion or surgery*

	AB	**AB + TP**	**All CS**	**PAD**	**PAD + EPO**	**ANH**	**AFs**	**FSs**	**EPO**
Cardiac problems	0.21[a]	0.21[a]	0.21[a]	0.21[a]	0.21[a]	0.21[a]	0.21[a]	0.21[a]	0.21[a]
Renal dysfunction	0.03[a]	0.03[a]	0.03[a]	0.03[a]	0.03[a]	0.03[a]	0.03[e]	0.03[a]	0.03[a]
Non-fatal MI	0.03[a]	0.03[a]	0.04[b]	0.04[b]	0.04[b]	0.04[b]	0.04[e]	0.03[a]	0.03[a]
Stroke	0.01[a]	0.01[a]	0.01[b]	0.01[b]	0.01[b]	0.01[b]	0.01[e]	0.00[f]	0.01[a]
Thrombosis	0.03[a]	0.03[a]	0.05[b]	0.04[c]	0.04[c]	0.05[b]	0.02[e]	0.03[a]	0.03[a]
Bleed and reoperation	0.04[a]	0.04[a]	0.04[b]	0.04[b]	0.04[b]	0.02[d]	0.02[e]	0.00[f]	0.04[a]
Wound complications	0.07[a]	0.07[a]	0.05[b]	0.05[b]	0.05[b]	0.05[b]	0.07[a]	0.04[f]	0.07[a]

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Estimates of allogeneic transfusion (with and without restrictive transfusion protocol) derived from pooling the control arms reported in the updated systematic reviews of CS and PAD and the published systematic reviews of the remaining interventions[13,21,29–33] and Chapter 3.
[b] Estimates derived from updated systematic review of CS[30] and Chapter 3.
[c] Estimates derived from updated systematic review of PAD[13] and Chapter 3.
[d] Estimates derived from published systematic review of ANH.[29]
[e] Estimates derived from published systematic review of AF.[31]
[f] Estimates derived from published systematic review of FSs.[32]

from *Table 15*. It was assumed that patients treated by autologous transfusion strategies who required a transfusion would have an autologous transfusion first followed by an allogeneic transfusion if necessary.

Table 17 summarises the probability of adverse events that could be due to either allogeneic blood transfusion, or to surgery, by transfusion strategy. These data were estimated from the events reported by the systematic reviews. There were insufficient data to estimate the probability of an event for some of the transfusion strategies. In this case, the probability of an alternative autologous strategy was used for those strategies that used autologous blood. For those strategies that did not use autologous blood, if there were insufficient data to estimate a strategy specific probability of an adverse event, the probability for the allogeneic comparison was used to approximate the probability of the adverse event. This required the assumption that the probability of allogeneic blood transfusion was the primary determinant of the occurrence of the event. The validity of this assumption is unclear, since the event may have been caused by the use of allogeneic transfusion, or be a consequence of surgery.

Tables 18 and *19* summarise the conditional probability of events related to transfusion only, given that a transfusion has been administered. These were estimated as the mean number of events per year divided by the estimated number of transfusions per year. The average number of

TABLE 18 *Conditional probability of events for transfusion of allogeneic blood only*

Transfusion complication	Mean	Minimum	Maximum
Graft vs host disease	0.000002[a]	0.000000[a]	0.000005[a]
IBCT	0.000244[a]	0.00010[a]	0.00045[a]
HTR acute	0.000043[a]	0.000038[a]	0.000055[a]
HTR delayed	0.000038[a]	0.000030[a]	0.000050[a]
PTP	0.000008[a]	0.000001[a]	0.000014[a]
TRALI	0.000025[a]	0.000014[a]	0.000046[a]
FAE	0.00000[a]	0.00000[a]	0.00000[a]

FAE, fatal air embolism; HTR, haemolytic transfusion reaction; IBCT, incorrect blood component transfused; PTP, post-transfusion purpura; TRALI, transfusion-related lung injury.
[a] Estimates derived from reports of the serious hazards of transfusion between 1996 and 2003[6] survey of the implementation of the Health Services circular 'Better blood transfusion'[26] and the National Audit Office.[4]

TABLE 19 *Conditional probability of events related to transfusion of autologous blood only*

Transfusion complication	Unwashed CS only	PAD	PAD + EPO	ANH
Graft vs host disease	0.00000[a]	0.00000[a]	0.00000[a]	0.00000[a]
IBCT	0.00000[a]	0.000122[a]	0.000122[a]	0.00000[a]
HTR acute	0.000004[a]	0.00000[a]	0.00000[a]	0.00000[a]
HTR delayed	0.00000[a]	0.00000[a]	0.00000[a]	0.00000[a]
PTP	0.00000[a]	0.00000[a]	0.00000[a]	0.00000[a]
TRALI	0.00000[a]	0.00000[a]	0.00000[a]	0.00000[a]
FAE	0.00003[b]	0.00000[a]	0.00000[a]	0.00000[a]

FAE, fatal air embolism; HTR, haemolytic transfusion reaction; IBCT, incorrect blood component transfused; PTP, post-transfusion purpura; TRALI, transfusion-related lung injury.
[a] Estimates derived from reports of the serious hazards of transfusion,[6,68,69] a survey of the implementation of the Health Services circular 'Better blood transfusion'[26] and the National Audit Office.[4]
[b] Estimates reported by Linden and colleagues.[74]

events per year was estimated from the number of events reported between 1996 and 2003 adjusted by the participation rate in the serious hazards of transfusion reporting scheme to take account of non-reporting by some hospitals.[6] The number of transfusions per year was estimated at 800,000.[4]

The majority of events reported were associated with allogeneic blood transfusions. However, a limited number of events following autologous blood transfusion were reported.[6,68,69,74] For example, in 2003, two cases of incorrect blood component transfused (IBCT) and one case of acute haemolytic transfusion reaction following an autologous blood transfusion were reported to SHOT. However, there are no firm data to indicate the number of autologous transfusions used in 2003. A survey of practice suggests that the use of PAD is relatively low in the UK.[26] The data reported in the survey suggest that the maximum number of units transfused with PAD is in the region of 2600 per year. This gives an estimate of the probability of IBCT for PAD of 0.0008, which is nearly twice that of allogeneic blood. However, the data on the use of PAD reported in the survey relied on self-report of managers about the estimated number of units transfused. The use of PAD may therefore be under-reported in the survey, giving a high estimate of the probability of adverse events. Against this, the number of adverse events following autologous blood may be under-reported to SHOT, and has been highlighted as a concern by the SHOT Steering Group.[6] It is also possible that PAD is associated with bacterial contamination of the autologous blood product. However, there were no reported cases of this occurring.

For these reasons, the probability of IBCT for PAD transfusion was assumed to be equal to the probability of IBCT of any blood transfusion (allogeneic or autologous) due to bedside errors in matching units of blood issued to the patient. This excludes errors due to inaccurate matching of blood products prior to issue of the blood from the blood transfusion service or the local hospital. The rationale for this approach is that there is no *a priori* reason why there should be differences in

inconsistent matching of blood back to the patients between PAD and allogeneic blood transfusion strategies when the blood donation is separated from the patient, as occurs with both PAD and allogeneic blood. However, it should be noted that the probability of mismatching a unit of PAD blood to patient details at the patient bedside may depend on whether the PAD was done by the blood transfusion service or local hospital site. It was not possible to explore this further in this analysis.

For the other autologous transfusion strategies and adverse events, if an adverse event was not reported to SHOT as following an autologous transfusion, it was assumed that the probability of this event was zero. However, this may underestimate the incidence of adverse events reported to SHOT. The SHOT report of 2003 suggests that the probability of adverse events associated with autologous transfusion may be as high as 2–3%, and notes that this suggests that the occurrence of serious hazards of autologous transfusion may be under-reported.[6] However, that estimate of the probability of adverse events associated with autologous blood transfusion was published in 1992, and both the technology used for autologous blood transfusion and blood transfusion working practices have changed since then, to improve the safety of blood transfusion. The maximum total probability of events related to autologous blood transfusion for the PSA was set equal to that for transfusion with allogeneic blood.

Table 20 summarises the probability of transfusion transmitted infections.[6,68,69,75] It was assumed that these would only apply to people having an allogeneic blood transfusion. It should be noted that the data used to derive the probability of transfusion transmitted infections are less robust for bacterial contamination, variant Creutzfeldt–Jakob disease (vCJD), HTLV, malaria and hepatitis A. These estimates were based on the number of events reported to SHOT, rather than well-designed and robust epidemiological studies.

The probability of mortality reported in the trials included in the systematic reviews was similar for all the alternative transfusion strategies at 0.03 (95% CI 0.00 to 0.21). The risk difference was 0.00 overall (95% CI –0.02 to 0.00). This was used to estimate mortality for the index admission for patients not having a transfusion, patients with no complications following transfusion and patients who had complications or adverse events that could have been due to either transfusion or

TABLE 20 *Conditional probability of transfusion transmitted infection from allogeneic blood*

Bacterial contamination	0.0000037[a]
vCJD	0.0000012[a]
HBV	0.0000001[b]
HCV	0.0000000[b]
HIV	0.0000001[b]
HTLV	0.0000000[a]
Malaria	0.0000012[a]
Hepatitis A	0.0000012[a]

HBV, hepatitis B virus; HCV, hepatitis C virus; HTLV, human T-cell lymphotrophic virus; vCJD, variant Creutzfeldt–Jakob disease.

[a] Estimates derived from reports of the serious hazards of transfusion,[6,68,69] survey of the implementation of the Health Services circular 'Better blood transfusion'[16] and the National Audit Office.[4]

[b] Estimates reported by Soldan and colleagues.[75]

TABLE 21 *Conditional probability of survival, complications due to transfusion only*

Transfusion complication[a]	Conditional probability (95% CI)
Transfusion-related graft vs host disease	
Die	1.00
Survive major morbidity	0
Survive no ill effects	0
Incorrect blood component transfused	
Die	0.012 (0.001 to 0.022)
Survive major morbidity	0.061 (0.026 to 0.096)
Survive no ill effects	0.928 (0.882 to 0.973)
Acute haemolytic transfusion reaction	
Die	0.043 (0.000 to 0.097)
Survive major morbidity	0.021 (0.000 to 0.056)
Survive no ill effects	0.936 (0.847 to 1.000)
Delayed haemolytic transfusion reaction	
Die	0.038 (0.000 to 0.064)
Survive major morbidity	0.108 (0.000 to 0.045)
Survive no ill effects	0.854 (0.891 to 1.000)
Post-transfusion purpura	
Die	0.046 (0.000 to 0.091)
Survive major morbidity	0.295 (0.000 to 1.000)
Survive no ill effects	0.660 (0.000 to 1.000)
Transfusion-related lung injury	
Die	0.237 (0.212 to 0.333)
Survive major morbidity	0.640 (0.462 to 0.750)
Survive no ill effects	0.123 (0.000 to 0.326)
Fatal air embolism	
Die	1.00

[a] Estimates derived from reports of the serious hazards of transfusion,[6,68,69] survey of the implementation of the Health Services circular 'Better blood transfusion'[26] and the National Audit Office.[4]

TABLE 22 *Cost per case of cell salvage equipment, maintenance, consumables and staff (washed cell salvage)*

	Unit cost (£s, 2003–4)			Source
	Low cost/case (Dideco[a])	Medium cost/case (Hameonetics[a])	High cost/case (Fresenius[a])	
Annual cost per cell saver (including VAT at 17.5%)				
Annual equivalent capital cost	711	2343	2343	SMUHT, manufacturer's list price
Maintenance[b]	963	2270	3084	SMUHT, manufacturer's list price
Consumables (per case)	71	108	100	SMUHT, manufacturer's list price
Average cost per case (including VAT at 17.5%)				
50 cases per year	137	214	217	SMUHT, manufacturer's list price
100 cases per year	104	161	158	SMUHT, manufacturer's list price
150 cases per year	93	143	139	SMUHT, manufacturer's list price

[a] Manufacturer of cell salvage equipment.
[b] Average annual maintenance cost over the estimated 8-year life of a machine, where the first year maintenance cost is zero with manufacturer's 12-month warranty.

surgery. *Table 21* summarises the probability of mortality following adverse events related to transfusion only for the index admission and 1 month following. Longer term mortality associated with adverse events was not included in the model.

Costs of events

Unit costs of transfusion, operation and hospital inpatient stay

The costs of washed cell salvage were estimated as the annual equivalent cost of the cell saver equipment and the annual costs of maintenance, consumables and cell salvage operator. The annual equivalent cost of the cell salvage equipment was estimated by discounting the acquisition price of the equipment over an estimated life of 8 years at 3.5% per annum (UK Treasury recommended rate).[76] The cost per case of equipment, maintenance, consumables and staff was estimated for three rates of annual activity per cell saver: 50, 100 and 150 operations. Utilisation of cell salvage depends on surgical demand, which can vary from week to week. A recent survey found that the estimated number of units transfused per year ranged from less than 10 to over 200 units.[26] The annual use per cell saver at SMUHT lay within this range at 100–150 operations per year. A previous economic study of cell salvage used 100 operations ±50%.[20] This equates to an estimated weekly use of a cell saver of one, two or three operations. This range of activity per cell saver was used to estimate the costs of cell saver equipment. *Table 22* details the estimated costs of equipment, maintenance and consumables for washed cell salvage. Unwashed cell salvage, which is typically performed postoperatively, requires autologous wound drain kits. The costs of these are between £58 (Unomedical HandyVac ATS) and £182 (Stryker ConstaVac) per case. The costs of washed cell salvage were used for the primary analysis of all cell salvage, for all procedures. The impact of using unwashed cell salvage costs was explored in the secondary analyses of postoperative cell salvage and using cell salvage for orthopaedic procedures. These represent the situations where unwashed cell salvage is typically used. In addition, the secondary analyses compared unwashed cell salvage to the alternative transfusion strategies.

Table 23 summarises the unit costs of transfusion and transfusion-related services.[5,72,77,78] The cost per unit of allogeneic blood has risen by 41% between the financial years 1999 and 2000 and 2003–4. This exceeds the total rate of health and community service inflation (12.2%) over the same period.[79] The additional increase in costs is primarily due to the costs of improving the safety of blood products, falls in demand for blood products that increase the fixed cost per unit of blood and investment in the NHS BTA to secure future donor supply and organisational capacity.[5]

Cost of transfusion strategies

The number of units of blood donated or salvaged pre- or perioperatively and the number of units of allogeneic blood transfused perioperatively were estimated from the trials included in the systematic reviews. *Table 24* presents the mean units of allogeneic blood transfused for the allogeneic transfusion strategy. This was calculated from

TABLE 23 *Units costs of transfusion and transfusion-related services*

	Average (range) unit cost (£, 2003–4)	Source
Group and save (per sample)	7.89	SMUHT[a]
Cross-match:		
Allogeneic blood (per sample)	23.24	NHS BTA[b]
Autologous blood (per sample)	23.24	NHS BTA[b]
Collection of autologous blood (per unit)	81.32	NHS BTA[b]
Unit of red cells, allogeneic blood	111.16	NHS BTA[b]
Blood collection bag (ANH)	5.00	NHS BTA[b]
Giving sets	2.71	SMUHT[a]
EPO	8.38/1000 units	BNF[c]
FSs	65.00/ml (Tisseel Kit)	MIMS[d]
AFs	20.53/500000 KIU vial	BNF[c]
Outpatient visit (preoperative)[a]	76.00	HRGs[e]
Inpatient day:		
All procedures	152.00	SMUHT[a]
Operating theatre (per minute)	11.15 (10.89–11.40)	SMUHT[a]
ICU per day	1493.00	SMUHT[a]
CCU per day	282.00	SMUHT[a]

[a] South Manchester University Hospital Trust local activity and financial data.
[b] National Blood Service.[5]
[c] British National Formulary.[77]
[d] Monthly Index of Medical Specialties.[78]
[e] Cost of preoperative outpatient visit to collect autologous blood and/or treatment with EPO estimated as cost of blood transfusion visit, from the Department of Health Reference Costs: follow-up outpatient visit costs.[72]

TABLE 24 *Units of allogeneic blood transfused in patients having an allogeneic transfusion*

	All procedures	Cardiac procedures	Orthopaedic procedures
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**
AB[a]	3.13 (2.52 to 3.73)[a]	3.13 (2.41 to 3.86)[a]	1.92 (1.40 to 2.45)[a]
	Mean (95% CI) difference	**Mean (95% CI) difference**	**Mean (95% CI) difference**
All CS	–0.9 (–1.23 to –0.56)	–0.97 (–1.40 to –0.55)	–1.13 (–1.78 to –0.48)
IOCS[b]	–0.64 (–1.45 to +0.17)	–0.46 (–0.86 to –0.05)	–0.64 (–1.45 to +0.17)
POCS[b]	–0.83 (–1.06 to –0.60)	–0.71 (–1.10 to –0.32)	–0.80 (–1.20 to –0.40)
CS washed[b]	–0.93 (–1.49 to –0.36)	–1.04 (–1.73 to –0.36)	–1.25 (–2.16 to –0.34)
CS unwashed[b]	–0.86 (–1.24 to –0.47)	–0.89 (–1.46 to –0.31)	–0.86 (–1.24 to –0.47)
PAD[c]	–1.9 (–2.7 to –1.1)	–1.24 (–2.44 to –0.04)	–1.01 (–1.28 to –0.74)
PAD + EPO[d]	–1.9 (–2.7 to –1.1)	–1.24 (–2.44 to –0.04)	–1.01 (–1.28 to –0.74)
ANH[e]	–1.9 (–2.7 to –1.1)	–1.24 (–2.44 to –0.04)	–1.01 (–1.28 to –0.74)
AFs[f]	–0.96 (–1.32 to –0.59)	–0.96 (–1.32 to –0.59)	–0.96 (–1.32 to –0.59)
FSs[g]	–0.56 (–0.84 to –0.29)	–0.62 (–0.98 to –0.26)	–0.48 (–0.91 to –0.05)
EPO[h]	NA	NA	NA

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; NA, estimate not available owing to lack of reported data; POCS, postoperative cell salvage.
[a] Estimates of allogeneic transfusion (with and without restrictive transfusion protocol) derived from pooling the control arms reported in the updated systematic reviews of CS and PAD and the published systematic reviews of the remaining interventions[13,21,29–33] and Chapter 3.
[b] Estimates derived from updated systematic review of CS[30] and Chapter 3.
[c] Estimates derived from updated systematic review of PAD[13] and Chapter 3.
[d] Estimates derived from published systematic review of PAD plus EPO, risk difference PAD plus EPO vs PAD.[21]
[e] Estimates derived from published systematic review of ANH.[29]
[f] Estimates derived from published systematic review of AFs.[31]
[g] Estimates derived from published systematic review of FSs.[32]
[h] Estimates derived from published systematic review of EPO.[21]

TABLE 25 *Cost of allogeneic blood per person having an allogeneic blood transfusion (£, 2003–4)*

	All procedures	Cardiac procedures	Orthopaedic procedures
	Mean (95% CI)[a,b]	**Mean (95% CI)[a,b]**	**Mean (95% CI)[a,b]**
AB	348 (280 to 415)	348 (280 to 415)	213 (156 to 272)
	Mean (95% CI) difference[a,b]	**Mean (95% CI) difference[a,b]**	**Mean (95% CI) difference[a,b]**
All CS	–100 (–137 to –62)	–108 (–156 to –61)	–126 (–198 to –53)
IOCS	–71 (–161 to +19)	–51 (–96 to –6)	–71 (–161 to +19)
POCS	–92 (–118 to –67)	–79 (–122 to –36)	–89 (–133 to –44)
CS washed	–103 (–166 to –40)	–116 (–192 to –40)	–139 (–240 to –38)
CS unwashed	–96 (–138 to –52)	–99 (–162 to –34)	–96 (–138 to –52)
PAD	–211 (–300 to –122)	–138 (–271 to –4)	–112 (–142 to –82)
PAD + EPO	–211 (–300 to –122)	–138 (–271 to –4)	–112 (–142 to –82)
ANH	–211 (–300 to –122)	–138 (–271 to –4)	–112 (–142 to –82)
AFs	–107 (–147 to –66)	–107 (–147 to –66)	–107 (–147 to –66)
FSs	–62 (–93 to –32)	–69 (–109 to –29)	–53 (–101 to –6)
EPO[c]	348 (280 to 415)	348 (280 to 415)	213 (156 to 272)

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Mean cost estimated as mean (or best guess estimate) resource use multiplied by average unit cost.
[b] Minimum and maximum costs estimated as minimum or maximum resource use multiplied by average unit cost.
[c] Cost of allogeneic blood in the EPO strategy assumed to be equal to that of the allogeneic strategy, owing to lack of data on quantity of allogeneic blood transfused in EPO trials.

pooling the data from the control arms of the trials included in the systematic reviews reported in Chapter 3. *Table 24* also gives the WMDs in units of allogeneic blood transfused between the allogeneic transfusion strategy and the alternative transfusion strategies. The mean cost of allogeneic blood per transfusion for the allogeneic blood transfusion strategy is shown in *Table 25*. *Table 25* also gives the WMD in cost of allogeneic blood between the allogeneic blood transfusion strategy and the other transfusion strategies.

The resources used to estimate the pre- and perioperative costs of blood transfusion are summarised in *Tables 26* and *27*. The use of cross-matching, group and screen tests and the number of units of blood cross matched preoperatively, plus the number of giving sets used, were estimated from secondary analysis of two trial databases held at SMUHT. The combined databases included details of the use of these resources for 303 patients (151 allocated to the control arm of allogeneic blood and 152 allocated to the active arm). The active arm included ANH only (n = 78) or cell salvage plus ANH (n = 74). The drug doses for the strategies that included EPO, AFs and FSs were estimated from those reported in the trials included in the systematic reviews.

The costs of ANH include the costs of cannulation to collect the blood, bags to store whole blood during the operation and crystalloids and/or colloids to maintain the haemodynamic volume of the patient during the perioperative period. Analysis of the SMUHT trial datasets indicates that the costs of cannulisation and crystalloids or colloids were incurred for both the patients allocated to ANH and control patients. The additional costs of ANH were estimated from the costs of bags for collection of the blood prior to the operation.

Tables 28 and *29* summarise the pre- and postoperative costs associated with each of the alternative transfusion strategies.

Cost of operation and index hospital admission

The cost of the index admission was estimated as the cost of the elective surgical procedure plus the cost of the hospital inpatient stay. Analysis of the trials included in the systematic reviews that reported the length of surgery found that there were no differences between the transfusion strategies (190 minutes for alternative strategies versus 195 minutes for the allogeneic transfusion strategy).

Table 30 presents the mean length of inpatient stay associated with the allogeneic transfusion strategy. This was calculated from pooling the data from the control arms of the trials included in the systematic reviews reported in Chapter 3. *Table 30*

TABLE 26 *Preoperative use of transfusion-related services*

	AB	IOCS	POCS	CSW	CSUW	PAD	PAD + EPO	ANH	EPO	FSs	AFs
Group and screen (%)	100[a] (0–100)[b]	100[a] (0–100)[b]	100[a] (0–100)[b]	100[a] (0–100)[b]	100[a] (0–100)[b]	100[d]	100[d]	100[a] (0–100)[b]	100[c] (0–100)[b]	100[c] (0–100)[b]	100[c] (0–100)[b]
Cross-match (%)	78[a] (48–100)[b]	48[a] (0–100)[b]	48[a] (0–100)[b]	48[a] (0–100)[b]	48[a] (0–100)[b]	100[d]	100[d]	48[a] (0–100)[b]	78[c] (48–100)[b]	78[c] (48–100)[b]	78[c] (48–100)[b]
No. of PAD donations	0	0	0	0	0	2.13 (1.78–4)[c]	2.90 (2–3.97)[c]	0	0	0	0
Drug dose/week (U/kg):											
Min.	0	0	0	0	0	0	1646[e]	0	1761[e]	0	0
Max.	0	0	0	0	0	0	2674[e]	0	3887[e]	0	0
No. of visits for drug therapy	0	0	0	0	0	0	3[d]	0	1[c]	0	0

AB, allogeneic blood; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage; CSW, washed cell salvage; CSUW, unwashed cell salvage.

[a] Estimated from SMUHT trial data for allogeneic blood, ANH and cell salvage.

[b] Assumed range.

[c] Assumed equal to allogeneic blood.

[d] Estimated from the assumption that PAD patients would donate sufficient blood preoperatively and not require group and screen tests for allogeneic blood and that all PAD products are cross-matched to the donating patient to minimise blood service error.

[e] Average drug dose reported in systematic reviews of PAD plus EPO and EPO.

TABLE 27 *Perioperative use of transfusion-related services*

	AB	IOCS	POCS	CS washed	CS unwashed	PAD	PAD + EPO	ANH	EPO	FSs	AFs
Intra-/postoperative transfusion given											
Additional allogeneic blood match	0.02[a]	0.92[b]	0.92[b]	0.92[b]	0.92[b]	1	1	0.92[a]	0.02[c]	0.02[c]	0.02[c]
Giving sets used (mean no.)	0.85[a]	1.03[b]	1.03[b]	1.03[b]	1.03[b]	1.03[b]	1.03[b]	1.03[a]	0.85[c]	0.85[c]	0.85[c]
FSs (applications)	0	0	0	0	0	0	0	0	0	1(1–2[d])	0
AFs (low-dose regimen)	0	0	0	0	0	0	0	0	0	0	1 low-dose regimen[e] (1 pump prime dose[f] – 1 high-dose regimen[g])

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Estimated from SMUHT data.
[b] Assumed equal to ANH.
[c] Assumed equal to allogeneic blood.
[d] Assumed dose for sensitivity analysis.
[e] Cost estimated as low-dose aprotinin (Half Hammersmith Regimen) as described in the Cochrane systematic review of antifibrinolytics.[31]
[f] Cost estimated as pump prime dose aprotinin as described in the Cochrane systematic review of antifibrinolytics.[31]
[g] Cost estimated as high-dose aprotinin (Full Hammersmith Regimen) as described in the Cochrane systematic review of antifibrinolytics.[31]

TABLE 28 *Summary of preoperative costs: all procedures*

	Mean[a] (range)[b] (£, 2003)
AB	20 (11–31)
IOCS	13 (0–26)
POCS	13 (0–26)
CS washed	13 (0–26)
CS unwashed	13 (0–26)
PAD	350 (330–510)
PAD + EPO	509 (410–599)
ANH	13 (0–26)
AFs	20 (11–31)
FSs	20 (11–31)
EPO	128 (102–140)

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Mean cost estimated as mean (or best guess estimate) resource use multiplied by average unit cost.
[b] Minimum and maximum costs estimated as minimum or maximum resource use multiplied by average unit cost.

also presents the WMDs in hospital inpatient stay between the allogeneic transfusion strategy and the alternative transfusion strategies. These were estimated from the trials reporting these data included in the systematic reviews. *Table 30* further reports the mean length of stay recorded in the two clinical trial databases at SMUHT and the average length of stay reported in the national Hospital Episode Statistics for all surgical procedures and by cardiac and orthopaedic procedures.[71]

Table 31 reports the costs of the hospital stay for the index admission, for patients with no complications. These were estimated from the average lengths of stay reported in *Table 30* multiplied by the average unit cost per day.

Costs of adverse events

Table 32 presents the mean length of stay and cost per day associated with events related to transfusion or surgery and transfusion-related adverse events. It was assumed that the adverse events caused by either transfusion or surgery, transfusion only and bacterial contamination would occur within 1 day of the transfusion. The cost of the index admission for each of these adverse events was estimated as

$$[(\text{length of stay}_{IA} - \text{length of stay}_{C}) \times \text{cost/day}_{IA}] + (\text{length of stay}_{C} \times \text{cost/day}_{C})$$

where length of stay_{IA} = mean length of stay of the index admission for the transfusion strategy and length of stay_{C} = mean length of stay of the adverse event.

These costs were estimated separately for each adverse event and replaced the mean cost of the index admission, for pathways in the model where the adverse event occurred. It was assumed that the duration of most of the transfusion or surgical adverse events and the adverse events related to transfusion alone would not extend past the index admission period. This meant that no additional costs were estimated for these adverse events for the timeframes of 1, 10 and 30 years. However, it was assumed that there would be longer term costs associated with disabling stroke. The probability of disabling stroke, for patients having a stroke, was estimated as 0.58 and the annual cost of disabling stroke was estimated at £11,000. The additional annual cost for non-disabling stroke was assumed to be zero.

With the exception of bacterial contamination (see above), transfusion-transmitted infections were

TABLE 29 *Summary of other peri-operative transfusion-related costs, £, 2003*

	Mean (range) (£, 2003)		
	All procedures	Cardiac procedures	Orthopaedic procedures
AB	3.00	3.00	3.00
IOCS	138	138	138
POCS	138	138	138
CS washed	138	138	138
CS unwashed	114	114	114
PAD	26	26	26
PAD + EPO	26	26	26
ANH	29	29	29
AFs	118 (85–232)	118 (85–232)	118 (85–232)
FSs	68 (68–133)	68 (68–133)	68 (68–133)
EPO	3.00	3.00	3.00

CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.

TABLE 30 *Mean length of stay (days)*

	All procedures	Cardiac procedures	Orthopaedic procedures
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**
AB[a]	13 (10 to 16)[a]	9.56 (6.77 to 12.35)	10.59 (5.94 to 15.25)
	Mean (95% CI) difference	**Mean (95% CI) difference**	**Mean (95% CI) difference**
All CS	–1.28 (–2.65 to 0.08)	–0.97 (–3.49 to 1.56)	–2.60 (–4.76 to –0.44)
IOCS[b]	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)
POCS[b]	–1.28 (–2.65 to 0.08)	–0.97 (–3.49 to 1.56)	–2.60 (–4.76 to –0.44)
CS washed[b]	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)
CS unwashed[b]	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)	–1.28 (–2.65 to 0.08)
PAD[c]	–0.74 (–1.86 to 0.39)	–0.74 (–1.86 to 0.39)	–0.74 (–1.86 to 0.39)
PAD + EPO[d]	–0.74 (–1.86 to 0.39)	–0.74 (–1.86 to 0.39)	–0.74 (–1.86 to 0.39)
ANH[e]	0.21 (–1.26 to 1.68)	0.21 (–1.26 to 1.68)	0.21 (–1.26 to 1.68)
AFs[f]	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)
FSs[g]	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)
EPO[h]	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)	–0.89 (–2.51 to 0.73)
Hospital Episode Statistics	Not estimated	10.00	10.28
Reference Costs (elective admissions)	Not estimated	7.61	10.65

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.
[a] Estimates of allogeneic transfusion (with and without restrictive transfusion protocol) derived from pooling the control arms reported in the updated systematic reviews of CS and PAD and the published systematic reviews of the remaining interventions[13,21,29–33] and Chapter 3.
[b] Estimates derived from updated systematic review of CS[30] and Chapter 3.
[c] Estimates derived from updated systematic review of PAD[13] and Chapter 3.
[d] Estimates derived from published systematic review of PAD plus EPO, risk difference PAD plus EPO vs PAD.[21]
[e] Estimates derived from published systematic review of ANH.[29]
[f] Estimates derived from published systematic review of AFs.[31]
[g] Estimates derived from published systematic review of FSs.[32]
[h] Estimates derived from published systematic review of EPO.[21]

TABLE 31 *Cost of index admission, no complications*

	All procedures	Cardiac procedures	Orthopaedic procedures
	Mean (95% CI)/£	**Mean (95% CI)/£**	**Mean (95% CI)/£**
AB[a]	1976 (1520 to 2432)[a]	1453 (1029 to 1877)	1610 (903 to 2318)
	Mean (95% CI) difference	**Mean (95% CI) difference**	**Mean (95% CI) difference**
All CS			
IOCS[b]	–195 (–403 to 12)	–195 (–403 to 12)	–195 (–403 to 12)
POCS[b]	–195 (–403 to 12)	–147 (–530 to 237)	–395 (–724 to –67)
CS washed[b]	–195 (–403 to 12)	–195 (–403 to 12)	–195 (–403 to 12)
CS unwashed[b]	–195 (–403 to 12)	–195 (–403 to 12)	–195 (–403 to 12)
PAD[c]	–112 (–283 to 59)	–112 (–283 to 59)	–112 (–283 to 59)
PAD + EPO[d]	–112 (–283 to 59)	–112 (–283 to 59)	–112 (–283 to 59)
ANH[e]	32 (–192 to 255)	32 (–192 to 255)	32 (–192 to 255)
AFs[f]	–135 (–382 to 111)	–135 (–382 to 111)	–135 (–382 to 111)
FSs[g]	–135 (–382 to 111)	–135 (–382 to 111)	–135 (–382 to 111)
EPO[h]	–135 (–382 to 111)	–135 (–382 to 111)	–135 (–382 to 111)

AB, allogeneic blood; CS, cell salvage; IOCS, intraoperative cell salvage; POCS, postoperative cell salvage.

TABLE 32 *Costs of adverse events*

Transfusion complication	Source	Length of stay (days)	Cost/day (£)
Other cardiac problems	Reference costs[a]	2.94	413[f]
Renal dysfunction (acute renal failure)	Reference costs[a]	5.68	239[f]
Non-fatal MI	Reference costs[a]	8.91	110[f]
Stroke	Reference costs[a]	8.76	193[f]
Thrombosis	Reference costs[a]	3.32	228[f]
Bleed and reoperation	SMUHT[b]	190 minutes	11/minute
Wound complications	Reference costs[a]	12	175[f]
Transfusion-related graft vs host disease	HES[c], SHOT[d], CIPFA[e]	6.28	372–1434
Incorrect blood component transfused	HES[c], SMUHT[b]	11.9	152
Haemolytic transfusion reaction:			
Acute	HES[c], CIPFA[e]	11.9	585
Delayed	HES[c], CIPFA[e]	11.9	585
Post-transfusion purpura (allergic purpura)	HES[c], CIPFA[e]	2.5	585
TRALI (44% ICU admission 1–9 days)	SHOT[d], SMUHT[b]	1.98 (ICU)	1434
Fatal air embolism	HES[c], CIPFA[e]	10	251
Bacterial contamination	HES[c], SMUHT[b]	8.4	152
vCJD			
HBV acute	HES[c], CIPFA[e]	4.7	340
HBV chronic	HES[c], CIPFA[e]	7.4	340
HCV acute	HES[c], CIPFA[e]	4.6	244
HCV chronic	HES, CIPFA[e]	3.5	244
HIV	Reference costs[a]	6.97	428[f]
HTLV	HES[c], Reference costs[a]	1	428[g]
Malaria	HES[c], CIPFA[e]	3.4	340
Hepatitis A acute	HES[c], CIPFA[e]	5.1	340
Hepatitis B acute	HES[c], CIPFA[e]	4.7	340
Hepatitis C acute	HES[c], CIPFA[e]	4.6	340
Hepatitis A contact/exposure to or carrier	HES[c], CIPFA[e]	1.6	340
Hepatitis B contact/exposure to or carrier	HES[c], CIPFA[e]	1.6	340
Hepatitis C contact/exposure to or carrier	HES[c], CIPFA[e]	1.6	340
HIV contact/exposure/carrier/asymptomatic	HES[c], CIPFA[e]	4.1	428
HIV (outpatient visit)	Reference costs[a]	1	691[f]
HTLV (outpatient visit)	Reference costs[a]	1	190[f,g]
Malaria (outpatient visit)	Reference costs[a]	1	190[f,g]
Hepatitis A (outpatient visit)	Reference costs[a]	1	190[f,g]
Hepatitis B (outpatient visit)	Reference costs[a]	1	190[f,g]
Hepatitis C (outpatient visit)	Reference costs[a]	1	190[f,g]

[a] Reference costs.[72]
[b] South Manchester University Hospitals Trust.
[c] Hospital Episode Statistics.[71]
[d] SHOT.[6,68,69]
[e] Estimated as reference cost for an inpatient episode divided by the average length of stay for an inpatient episode (CIPFA, Chartered Institute of Public Finance and Accountancy).
[f] Assumed equal to infectious disease outpatient visits and costs reported in the reference cost data set.[72]
[g] Length of stay assumed equivalent to that of aplastic anaemia.[6,68,69,72]

assumed to be diagnosed after discharge from the index admission. The cost of these events for the 12-month follow-up period was estimated as the cost of two additional hospital admissions for malaria and HTLV (*Table 32*). For HAV, HBV and HCV, the cost for the 12-month follow-up period was estimated as the cost of hospital inpatient care for two acute episodes plus three outpatient visits. For HIV, the cost for the 12-month follow-up period was estimated as the cost of two episodes of hospital inpatient care for exposure to the HIV virus plus three outpatient visits (*Table 32*). For HAV, HBV and HCV, the cost of a chronic admission was used. For HIV, the cost of hospital inpatient care for exposure to the HIV virus was used (*Table 32*). The costs of drug therapy were included in the costs for the longer timeframes of 1 year or more.

For the secondary analysis to explore the impact of using a longer time horizon, the lifetime costs of transfusion-transmitted infection were estimated.

TABLE 33 *Utility values assigned to different health states*

	All procedures[a]		
	Mean	**25th percentile**	**75th percentile**
Utility values surgery to hospital discharge[b]			
No adverse events	0.64	0.59	0.80
Adverse events	0.64	0.59	0.80
Utility values hospital discharge to 30 days	0.88	0.80	1.00
No adverse events[c]	0.88	0.80	1.00
Stroke[d]	0.64	0.31	0.88
Other adverse events[c]	0.88	0.80	1.00
1–12 months following surgery			
No adverse events[e]	0.93	0.85	1.00
Stroke[b]	0.64	0.31	0.88
vCJD[e]	0.93	0.85	1.00
HAV/HBVHCV:			
Acute[e]	0.93	0.85	1.00
Chronic[c]	0.88	0.80	1.00
HIV[c]	0.88	0.80	1.00
HTLV[c]	0.88	0.80	1.00
Malaria[c]	0.88	0.80	1.00

[a] Utility values estimated from the Health Survey for England 1996.[73]
[b] Utility values estimated from those reported for long-standing limiting illness.[73]
[c] Utility values estimated from those reported for long-standing non-limiting illness.[73]
[d] Utility values estimated from those reported by Dorman and colleagues[81] for stroke.
[e] Utility values estimated from those reported for no long-standing illness.[73]

The lifetime costs of HIV were derived from a recent economic model that modelled the lifetime costs and QALYs associated with HIV.[67] The costs included the costs of health services and highly active antiretroviral therapy. The cost data were converted from US dollars using purchasing power parity rates.[80] The lifetime costs for HIV were estimated as £161,250 (range £82,079–255,833). The lifetime costs for HIV were used to represent high estimates of the lifetime costs of hepatitis, HTLV and vCJD.

Outcomes, utility and QALYs

The review of the published economic evaluation literature (Chapter 4) indicated that, to date, economic analyses have concentrated on the morbidity due to transfusion-transmitted infections. There was no evidence about the utility associated with complications due to surgery or transfusion, or complications due to transfusion only. In addition, this economic model focuses on elective surgery for mainly long standing or chronic health states. The utility data used for the model are summarised in *Table 33*.[73,81]

The 1996 Health Survey for England[73] suggests that the mean utility values of health states associated with long-standing illness range between 0.64 for limiting illness and 0.88 for non-limiting illness. The mean utility values for people with no long-standing illness are estimated at 0.93. These are similar to the estimates of utility for stroke and other surgical or transfusion-related complications.[81] However, they are lower than the estimates of health states associated with transfusion-transmitted illness, which were used in the published economic analyses (0.75–0.99).[36–38,57–65] These data suggest that the impact of most of the adverse events associated with transfusion on health and HRQoL are likely to be minimal compared with the impact of the underlying reasons for surgery, the short-term disutility associated with surgery and hospital admission. To minimise bias associated with overestimation of the relative impact of transfusion-associated complications, utility values were assigned using the data from the 1996 Health Survey for England.[73] For the secondary analysis to explore the impact of using a longer time horizon, the lifetime QALYs associated with transfusion-transmitted infections were derived from a published study that modelled the lifetime QALYs associated with HIV.[67] The lifetime QALYs were estimated from a distribution based on the minimum and maximum (10 and 13) QALYS gained.

Chapter 7

Results of the economic model

Primary analysis

Expected costs and outcomes at 1 month post-surgery, all surgical procedures

Table 34 presents the expected costs of the alternative transfusion strategies for the 1-month timeframe. The expected outcomes of the alternative transfusion strategies for the 1-month timeframe are shown in *Table 35*.

Table 34 indicates that cell salvage is associated with expected costs per person that are similar to, or slightly lower than those of the alternative transfusion strategies. The 2.5th to 97.5th percentile ranges for all the strategies overlap. This suggests that the differences between cell salvage and alternative transfusion strategies may be due to variations in the data rather than true differences in the cost of the alternative transfusion strategies.

The data in *Table 35* suggest that cell salvage is associated with similar rates of lives gained for all the transfusion strategies. Cell salvage is associated with improved outcomes, in terms of lives and life-years gained with no adverse events and QALYs, than most of the alternative transfusion strategies. The exception is the PAD transfusion strategy, which is associated with higher expected outcomes than cell salvage. As with the expected costs, the 2.5th to 97.5th percentile ranges for all the strategies overlap. This suggests that the differences in outcomes between cell salvage and alternative transfusion strategies may be due to variations in the data rather than true differences in the outcomes of the alternative transfusion strategies.

TABLE 34 *Expected cost per person: all surgical procedures*

	Mean cost (£, 2003–4) (2.5th; 97.5th percentile)
AB	5006 (4550; 5454)
All CS	4930 (4377; 5426)
IOCS	4953 (4391; 5467)
POCS	4941 (4387; 5443)
CS washed	4915 (4365; 5421)
CS unwashed	4886 (4309; 5376)
PAD	5078 (4595; 5556)
PAD + EPO	5266 (4779; 5730)
ANH	4818 (4352; 5270)
AFs	4958 (4473; 5423)
FSs	4927 (4429; 5403)
EPO	4958 (4448; 5443)

Incremental cost-effectiveness of cell salvage at 1 month post-surgery, all surgical procedures

The relative cost-effectiveness of cell salvage was assessed by comparison of the ICER, calculation of the CEACs and the net benefit of cell salvage. The

TABLE 35 *Expected outcome per person, by type of outcome: all surgical procedures*

	Mean no. of patients alive (2.5th; 97.5th percentile)	Mean no. of patients alive with no adverse events (2.5th; 97.5th percentile)	Mean life-years no adverse events (2.5th; 97.5th percentile)	Mean QALYs (2.5th; 97.5th percentile)
AB	0.974 (0.915; 1.000)	0.552 (0.466; 0.642)	0.0454 (0.0383; 0.0528)	0.0632 (0.0528; 0.0736)
All CS	0.974 (0.915; 1.000)	0.562 (0.473; 0.653)	0.0462 (0.0389; 0.0537)	0.0680 (0.0587; 0.0768)
IOCS	0.974 (0.915; 1.000)	0.562 (0.473; 0.654)	0.0462 (0.0389; 0.0537)	0.0679 (0.0583; 0.0767)
POCS	0.974 (0.915; 1.000)	0.562 (0.473; 0.654)	0.0462 (0.0389; 0.0537)	0.0679 (0.0584; 0.0768)
CS washed	0.974 (0.915; 1.000)	0.562 (0.474; 0.654)	0.0462 (0.0389; 0.0537)	0.0683 (0.0592; 0.0770)
CS unwashed	0.974 (0.915; 1.000)	0.561 (0.473; 0.653)	0.0462 (0.0389; 0.0537)	0.0677 (0.0581; 0.0766)
PAD	0.974 (0.915; 1.000)	0.565 (0.463; 0.665)	0.0464 (0.0381; 0.0547)	0.0692 (0.0606; 0.0778)
PAD + EPO	0.974 (0.915; 1.000)	0.561 (0.462; 0.661)	0.0461 (0.0380; 0.0543)	0.0673 (0.0572; 0.0764)
ANH	0.974 (0.915; 1.000)	0.572 (0.483; 0.661)	0.0470 (0.0397; 0.0543)	0.0675 (0.0579; 0.0764)
AFs	0.974 (0.915; 1.000)	0.553 (0.466; 0.642)	0.0455 (0.0383; 0.0528)	0.0632 (0.0528; 0.0736)
FSs	0.974 (0.915; 1.000)	0.553 (0.466; 0.642)	0.0455 (0.0383; 0.0528)	0.0632 (0.0528; 0.0736)
EPO	0.974 (0.915; 1.000)	0.553 (0.466; 0.642)	0.0455 (0.0383; 0.0528)	0.0632 (0.0528; 0.0736)

TABLE 36 *Incremental cost-effectiveness: all cell salvage versus allogeneic transfusion strategies, all surgical procedures, 1-month timeframe*

	Net cost of cell salvage (£) (2.5th; 97.5th percentile)	Net QALY of cell salvage (2.5th; 97.5th percentile)	Cost/QALY gained (£) (mean values only)
AB	–76 (–368; 208)	0.00477 (–0.00114; 0.01497)	CS dominates
AFs	–28 (–353; 282)	0.00477 (–0.00114; 0.01497)	CS dominates
FSs	3 (–305; 319)	0.00477 (–0.00114; 0.01497)	629
EPO	–28 (–326; 306)	0.00477 (–0.00114; 0.01497)	CS dominates

TABLE 37 *Net benefits of cell salvage (£)[a] compared with allogeneic methods of transfusion: all surgical procedures, 1-month timeframe*

	AB	FS	AF	EPO
Mean	220	141	171	171
2.5th percentile	–95	–194	–162	–173
97.5th percentile	686	616	666	633

[a] Net benefit equals net cost minus the willingness-to-pay value for a net gain in QALYs.

QALY was used as the primary outcome measure in the calculation of the ICER. The CEACs present the proportion of simulations when cell salvage has an ICER less than the range of ceiling ratio willingness to pay values to gain a QALY. The CEAC indicates the probability that cell salvage is cost-effective when compared with alternative transfusion strategies. The CEACs presented below are estimated from the incremental costs and effects of cell salvage. They do not provide a comparison between the alternative transfusion strategies. For example, the CEAC for allogeneic blood provides an estimate of the cost-effectiveness of cell salvage compared with allogeneic blood. The CEAC for allogeneic blood cannot be compared with that for PAD.

The comparison of cell salvage with other transfusion strategies is based on analyses using pooled data for all types of cell salvage and the costs of washed cell salvage for the primary analysis. The secondary analyses explore whether the type or timing of cell salvage affect the relative cost-effectiveness of cell salvage.

Cell salvage versus allogeneic transfusion strategies

Tables 36 and *37* and *Figure 11* indicate that cell salvage is cost-effective when compared with the allogeneic blood transfusion strategy. However, cell salvage is associated with higher costs and higher QALYs when compared with FSs, AFs or EPO to reduce exposure to allogeneic blood.

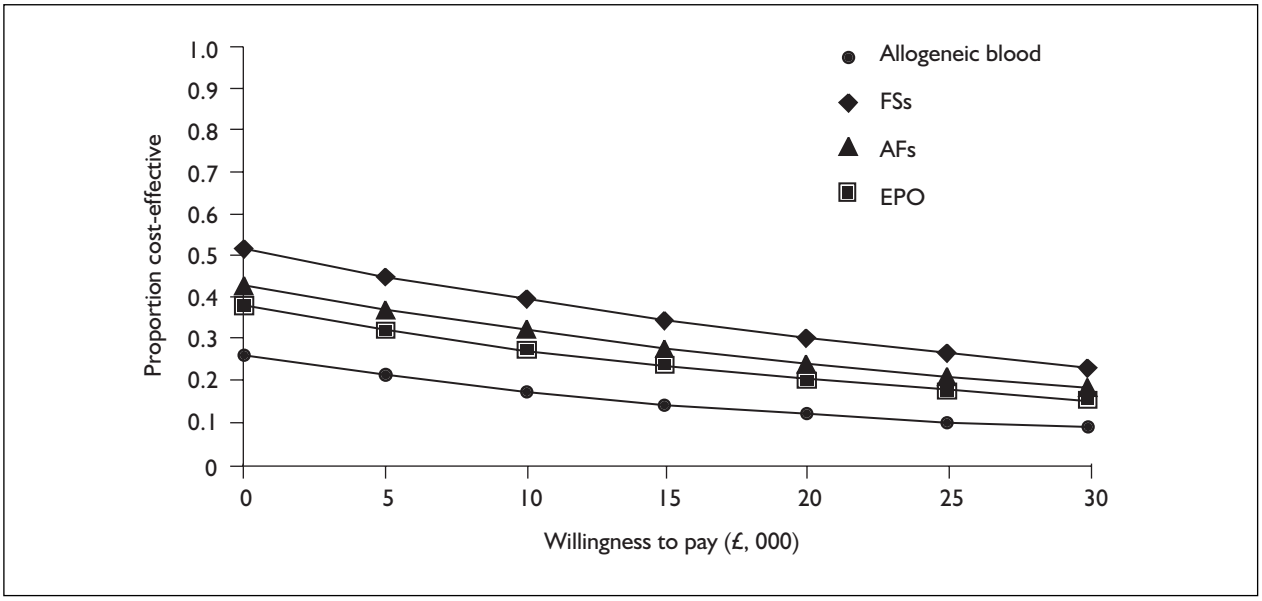

FIGURE 11 *Incremental CEACs for allogeneic blood transfusion strategies compared with cell salvage, all surgical procedures, 1-month timeframe*

TABLE 38 *Incremental cost-effectiveness: all cell salvage versus autologous transfusion strategies, all surgical procedures, 1-month timeframe*

	Net cost (£) (2.5th; 97.5th percentile)	Net QALY (2.5th; 97.5th percentile)	Cost/QALY gained (£) (mean values only)
PAD	–148 (–471; 86)	–0.00120 (–0.00456; 0.00062)	123,333[a]
PAD + EPO	–336 (–610; –128)	0.00078 (–0.00083; 0.00282)	CS dominates
ANH	112 (–165; 287)	0.00050 (–0.00106; 0.00249)	224,000[b]

[a] Incremental cost per QALY gained by PAD compared with cell salvage.
[b] Incremental cost per QALY gained by cell salvage compared with ANH.

Figure 11 shows the CEACs for allogeneic blood, FSs, AFs and EPO compared with cell salvage. *Figure 11* indicates that the proportion of simulations when these interventions were more cost-effective was less than 50%. This means that cell salvage was more cost-effective than these alternatives in more than 50% of simulations. The probability that cell salvage was cost-effective ranged between 91% if a decision-maker is prepared to pay £30,000 to gain an additional QALY with cell salvage compared with allogeneic blood, and 48% if a decision-maker is not prepared to pay to gain an additional QALY with cell salvage compared with FSs. This indicates that there is a high probability that cell salvage is cost-effective compared with allogeneic blood, FSs, AFs and EPO. In addition, using the ceiling value of £30,000 to gain one QALY, the mean net benefit of cell salvage was between £141 and £220 when compared with these transfusion strategies, indicating that cell salvage could be cost-effective (*Table 37*).

Cell salvage versus other autologous transfusion strategies

Overall, the expected costs of cell salvage were lower than those associated with PAD and PAD plus EPO, but higher than those associated with ANH. Cell salvage was associated with lower QALYs than PAD, but higher QALYs than PAD plus EPO or ANH. *Tables 38* and *39* and *Figure 12* indicate that there is a high probability that cell salvage is cost-effective relative to PAD or PAD plus EPO. However, ANH may be more cost-effective than cell salvage. The proportion of simulations when ANH was more cost-effective than cell salvage was always higher than 50%, with a net benefit in favour of ANH of £97. This means that using a ceiling value of £30,000 to gain one QALY, the net benefit of ANH was higher than the net cost of ANH, when compared with cell salvage. In contrast, the proportion of simulations when PAD or PAD plus EPO were more cost-effective than cell salvage were less than 50% across the range of willingness to pay ceiling values. In addition, using the ceiling value of £30,000 to gain one QALY, the net benefit of these transfusion strategies was lower than their net cost, when compared with cell salvage.

TABLE 39 *Net benefits of all cell salvage (£)[a] compared with alternative methods of transfusion: all surgical procedures, 1-month timeframe*

	PAD	PAD + EPO	ANH
Mean	112	359	–97
2.5th percentile	–167	138	–282
97.5th percentile	457	633	184

[a] Net benefit equals net cost minus the willingness-to-pay value for a net gain in QALYs.

Secondary analyses

Secondary analyses were conducted to explore whether there were differences between the different methods of cell salvage (washed versus unwashed, intraoperative versus postoperative). Secondary analyses were also used to assess the potential impact on the results of variations in structural variables or the data sets used to populate the model. These included using the subsets of data specific to the:

- different cell salvage techniques
- use of restrictive transfusion protocols for the allogeneic blood transfusion strategy
- the type of surgical procedure evaluated
- the timeframe of the analysis
- different levels of use of cell salvage equipment that affect the average costs of cell salvage.

Technique and timing of cell salvage

Washed cell salvage versus unwashed cell salvage

Unwashed cell salvage is unlikely to be appropriate or acceptable for intraoperative cell

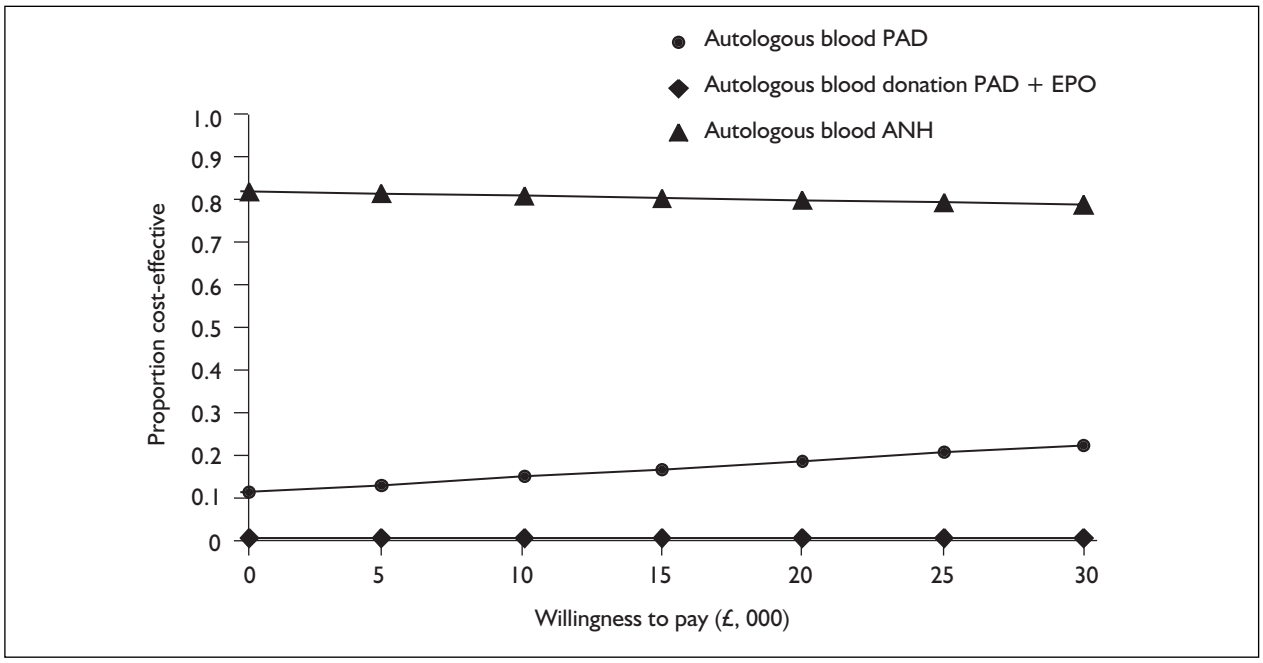

FIGURE 12 *Incremental CEACs for autologous blood transfusion strategies compared with cell salvage, all surgical procedures, 1-month timeframe*

salvage in the UK. The quality of unwashed salvaged blood is highly variable and could contain a number of potentially dangerous contaminants that would not be removed on filtration. For example, excessive haemolysis could result in high levels of free Hb and cell stroma, which on infusion may cause problems with renal function. If excessive amounts of the citrate anticoagulant are reinfused, the patient may become dangerously hypocalcaemic. Coagulation disorders may result from infusion of coagulation factors such as fibrinogen, antithrombin III and fibrinogen degradation products. Microemboli (fat, foreign bodies or cell membranes) can cause pulmonary problems. Current transfusion guidelines refer explicitly to the use of washed rather than unwashed cell salvage.[82] However, the trials included in the systematic reviews of cell salvage did include comparisons of washed versus unwashed cell salvage, so an economic comparison is presented here for completeness. This compares washed with unwashed cell salvage using pooled data for intra- and postoperative timings of the procedure. The expected costs and QALYs for unwashed and washed cell salvage are given in *Tables 34* and *35*. Comparison of the incremental costs and outcomes suggests that unwashed cell salvage is more cost effective than washed cell salvage. *Figure 13* indicates that the proportion of simulations when the unwashed cell salvage transfusion strategy was more cost-effective than washed cell salvage ranged from 70% if a decision-maker is willing to pay £30,000 to gain one QALY to 80% if a decision-maker is prepared to pay nothing to gain one QALY. This suggests that unwashed cell salvage is likely to be more cost-effective than washed cell salvage.

Intraoperative cell salvage versus postoperative cell salvage

Some of the trials of cell salvage used unwashed cell salvage systems both intra- and postoperatively, and some used washed cell salvage systems both intra- and postoperatively. As noted above, it is unlikely that intraoperative unwashed cell salvage would currently be acceptable in the UK. Devices currently available for intraoperative cell salvage all have a washing function, with unwashed systems being reserved exclusively for postoperative salvage where blood is lost into wound drains. New machines have also been developed to enable both intra- and postoperative blood loss to be collected continuously, providing washed cell salvage for the majority of the blood loss experienced. Two separate analyses were used to compare the effect of timing on the cost-effectiveness of cell salvage. The first compared intraoperative versus postoperative cell salvage using the data from the primary analysis for all cell salvage. The second analysis compared the costs and effects of intraoperative cell salvage, using the costs of washed cell salvage equipment, maintenance and consumables, with the costs and effects of postoperative cell salvage, using the costs of unwashed cell salvage disposable equipment. All

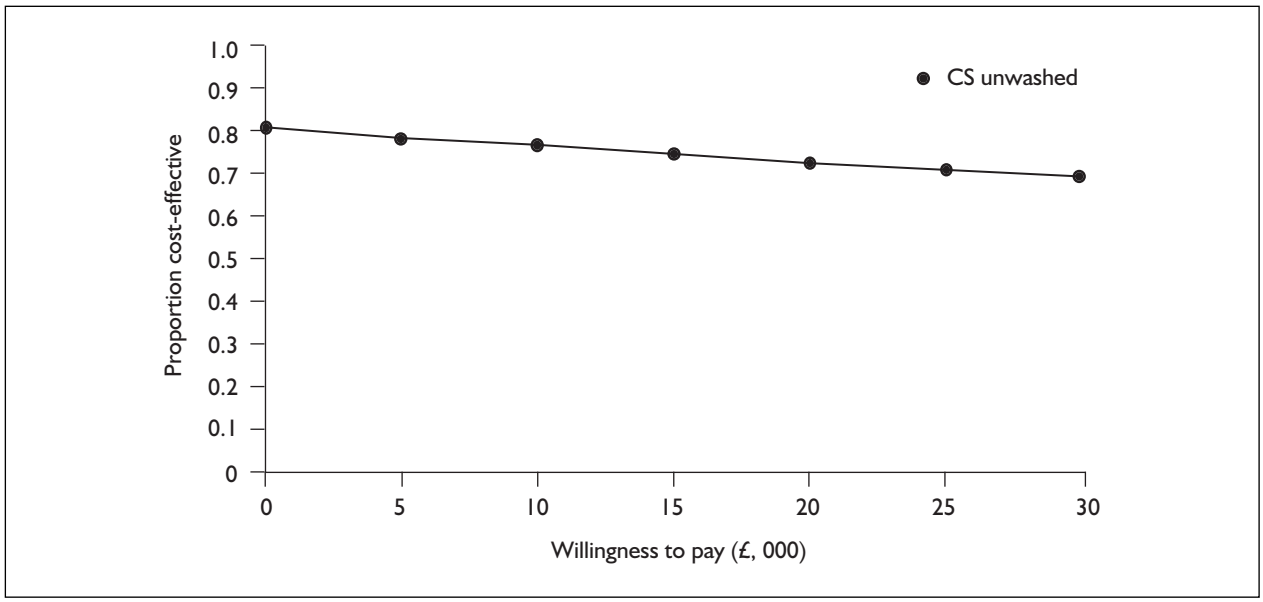

FIGURE 13 *Incremental CEAC for washed cell salvage compared with unwashed cell salvage, all surgical procedures, 1-month timeframe*

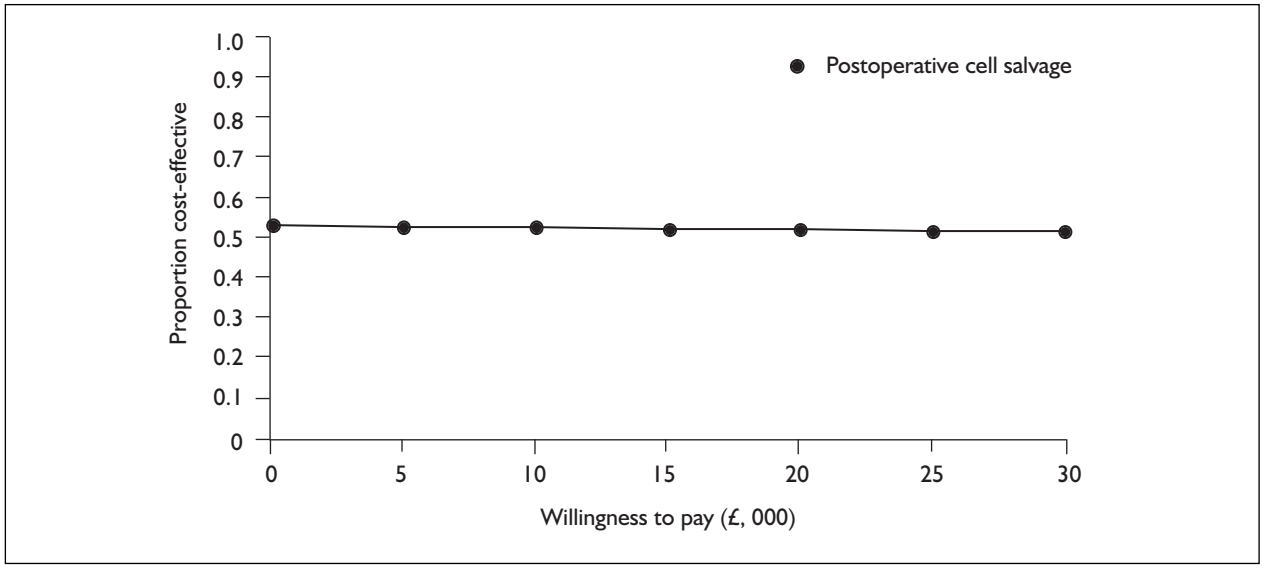

FIGURE 14 *Incremental CEAC for postoperative cell salvage compared with intraoperative cell salvage, all surgical procedures, 1-month timeframe*

of the trials used to estimate data for the intraoperative comparison used washed cell salvage. Of the 18 trials used to estimate data for postoperative cell salvage, four used washed cell salvage. Data from these four studies were excluded from the second comparison, so that this only included data relevant to unwashed postoperative cell salvage.

The expected costs and QALYs for intra- and postoperative cell salvage are described in *Tables 34* and *35*. This suggests that intraoperative cell salvage is associated with higher expected costs and lower expected QALYs than postoperative cell salvage. *Figure 14* indicates that the proportion of simulations when postoperative cell salvage was more cost-effective than intraoperative cell salvage was around 50%, across the range of willingness-to-pay values used for the analysis. This suggests that there are no substantive differences in the expected costs and benefits of intra- and postoperative cell salvage. However, this analysis uses pooled data for washed and unwashed cell salvage. The analysis below

TABLE 40 *Incremental cost-effectiveness: washed intraoperative cell salvage versus unwashed postoperative cell salvage, all surgical procedures, 1-month timeframe*

	Mean cost (£) (2.5th; 97.5th percentile)	**Mean QALY (2.5th; 97.5th percentile)**
Washed intraoperative cell salvage	4953 (4391; 5467)	0.0679 (0.0585; 0.0768)
Net cost of washed intraoperative cell salvage (£) (2.5th; 97.5th percentile)	**Net QALY of washed intraoperative cell salvage (2.5th; 97.5th percentile)**	**Cost/QALY gained (£) (mean values only)**
85 (–55; 218)	–0.00020 (–0.00172; 0.00246)	425,000

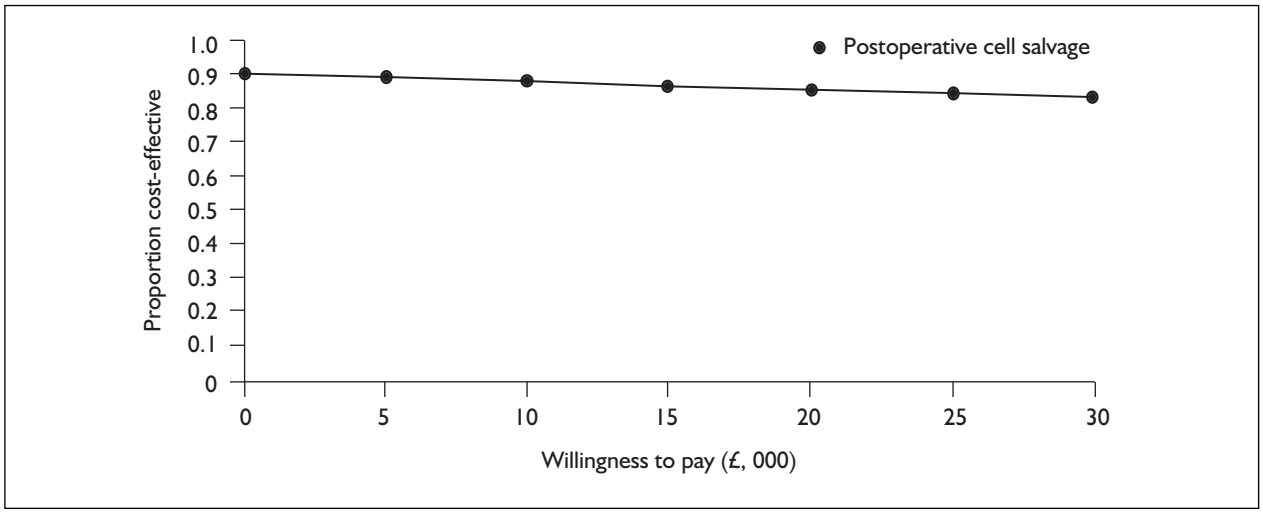

FIGURE 15 *Incremental CEAC for postoperative cell salvage compared with intraoperative cell salvage, all surgical procedures, 1-month timeframe*

compares washed intraoperative cell salvage with unwashed postoperative cell salvage.

Table 40 shows the incremental costs, QALYs and cost-effectiveness ratio for washed intraoperative cell salvage compared with unwashed postoperative cell salvage. These results suggest that washed intraoperative cell salvage is associated with higher expected costs and higher QALYs than unwashed postoperative cell salvage.

Figure 15 indicates that there is a lower probability that washed intraoperative cell salvage was cost-effective when compared with unwashed postoperative cell salvage, across the range of willingness to pay values used for the analysis. However, there may be differences in the rates of adverse events associated with unwashed and washed cell salvage that are not accounted for in this analysis. If unwashed cell salvage is associated with a higher rate of adverse events than washed cell salvage, this could increase the relative cost-effectiveness of washed intraoperative cell salvage.

Importantly, in practice the timing of cell salvage, that is intraoperative or postoperative, relates to the expected dynamics of blood loss for a given procedure. For example, in abdominal aortic aneurysm repair the majority of the blood loss would be expected to occur during surgery, whereas in total knee replacement under tourniquet, surgical bleeding is only initiated at the end of the procedure when the tourniquet is released. Similarly, there are also surgical procedures in which blood loss occurs both during and after the operation. The relative cost-effectiveness of cell salvage according to timing and category of surgical procedure is considered in more detail below.

Type of surgical procedure

Cardiac procedures

This analysis assesses the benefits of cell salvage in cardiac surgery and includes a comparison of all cell salvage in cardiac procedures and a comparison of cell salvage in cardiac procedures according to the timing of cell salvage.

TABLE 41 *Incremental cost-effectiveness: cell salvage versus alternative transfusion strategies, cardiac procedures, 1-month timeframe*

	Mean cost of cell salvage (£) (2.5th; 97.5th percentile)	**Mean QALY of cell salvage (2.5th; 97.5th percentile)**	
CS	4899 (4345; 5430)	0.0686 (0.0587; 0.0773)	
	Net cost of cell salvage (£) (2.5th; 97.5th percentile)	**Net QALY of cell salvage (2.5th; 97.5th percentile)**	**Cost/QALY gained (£) (mean values only)**
Allogeneic blood	–48 (–357; 258)	0.00523 (–0.00118; 0.01565)	All CS dominates AB
PAD	–156 (–478; 114)	–0.00166 (–0.00603; 0.00044)	93,976[a]
PAD + EPO	–332 (–637; 84)	–0.00033 (–0.00204; 0.00108)	100,6061[b]
ANH	95 (–169; 290)	–0.00035 (–0.00193; 0.00148)	ANH dominates CS
AFs	4 (–356; 354)	0.00523 (–0.00118; 0.01565)	765[c]
FSs	44 (–300; 397)	0.00523 (–0.00118; 0.01565)	8,413[c]
EPO	35 (–309; 398)	0.00523 (–0.00118; 0.01565)	6,692[c]

[a] Incremental cost per QALY gained by PAD compared with all cell salvage, cardiac procedures.
[b] Incremental cost per QALY gained by PAD plus EPO compared with all cell salvage, cardiac procedures.
[c] Incremental cost per QALY gained by cell salvage, cardiac procedures.

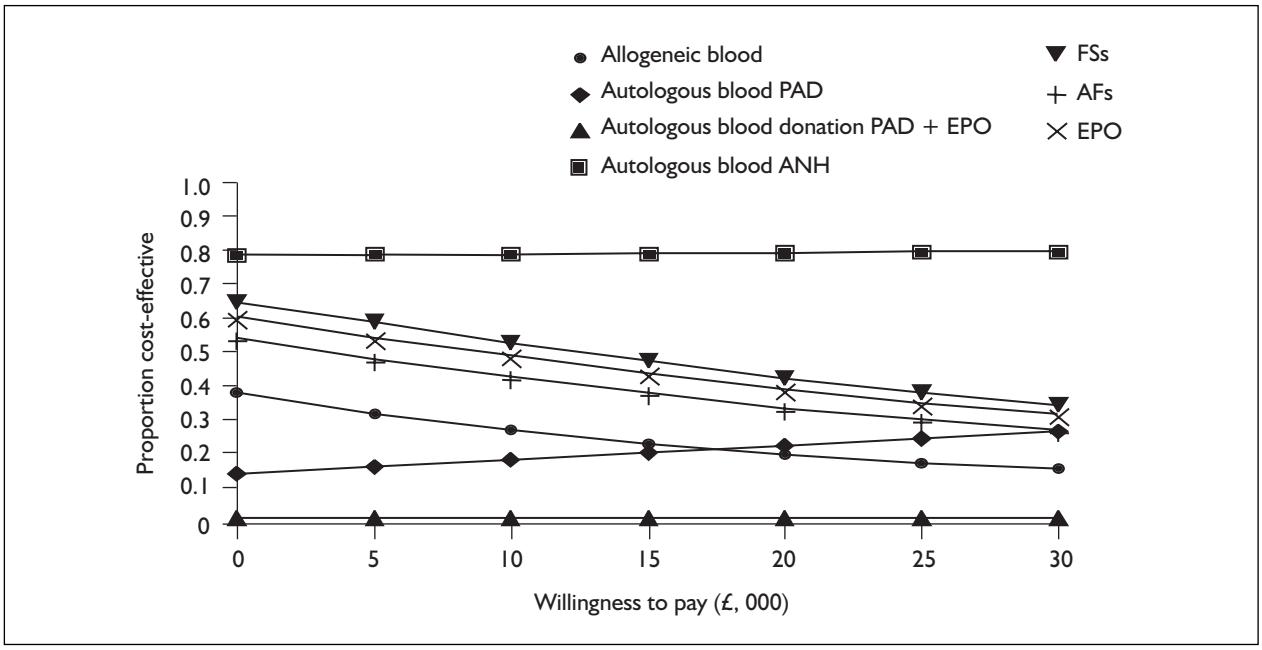

FIGURE 16 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, cardiac procedures, 1-month timeframe*

Table 41 and *Figure 16* show the incremental expected costs and QALYs and cost-effectiveness acceptability of cell salvage overall compared with each of the alternative transfusion strategies for cardiac procedures. As for the all procedures analysis above, there is a high probability that cell salvage is cost-effective compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. There is a low probability that cell salvage is cost-effective when compared with ANH. *Figure 16* indicates that the proportion of simulations when allogeneic blood, PAD and PAD plus EPO are more cost-effective than cell salvage is less than 50% across the range of willingness-to-pay values used. *Figure 16* also indicates that the proportion of simulations when ANH was more cost-effective than cell salvage was around 80%. FSs, AFs and EPO were more likely to be cost-effective if the willingness to pay value to gain a QALY was less than £15,000.

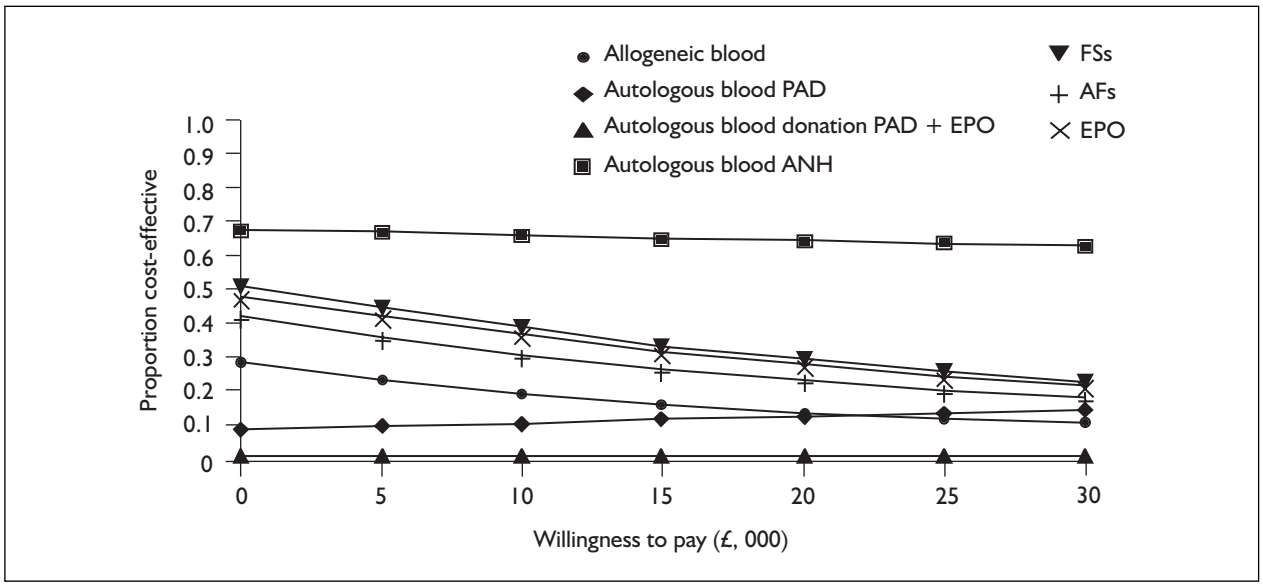

FIGURE 17 *Incremental CEACs for alternative transfusion strategies compared with intraoperative cell salvage, cardiac procedures, 1-month timeframe*

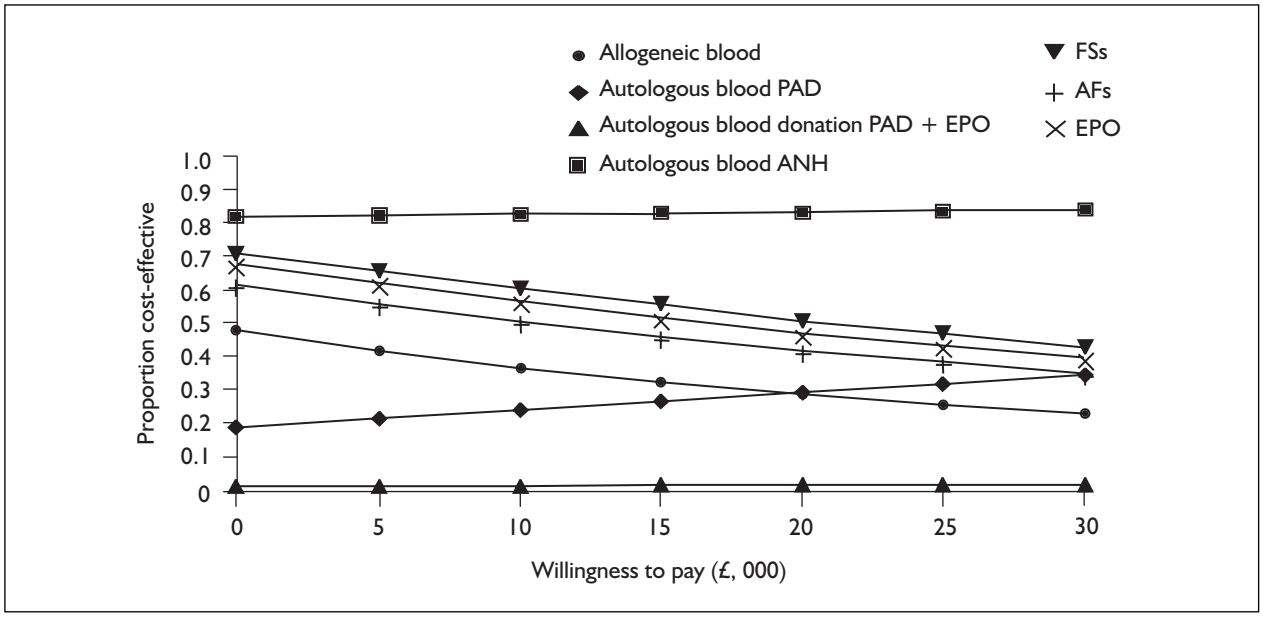

FIGURE 18 *Incremental CEACs for alternative transfusion strategies compared with postoperative cell salvage, cardiac procedures, 1-month timeframe*

As noted above, the relative cost-effectiveness of cell salvage may vary by the timing and technique used. *Figure 17* illustrates the CEACs for intraoperative cell salvage. These indicate that in cardiac procedures, there is a high probability that intraoperative cell salvage is cost-effective compared with all of the alternative transfusion strategies except ANH.

In contrast, there is a low probability that postoperative cell salvage is cost-effective compared with the alternative transfusion strategies, when used for cardiac procedures (*Figure 18*). Postoperative cell salvage is associated with higher costs and lower QALYs compared with ANH, FS, AFs and EPO.

Orthopaedic procedures

This analysis assesses the benefits of cell salvage in orthopaedic surgery and includes (i) a comparison of all cell salvage in orthopaedic procedures and (ii) a comparison of cell salvage in orthopaedic

TABLE 42 *Incremental cost-effectiveness: cell salvage versus alternative transfusion strategies, orthopaedic procedures, 1-month timeframe*

	Mean cost of cell salvage (£) (2.5th; 97.5th percentile)	**Mean QALY of cell salvage (2.5th; 97.5th percentile)**	
CS	4842 (4315; 5395)	0.0704 (0.0626; 0.0783)	
	Net cost of cell salvage (£) (2.5th; 97.5th percentile)	**Net QALY of cell salvage (2.5th; 97.5th percentile)**	**Cost/QALY gained (£) (mean values only)**
Allogeneic blood	–157 (–523; 278)	0.00728 (–0.00192; 0.01757)	All CS dominates AB
PAD	–262 (–556; 15)	–0.00014 (–0.00197; 0.00198)	1,871,429[a]
PAD + EPO	–458 (–745; 143)	0.00192 (–0.00109; 0.00624)	All CS dominates PAD + EPO
ANH	–22 (–260; 213)	0.00159 (–0.00135; 0.00582)	All CS dominates ANH
AFs	–131 (–526; 333)	0.00728 (–0.00192; 0.01757)	All CS dominates AF
FSs	–89 (–479; 385)	0.00728 (–0.00192; 0.01757)	All CS dominates FSs
EPO	–121 (–503; 348)	0.00728 (–0.00192; 0.01757)	All CS dominates EPO

[a] Incremental cost per QALY gained by PAD compared with all cell salvage, orthopaedic procedures.

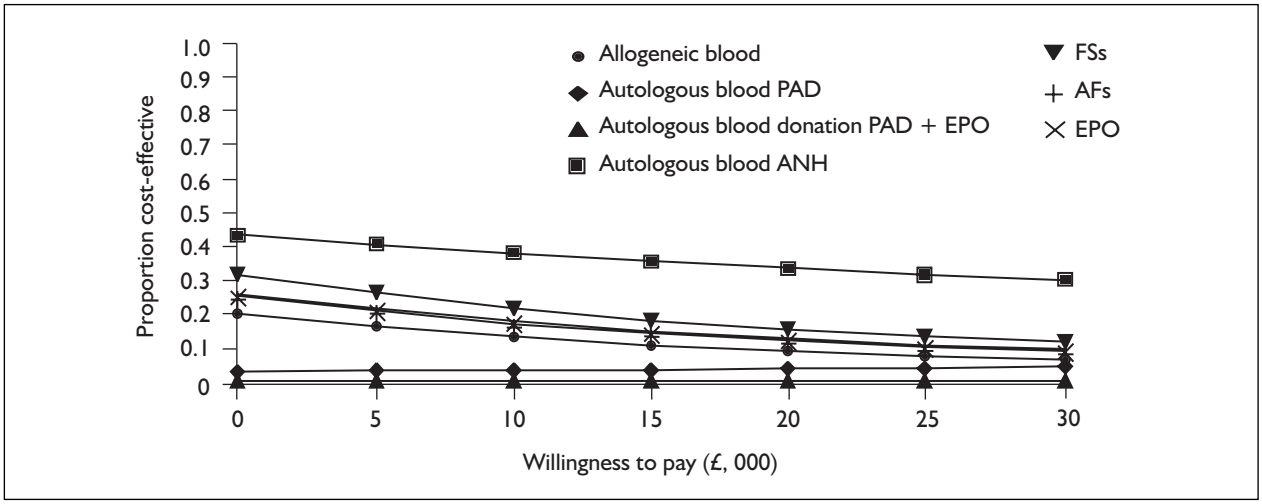

FIGURE 19 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, orthopaedic procedures, 1-month timeframe*

procedures according to the timing of cell salvage. *Table 42* and *Figure 19* show the incremental expected costs and QALYs and CEACs for cell salvage compared with the alternative transfusion strategies for orthopaedic procedures. As for the all-procedures analysis above, there is a high probability that cell salvage is cost-effective when compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. In contrast to the primary analysis, for orthopaedic procedures there is a high probability that cell salvage is cost-effective when compared with ANH. The CEACs in *Figure 19* indicate that the proportion of simulations when these transfusion strategies are more cost-effective than cell salvage is less than 50% across the range of willingness-to-pay values used.

Figure 20 shows the CEACs for intraoperative cell salvage for orthopaedic procedures, compared with the alternative transfusion strategies. There is a high probability that intraoperative cell salvage is cost-effective compared with all of the alternative transfusion strategies, except ANH. In contrast, there is a high probability that postoperative cell salvage for orthopaedic procedures is cost-effective compared with all of the alternative transfusion strategies, including ANH. *Figure 21* shows the CEACs for postoperative cell salvage compared with the alternative transfusion strategies for orthopaedic procedures.

Use of restrictive transfusion protocols

The use of a transfusion protocol reduced the probability of allogeneic blood transfusion from

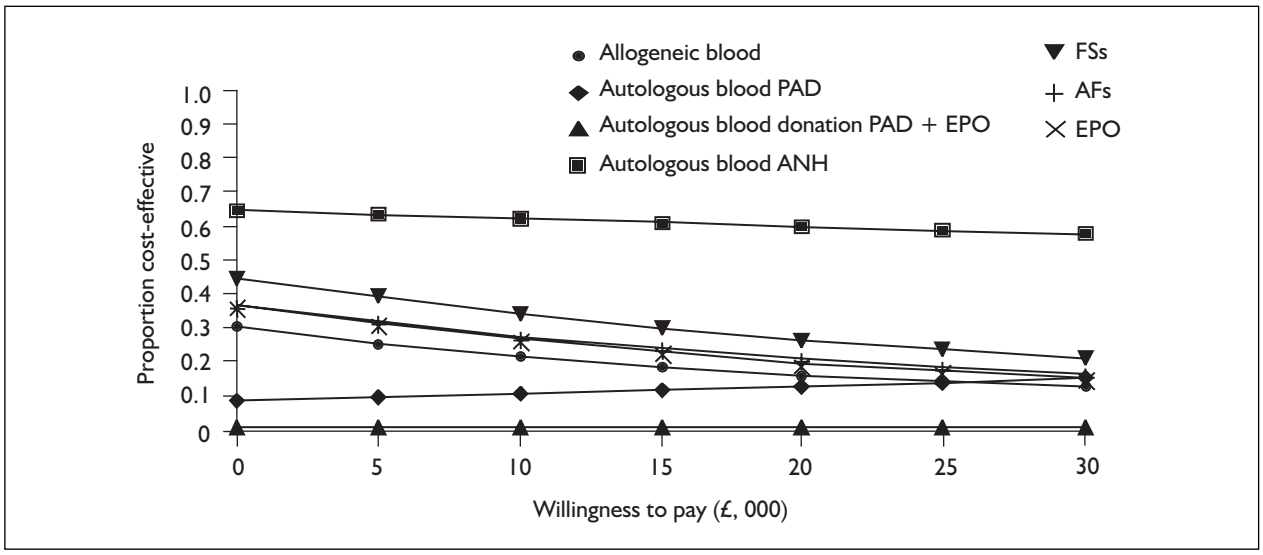

FIGURE 20 *Incremental CEACs for alternative transfusion strategies compared with intraoperative cell salvage, orthopaedic procedures, 1-month timeframe*

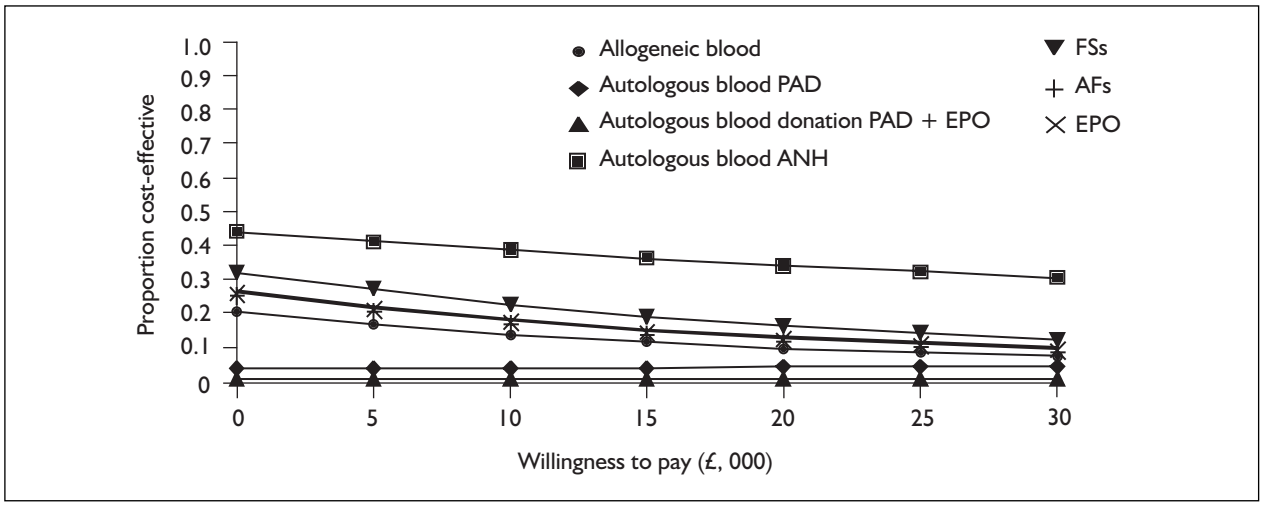

FIGURE 21 *Incremental CEACs for alternative transfusion strategies compared with postoperative cell salvage, orthopaedic procedures, 1-month timeframe*

0.66 to 0.61. *Table 43* and *Figure 22* show the incremental expected costs and QALYs and CEACs for cell salvage compared with the alternative transfusion strategies for all procedures, when data on the probability of allogeneic blood transfusion from trials using transfusion protocols are used. As with the primary analysis, there is a high probability that cell salvage is cost-effective compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. In contrast, there is a low probability that cell salvage is cost-effective compared with ANH. *Figure 22* indicates that the proportion of simulations when these transfusion strategies are more cost-effective than cell salvage is less than 50% across the range of willingness to pay values used. *Figure 22* indicates that the proportion of simulations when ANH is more cost-effective than cell salvage is around 80%.

Timeframe of analysis

The timeframe of the analysis was varied between 1, 10 and 30 years to assess whether the longer term costs and morbidity of transfusion-related complications and transfusion-transmitted infection affected the relative cost-effectiveness of cell salvage. Extending the time horizon to 1 year does not affect the relative expected costs and QALYs of cell salvage or the expected net benefits of cell salvage. *Figure 23* summarises the results for the 1-year timeframe. As with the primary analysis, there is a high probability that cell

TABLE 43 *Incremental cost-effectiveness: cell salvage versus alternative transfusion strategies, all surgical procedures, transfusion protocol, 1-month timeframe*

	Mean cost (£) (2.5th; 97.5th percentile)	**Mean QALY (2.5th; 97.5th percentile)**	
CS	4896 (4390; 5385)	0.0686 (0.0602; 0.0767)	
	Net cost (£) (2.5th; 97.5th percentile)	**Net QALY (2.5th; 97.5th percentile)**	**Cost/QALY gained (£) (mean values only)**
Allogeneic blood	–90 (–370; 213)	0.00531 (–0.00132; 0.01469)	All CS dominates AB
PAD	–159 (–452; 84)	–0.00127 (–0.00462; 0.00056)	125,197[a]
PAD + EPO	–351 (611; 131)	0.00083 (–0.00078; 0.00291)	All CS dominates PAD plus EPO
ANH	92 (–150; 274)	0.00055 (–0.00108; 0.00272)	167,273[b]
AFs	–39 (–354; 292)	0.00531 (–0.00132; 0.01469)	All CS dominates AF
FSs	–7 (–308; 331)	0.00531 (–0.00132; 0.01469)	All CS dominates FS
EPO	–32 (–320; 313)	0.00531 (–0.00132; 0.01469)	All CS dominates EPO

[a] Incremental cost per QALY gained by PAD compared with all cell salvage, all procedures.
[b] Incremental cost per QALY gained by cell salvage compared with ANH, all procedures.

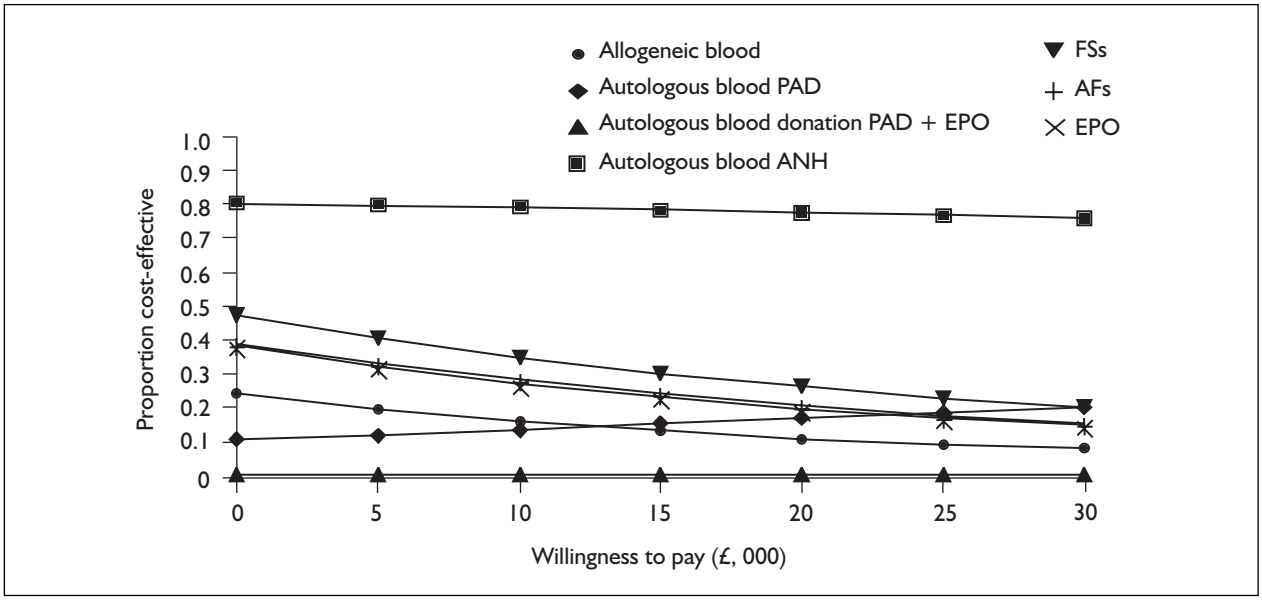

FIGURE 22 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, transfusion protocol, 1-month timeframe*

salvage is cost-effective compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. There is a low probability that cell salvage is cost-effective compared with ANH.

Extending the analysis to 10 and 30 years gives similar results to the primary analysis, in that there is a high probability that cell salvage is cost-effective compared with the allogeneic blood transfusion strategy, PAD plus EPO, FSs, AFs and EPO. There is a lower probability that cell salvage is cost-effective compared with ANH. However, the longer time horizons indicate that PAD may be more cost-effective when compared with cell salvage. In addition, for the longer time horizons, the probability that ANH is more cost-effective than cell salvage decreases from over 90% to around 55%. *Figures 24* and *25* summarise the results for the 10- and 30-year time horizons, respectively.

Threshold analysis was used to estimate the minimum time horizon required for cell salvage to be less cost-effective than the alternative transfusion techniques (*Figure 26*). The probability

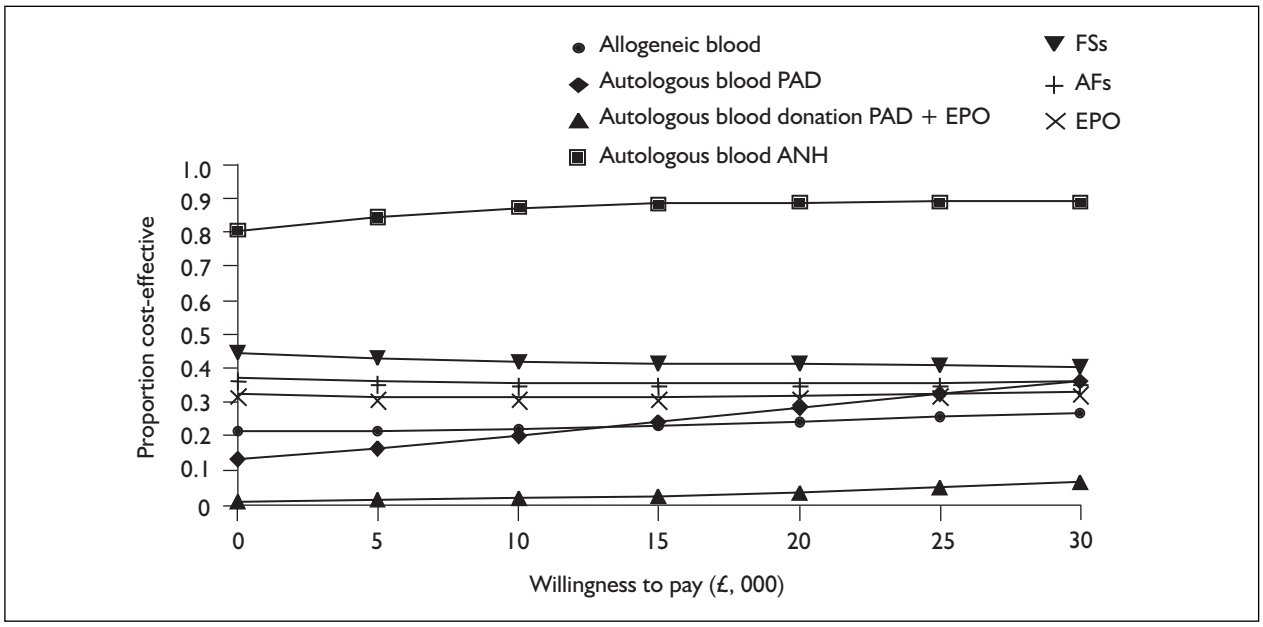

FIGURE 23 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, 1-year timeframe*

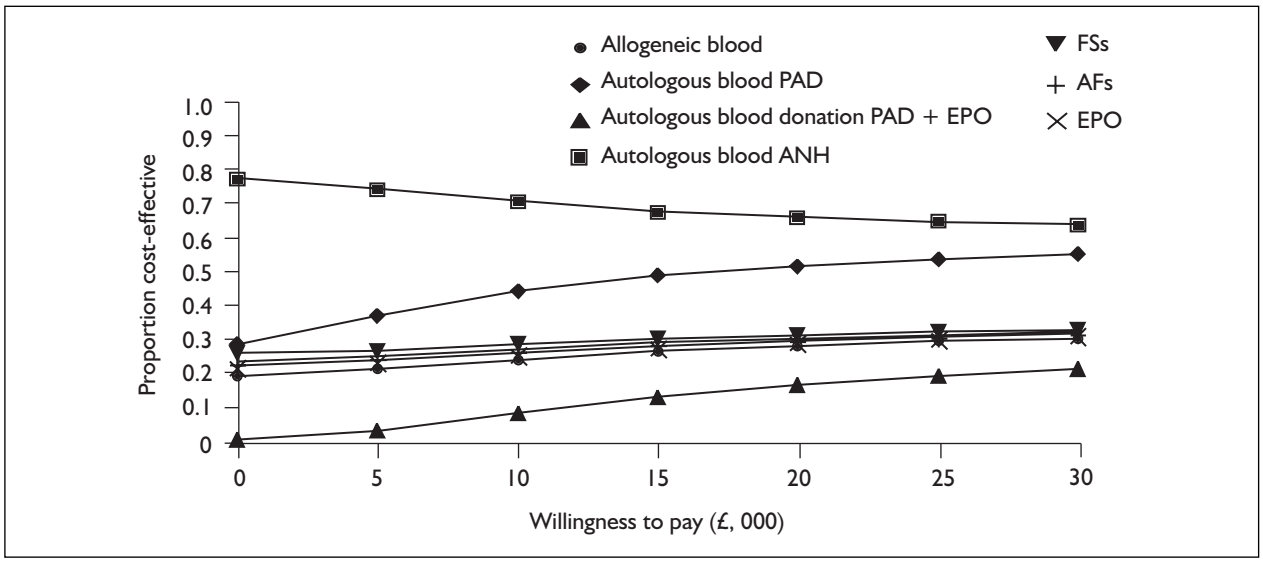

FIGURE 24 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, 10-year timeframe*

that PAD was cost-effective reached 50% over a 5-year time horizon if decision-makers are willing to pay £30,000 to gain one QALY. This means that for a patient with a predicted life expectancy of 5 years, the costs and QALYs associated with PAD and cell salvage are likely to be similar. If a patient has a predicted life expectancy of greater than 5 years, PAD may be more cost-effective than cell salvage. No threshold values were found for any of the other transfusion alternatives. Within the context of this analysis, this suggests that the time horizon does not affect the relative cost-effectiveness of cell salvage compared with allogeneic blood only, PAD plus EPO, ANH, FSs, AFs and EPO.

Costs of cell salvage

The costs of cell salvage depend on the level of activity assumed to estimate the cost per case from the annual costs of equipment and maintenance. The primary analysis used an estimate of the equipment being used for 100 cases per year. This was varied between 50 and 150 cases per year. *Table 44* and *Figure 27* show the incremental

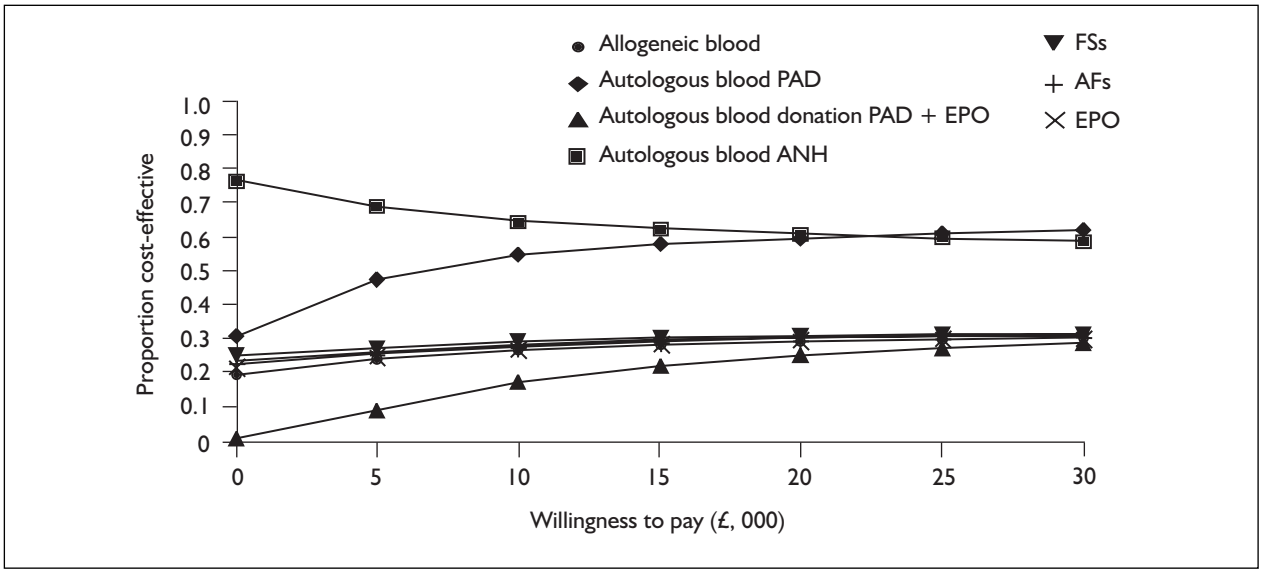

FIGURE 25 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, 30-year timeframe*

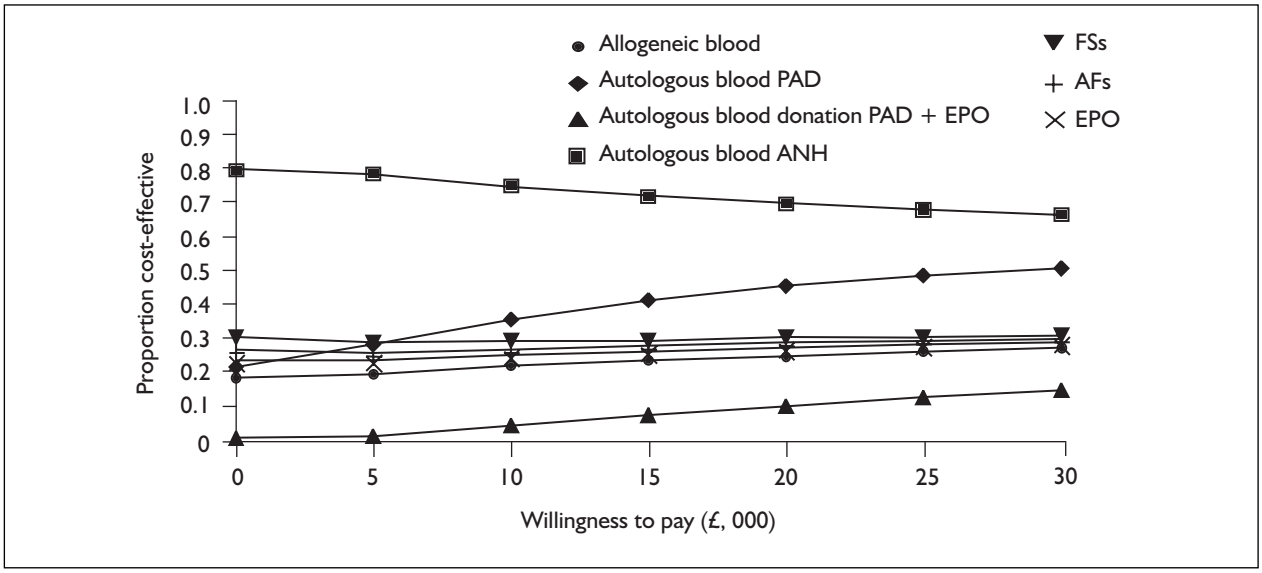

FIGURE 26 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, 5-year timeframe*

expected costs and QALYs and cost-effectiveness acceptability of cell salvage compared with the alternative transfusion strategies for all procedures, when a cell salvage machine is used for 50 operations per year. As with the primary analysis, cell salvage is likely to more cost-effective than the allogeneic blood transfusion strategy, PAD and PAD plus EPO. Cell salvage is less likely to be cost-effective than ANH, FSs, AFs and EPO. *Figure 27* indicates that the proportion of simulations when allogeneic blood, PAD and PAD plus EPO are more cost-effective than cell salvage is less than 50% across the range of willingness to pay values used. *Figure 27* also indicates that the proportion of simulations when ANH was more cost-effective than cell salvage was around 80% and that cell salvage was only cost-effective compared with FSs, AFs and EPO if a decision-maker is prepared to pay more than £10,000 to gain one QALY. If more patients are treated per year with one cell saver machine than estimated in the primary analysis (150 per year rather than 100 per year), the costs per person of cell salvage would decrease. This increases the probability that

TABLE 44 *Incremental cost-effectiveness: cell salvage versus alternative transfusion strategies, all surgical procedures, higher cost of cell salvage, 1-month timeframe*

	Mean cost of cell salvage (£) (2.5th; 97.5th percentile)	**Mean QALY of cell salvage (2.5th; 97.5th percentile)**	
CS	4972 (4422; 5472)	0.0680 (0.0587; 0.0768)	
	Net cost of cell salvage (£) (2.5th; 97.5th percentile)	**Net QALY of cell salvage (2.5th; 97.5th percentile)**	**Cost/QALY gained (£) (mean values only)**
Allogeneic blood	–30 (–326; 254)	0.00487 (–0.00118; 0.01511)	All CS dominates AB
PAD	103 (–416; 88)	–0.00117 (–0.00443; 0.00064)	88,034[a]
PAD + EPO	–290 (–565; 75)	0.00076 (–0.00083; 0.00278)	All CS dominates PAD + EPO
ANH	157 (–120; 339)	0.00049 (–0.00107; 0.00256)	320,408[b]
AFs	18 (–318; 324)	0.00487 (–0.00118; 0.01511)	4,423[b]
FSs	49 (–266; 369)	0.00487 (–0.00118; 0.01511)	12,039[b]
EPO	18 (–283; 354)	0.00487 (–0.00118; 0.01511)	4,423[b]

[a] Incremental cost per QALY gained by PAD compared with all cell salvage, all procedures.
[b] Incremental cost per QALY gained by cell salvage, all procedures.

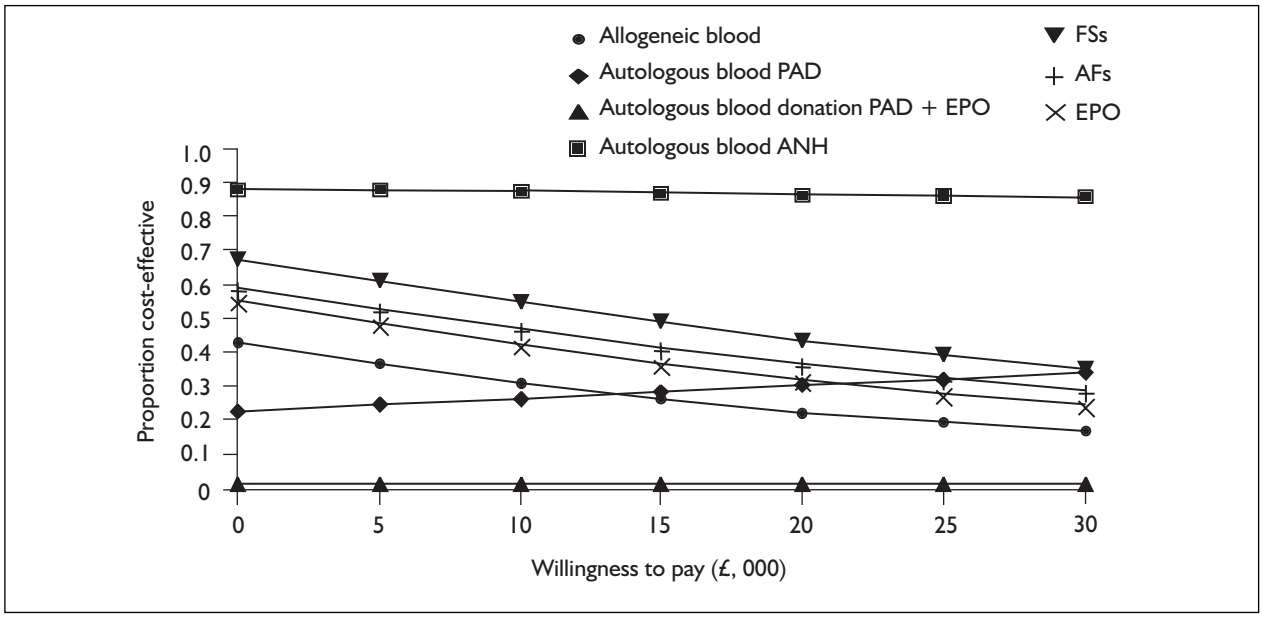

FIGURE 27 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, higher costs of cell salvage, 1-month timeframe*

cell salvage is cost-effective, as shown in *Figure 28*. However, cell salvage is still less cost-effective than ANH.

Impact of cell salvage on the NHS BTA

There were insufficient data available from national statistics, published literature or SMUHT databases to estimate the actual proportion of elective operations in which allogeneic blood transfusion and the other transfusion strategies are used in England. Therefore, this analysis of the impact of replacing allogeneic blood transfusion with cell salvage on the National Blood Service is exploratory. The analysis is based on estimation of changes in the requirements for allogeneic blood under different assumptions about the use of cell salvage and the number of operations where cell salvage could reduce allogeneic blood transfusion.

Table 45 presents the expected volume of blood transfused per operation (i.e. averaged over those operations with and without transfusion),

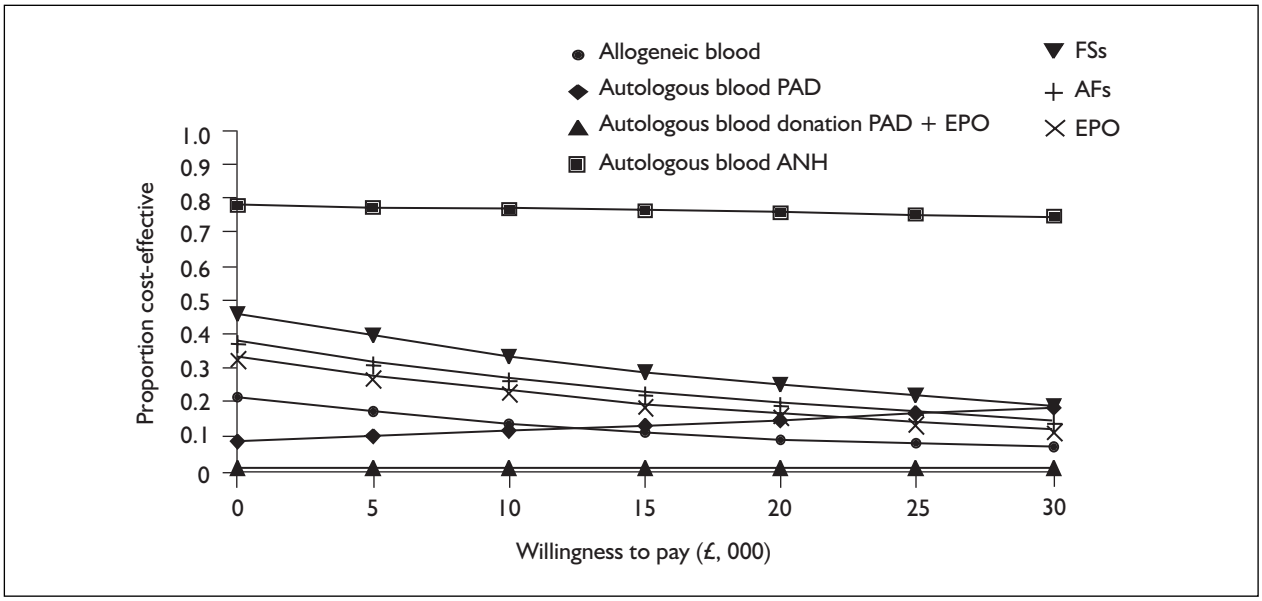

FIGURE 28 *Incremental CEACs for alternative transfusion strategies compared with cell salvage, all surgical procedures, lower costs of cell salvage, 1-month timeframe*

TABLE 45 *Expected volume of blood transfused per operation: all procedures*

	Mean volume (units) per operation (2.5th; 97.5th percentile)
Allogeneic blood	2.03 (0.27; 3.47)
All CS	0.91 (0.00; 1.95)
PAD	0.34 (0.00; 1.09)
PAD + EPO	0.63 (0.00; 1.53)
ANH	0.55 (0.0; 1.41)
AFs	0.99 (0.00; 2.05)
FSs	1.20 (0.00; 2.40)
EPO	1.37 (0.00; 2.74)

TABLE 46 *Number of elective operations per year*

Elective procedure	**No. of procedures per year (2003–4)**
All procedures[a]	5,813,891
Cardiac/vascular procedures[b]	36,636
Orthopaedic procedures[c]	114,740

[a] All procedures = all non-emergency admissions for surgery.[71]
[b] Cardiac procedures = all non-emergency procedures on heart arteries and veins included in OPCS codes K1–15, K18–34, K37–49, K52–55, L5–12, L16–25, L29–30, L33–34, L37–38, L41–42, L45–46, L48–53, L56–62 and L65–70.[71]
[c] Orthopaedic procedures = all non-emergency joint replacement procedures and amputation of the leg, OPCS codes W37–58, X9.[71]

estimated by the economic model, using the data on the likelihood of allogeneic blood transfusion and units of blood transfused for each of the transfusion strategies. *Table 46* summarises the number of operations per year, for the year 2003–4, from the Hospital Episode Statistics for England.[71]

Table 47 provides estimates of the total allogeneic blood transfusion requirements with the allogeneic blood transfusion strategy, under different assumptions about the proportion of elective operations where blood transfusion is likely to be required. These are based on current estimates of actual allogeneic blood use in the UK, and so reflect the current use of alternative strategies to minimise the use of allogeneic blood in elective surgery. In 2003–4, the National Blood Service issued a total of 2,142,353 units of red cells.[83] A recent observational study estimated that 41% of all blood transfused is accounted for by surgery, which equals 878,365 units transfused as a consequence of surgery.[3] In 2004, elective surgery comprised 90% of all surgery. This suggests that the total volume of red cells transfused as a consequence of elective surgery was in the region of 793,463 units (878,365 × 90%). *Table 45* indicates that the average allogeneic transfusion requires two units of red cells per operation. Multiplying the number of operations by the average volume of allogeneic blood per operation gives an estimate of the total volume of allogeneic blood transfused for elective surgery. These estimates are shown in *Table 47*. This indicates that

TABLE 47 *Expected allogeneic blood requirements, allogeneic blood transfusion strategy*

All elective surgical procedures		Estimated volume of allogeneic blood transfused (units)		Reduction in volume of allogeneic blood transfused with cell salvage (units)
Proportion of procedures with transfusion (%)	No. of operations	Allogeneic transfusion strategy	Cell salvage	
1	58,139	118,196	52,790	–65,406
2	116,278	236,393	105,580	–130,813
3	174,417	354,589	158,370	–196,219
4	232,556	472,786	211,161	–261,625
5	290,695	590,982	263,951	–327,031
6	348,833	709,178	316,741	–392,438
7	406,972	827,375	369,531	–457,844

TABLE 48 *Expected reductions in allogeneic blood requirements when cell salvage is used*

Proportion of procedures with cell salvage (%)	Reduction in volume of allogeneic blood transfused with cell salvage (units)		
	58,139 operations	232,556 operations	348,833 operations
10	–6541	–26163	–45784
20	–13081	–52325	–91569
30	–19622	–78488	–137353
40	–26163	–104650	–183138
50	–32703	–130813	–228922
60	–39244	–156975	–274706
70	–45784	–183138	–320491

a maximum of 6–7% of elective surgical procedures account for the estimated volume of allogeneic blood transfused as a consequence of surgery. *Table 47* also shows the maximum reduction in allogeneic blood requirements if cell salvage were to be used for 100% of the operations.

Table 48 presents the estimated reduction in units of allogeneic blood required at different rates of use of cell salvage. These results indicate that cell salvage could reduce the annual allogeneic blood requirement for elective surgery by 6541 units if cell salvage is used in 10% of 58,139 operations. This would increase to 26,150 units of allogeneic blood saved if cell salvage is used in 10% of 232,556 operations per year and 45,800 units of allogeneic blood saved if cell salvage is used in 10% of 348,833 operations per year. If cell salvage were to be used in 50% of operations per year, the reduction in allogeneic blood requirements would be between 32,700 units for 58,139 operations and 228,900 units for 348,833 operations.

If the supply of blood is reduced by 10% of current supplies (owing to increased stringency of tests and criteria about who is eligible to donate blood to reduce the risks of transfusion-transmitted infection in general and vCJD in general), then demand for blood would need to reduce by at least 214,235 units per annum. Increasing the use of cell salvage to 50% of all operations could meet this reduction, if the technique could be used to reduce allogeneic blood requirements by one unit per operation, in 348,833 operations. If cell salvage is used for a lower proportion of operations, or is effective in reducing allogeneic blood requirement in fewer operations, then other measures would be required for the NHS BTA to meet demand for allogeneic blood in the future.

The cost savings to the NHS BTA shown in *Table 49* assume that demand for allogeneic blood and the price of allogeneic blood are stable. However, there was a fall in demand of allogeneic blood in 2002–3 and the NHS BTA projected a further reduction in demand in 2003–4. If the demand for allogeneic blood falls, as a consequence of either increased use of cell salvage or the more general implementation of the Better Blood Transfusion initiative, then the average cost of fixed overheads per unit of blood will increase.[5,22] This was identified by the NHS BTA as one of the main

TABLE 49 *Expected cost savings to the NHS BTA when cell salvage is used*

Proportion of procedures with cell salvage (%)	Cost savings due to reduction in volume of allogeneic blood transfused with cell salvage (£ million)		
	58,139 operations	232,556 operations	348,833 operations
10	0.73	2.91	–5.09
20	1.45	5.82	–10.18
30	2.18	8.73	–15.27
40	2.91	11.63	–20.36
50	3.64	14.54	–25.45
60	4.36	17.45	–30.54
70	5.09	20.36	–35.63

TABLE 50 *Expected annual savings and QALYs when cell salvage is used*

Proportion of procedures with cell salvage (%)	Cost savings due to reduction in volume of allogeneic blood transfused with cell salvage					
	58,139 operations		232,556 operations		348,833 operations	
	Saving (£ million)	QALY gain	Saving (£ million)	QALY gain	Saving (£ million)	QALY gain
10	0.44	28	1.77	111	2.65	166
20	0.88	55	3.53	222	5.30	333
30	1.33	83	5.30	333	7.95	499
40	1.77	111	7.07	444	10.60	666
50	2.21	139	8.84	555	13.26	832
60	2.65	166	10.61	666	15.91	998
70	3.09	194	12.38	777	18.56	1165

reasons for recent increases in the price per unit of allogeneic blood. However, other reasons for increases in the price of allogeneic blood may be more important. These include general cost pressures, increased safety measures, developments to secure the donor base and improvements in the infrastructure of the NHS BTA.

As indicated by the primary analysis of the expected costs and outcomes of cell salvage above, cell salvage is associated with lower expected costs and QALYs from elective surgery than the allogeneic blood transfusion strategy. *Table 50* shows the total expected annual savings and QALY gains from implementing cell salvage at different levels of surgical activity and rates of use of cell salvage.

Table 50 indicates that implementing cell salvage in 10% of elective operations could save £0.44 million per year, with an associated gain of 28 QALYs per year, if cell salvage can be used in 10% of 58,000 operations. This saving could increase to £3 million per year with a gain of 194 QALYs if cell salvage was used in 70% of 58,000 elective operations.

The extent of the savings and gain in QALYs will also depend on the type of surgical procedure, timing and technique of cell salvage. The figures shown in *Table 50* are for cell salvage overall. If washed intraoperative cell salvage was used for 10% of 37,000 cardiac operations (*Table 46*), the expected savings and gain in QALYs would be £0.33 million and 22 QALYs per year, respectively. If washed intraoperative cell salvage was used for 70% of 37,000 cardiac operations (*Table 46*), the expected savings and gain in QALYs would be £2.33 million and 156 QALYs per year, respectively. If unwashed postoperative cell salvage was used for 10% of 115,000 orthopaedic operations (*Table 46*), the expected savings and gain in QALYs would be £1.82 million and 84 QALYs per year, respectively. If unwashed postoperative cell salvage was used for 70% of 115,000 orthopaedic operations (*Table 46*), the expected savings and gain in QALYs would be £12.72 million and 588 QALYs per year respectively.

Overall, adoption of cell salvage could reduce the demand for allogeneic blood for elective surgery. The extent of savings in allogeneic blood could be as high as 10% of the total volume of blood issued in 2003. However, this would require 6% of operations per year to require blood transfusion, and that cell salvage is used in 50% of elective operations where a blood transfusion is required. A recent survey distributed to hospital haemotologists in charge of blood transfusion found an increase in the availability of cell salvage.[26] Overall, 95% of NHS Trusts and 37% of private hospitals responded to the survey. The responses indicated that intraoperative cell salvage was used in 61% of NHS hospitals and postoperative cell salvage was used in 56% of NHS hospitals. This represents an increase from a previous survey in 2001, when 41% of respondents reported that perioperative cell salvage was available.[26] However, the extent to which cell salvage was used ranged from 14% of NHS hospitals transfusing less than 20 units of intraoperative cell salvage products per year to 16% transfusing more than 200 units per year. Approximately one-third of respondents did not know how many units of blood were transfused using cell salvage.[26]

Adopting cell salvage more widely within NHS hospitals may have significant organisational and management implications. Hospital Trusts will have to decide who will operate cell salvage devices and if it is possible to accommodate these activities within their existing establishment. Currently throughout the UK, cell salvage machines are operated by a range of healthcare staff, e.g. nurses, perfusionists and anaesthetists, each centre having devised a solution that meets their individual circumstances. Regardless of who operates the equipment, all staff need to be satisfactorily trained and their competency assessed. Until recently, users were largely reliant on machine manufacturers to provide specialised training with competencies determined locally. The advent of national occupational standards, via the Skills for Health organisation, has improved this situation.

The expectation that hospitals will automatically adopt new approaches to blood transfusion and change longstanding practices is probably naïve. Without a coordinated approach, led by the Department of Health and NHS BTA, providing specialist resources and training, uptake is likely to be variable. There still exist some areas of controversy surrounding the use of cell salvage techniques in particular clinical situations. Existing guidelines[14] are outdated and do not reflect current practice. For example, cell salvage in malignancy is contraindicated. There are, however, several centres throughout the UK using cell salvage routinely in radical prostatectomy for malignancy. Some sites use leucodepletion filters to mitigate the risk of reinfusing malignant cells systemically, others do not. Without adequate guidance and a solid evidence base informing a consensus of expert opinion, inconsistency in practice is likely to continue. The National Blood Conservation Strategy, produced by the National Blood Transfusion Committee and NHS BTA in 2004,[24] suggested the following measures to promote the introduction of cell salvage: appropriate use of cell salvage as an achievable target for trusts; a website-based 'tool kit'; review of budget allocation; training initiatives; and template protocols. As yet, these recommendations have been slow to be implemented. Without the necessary support, it is probable that the impact of cell salvage and appropriate transfusion alternatives will continue to be muted.

Chapter 8
Discussion

The overall aims of this study were to use secondary research methods to compare patient outcomes, resource use and costs to the NHS and National Blood Service associated with cell salvage, allogeneic blood transfusion and alternative methods of minimising perioperative allogeneic blood transfusion.

Summary of the clinical evidence

The systematic review updates and review of existing systematic reviews (Chapter 3) found that all but two of the transfusion strategies to minimise exposure to allogeneic blood transfusion significantly reduced exposure to allogeneic blood. The RR of exposure to allogeneic blood in these studies ranged from 0.36 (95% CI 0.25 to 0.51) for PAD to 0.70 (95% CI 0.64 to 0.76) for aprotinin. The RR of allogeneic blood transfusion with EACA was 0.48 (95% CI 0.19 to 1.19). The wide CI, crossing one, means that the reduction in exposure to allogeneic blood was not statistically significant. The use of restrictive transfusion thresholds appeared to reduce the use of blood transfusions. However, this included both allogeneic and autologous blood transfusion. The risk of receiving any blood transfusion (allogeneic and/or autologous) was increased in those randomised to PAD compared with control; the RR of exposure to allogeneic or autologous blood was 1.33 (95% CI 1.10 to 1.61).

The RR of exposure to allogeneic blood was 0.59 for the pooled trials of cell salvage (95% CI 0.48 to 0.73). Analysis of subsets of the data were conducted to explore whether there were potential differences in the RR of exposure to allogeneic blood by type and timing of cell salvage and by type of surgical procedure. This follows the approach taken in previous systematic reviews of cell salvage. However, the use of subsets of the data, with relatively few studies to combine and small sample sizes, means that these analyses can be exploratory only. If the subgroup analyses suggest that the results for these groups may differ from the pooled analysis, this may be indicative of areas for further research. If the subgroup analyses find similar conclusions to the pooled analysis, this indicates that the conclusions from the pooled analysis are likely to be robust to differences between the subgroups. The RR of allogeneic blood transfusion for washed cell salvage was 0.54 (95% CI 0.43 to 0.68) compared with 0.71 (95% CI 0.60 to 0.84) for those trials that used unwashed cell salvage. The pooled RR of exposure to allogeneic blood transfusion was 0.53 (95% CI 0.35 to 0.80) for those trials that used intraoperative cell salvage, compared with 0.60 (95% CI 0.45 to 0.79) for postoperative cell salvage.

In addition, the RR of exposure to allogeneic blood differed by the type of surgical procedure used. For cell salvage, the RR of allogeneic blood transfusion was higher in cardiac surgery than in orthopaedic surgery. For PAD, PAD plus EPO and ANH the converse was found, in that the lower RRs of exposure to allogeneic blood were found in cardiac rather than orthopaedic surgery.

A number of comparisons by type of surgery, using subsets of the data, did not statistically significantly reduce exposure to allogeneic blood transfusion compared with control. These were cell salvage in vascular surgery, EPO and ANH in cardiac surgery, ANH in orthopaedic surgery and TXA without a transfusion protocol. The CIs around ANH with the use of a transfusion protocol reached the point of no effect.

Some of the transfusion strategies were not specifically assessed in cardiac (EACA, FSs) or orthopaedic surgery settings (aprotinin, TXA, EACA). If a transfusion protocol was used, this appeared to lessen the effectiveness of all the comparators to reduce exposure to allogeneic blood transfusion.

The data from the systematic reviews were re-analysed for use in the economic model (Chapter 6). The data from all the trials were pooled to estimate the probability of blood transfusion for the allogeneic blood transfusion strategy. A measure of difference was estimated (weighted risk difference, random effects model) to determine the extent to which the alternative methods of transfusion reduced exposure to allogeneic blood. Only trials that compared one of the transfusion strategy alternatives with allogeneic blood alone were included. These data were used

to compare the alternatives to cell salvage. Overall, the probability of allogeneic blood transfusion for the allogeneic transfusion strategy was 0.66 (range 0–1). This probability was reduced to 0.61 (range 0–1) if a subset of the data that used transfusion protocols was used. The risk difference between the alternative transfusion strategies and the allogeneic transfusion strategy was estimated at between –0.14 (95% CI –0.21 to –0.08) for PAD plus EPO and –0.42 (95% CI –0.68 to –0.17) for PAD. The overall risk difference for cell salvage was –0.26 (95% CI –0.36 to –0.16). This varied between –0.14 (95% CI –0.23 to –0.05) for cardiac surgery and –0.42 (95% CI –0.57 to –0.28) for orthopaedic surgery.

The weighted mean volume of blood transfused per person having a blood transfusion for the allogeneic transfusion strategy was 3.13 (95% CI 2.52 to 3.73). This ranged from 3.13 (95% CI 2.41 to 3.86) for cardiac surgery to 1.92 (95% CI 1.40 to 2.45) for orthopaedic surgery. The use of FSs was associated with the least average difference in the amount of allogeneic blood transfused (WMD –0.56, 95% CI –0.84 to –0.29) and ANH was associated with the greatest average difference in the amount (WMD –1.9, 95% CI –2.7 to –1.1). The WMD in blood transfused between cell salvage and the allogeneic blood control group was –0.9 (95% CI –1.23 to –0.56) overall, ranging from –0.64 (95% CI –1.45 to 0.17) for intraoperative cell salvage to –0.93 (95% CI –1.49 to –0.36) for washed cell salvage.

Overall, the transfusion strategies did not show a statistically significant effect (in either direction) on the RR of adverse events or mortality when compared with allogeneic blood (Chapter 3). The exceptions were aprotinin, which significantly reduced the RR of reoperation for bleeding by 60% (95% CI 34 to 75%), and ANH, which significantly reduced the RR of developing any thrombosis by 56% (95% CI 7 to 79%).

The probability of adverse events related to transfusion only and the probability of transfusion-transmitted infection, given infection, was estimated for the economic model from a number of sources (Chapter 6). The probability of adverse events related to transfusion only occurring with an allogeneic blood transfusion was very low, ranging from 2 per million for graft versus host disease to 244 per million for transfusion of an incorrect blood component. The probability of transfusion-transmitted infection was similarly low, ranging from 0.1 per million for HIV to 37 per million for bacterial infection due to contamination of blood. In comparison, there were fewer types of adverse events related to transfusion only associated with autologous transfusion and the only type of transfusion-transmitted infection was bacterial infection due to contamination of the autologous blood. PAD was associated with a probability of 122 per million for transfusion of an incorrect blood component. Cell salvage was associated with a probability of 4 per million for acute haemolytic transfusion reaction and with a probability of 30 per million for fatal air embolism. No data for other adverse events were reported and there were no data for adverse events occurring with ANH.

One trial[84] has been identified *ad hoc* since the search strategies for this report were carried out. The results of this trial concur with the evidence relating to the efficacy of washed intraoperative cell salvage used in adults undergoing elective CABG. Patients were randomised to autotransfusion (n = 98) receiving autotransfused washed blood from intraoperative cell salvage and postoperative mediastinal fluid cell salvage after CABG surgery or control (n = 102) receiving stored homologous blood only after CABG surgery. Patients in the autotransfusion group were significantly less likely to receive a homologous blood transfusion compared with controls (OR 0.40, 95% CI 0.22 to 0.71) and received significantly fewer units of blood per patient compared with controls (0.43 ± 1.5 versus 0.90 ± 2.0 U, p = 0.02).

Summary of the economic evidence

The published literature was systematically searched to identify published economic evaluations that assessed the cost-effectiveness of any of the alternative transfusion strategies included in this study (Chapter 4). Twelve papers were identified that met the inclusion criteria and were judged to be full economic evaluations. Economic evaluations comparing ANH, AFs, FSs or restrictive transfusion thresholds were not identified in this search. In general, EPO does not appear to be cost-effective, whereas cell salvage may have the potential to reduce risks and cost in the cardiac setting. Evidence regarding the cost-effectiveness of PAD varied considerably and PAD may be cost-effective when post-operative complications such as infection are considered.

Overall, the quality of the economic evaluations was judged to be low according to the quality assessment criteria used. Generally, the full details

of the economic evaluations were not reported. In particular, there were insufficient data available to judge the validity and robustness of the economic and clinical data used in the analyses, or the relevance of the data and results to the UK setting. The economic evaluations included transfusion-transmitted infections as the primary adverse event avoided, and differed in the type of infections included in the analysis. Adverse events due to either surgical or transfusion complications and complications due to transfusion only were generally not included.

Cost studies were also reviewed to extract any relevant resource use and unit cost data for the economic model. However, as with the economic evaluations, the quality and applicability of the data (to the UK setting) from these studies were limited.

Summary of the results of the economic model

A decision analytic model was developed to assess the costs, effectiveness and net benefit of cell salvage compared with allogeneic blood transfusion only and with alternative transfusion strategies relevant to UK practice. The primary source of clinical data for the economic model was the data included in the systematic review updates and review of systematic reviews reported in Chapter 3. This was supplemented by UK-specific data on the occurrence of transfusion-related complications, transfusion-transmitted infections and the use of allogeneic and autologous transfusions for elective surgery and in total.

Overall, small differences in health outcomes were found between the alternative transfusion strategies, due to the small differences in the frequency of transfusion-related complications and transfusion-transmitted infections. Driven by the data from the systematic reviews (Chapter 3), there were no differences in mortality and hence lives gained by cell salvage compared with any of the alternatives. There were small differences in lives gained with no adverse events and QALYs.

For the 1-month timeframe, used in the primary analysis, cell salvage was associated with lower costs and slightly higher QALYs compared with all the transfusion strategies except PAD and ANH. Cell salvage was associated with lower costs and QALYs compared with PAD and higher costs and higher QALYs compared with ANH, FSs, AFs and EPO. The range of expected costs, QALYs and net benefits was broad, with the 2.5th–97.5th percentiles of differences in expected costs and outcomes crossing zero. This suggests that the differences found between cell salvage and the alternative transfusion strategies may not be statistically significant.

CEACs and measures of net benefit provide a means of assessing the robustness of differences in expected costs and outcomes, when combined into ICERs. These analyses allow for the fact that there may be a relationship between resource use and costs and outcomes, so that, for example, higher resource use and therefore costs may be associated with improved outcomes. Overall, the primary analysis indicated that cell salvage was cost-effective compared with all the other transfusion strategies except ANH. The net benefit of cell salvage was between £112 and £359 per person, compared with the allogeneic blood transfusion strategy, PAD, PAD plus EPO, FSs, AFs and EPO. The associated likelihood that cell salvage is cost-effective compared with these strategies is over 50%. In contrast, ANH may be more cost-effective than cell salvage. ANH was associated with a net benefit compared with cell salvage of £97, with a probability of being cost-effective of around 80%.

As with the clinical review, a number of secondary analyses were used to explore subgroups of the data and test assumptions used in the model. However, the use of subsets of the data, with relatively few studies to combine and small sample sizes, means that these analyses can be exploratory only. The secondary analyses indicated that there were differences in the timing and technique of cell salvage. The use of different timings and techniques will depend on the surgical procedure and associated timing and extent of expected blood loss. In cardiac surgery, washed intraoperative cell salvage was more likely to be cost-effective than unwashed postoperative cell salvage. The converse was true for orthopaedic surgery, where unwashed postoperative cell salvage was more likely to be cost-effective than washed intraoperative cell salvage. These differences reflect differences in the dynamics and timing of blood loss.

Most of the secondary analyses indicated similar results to the primary analysis. The main exceptions to this were the analyses that explored the time horizon and lower rates of use of cell salvage equipment. If the time horizon is extended to 5 years, the costs and QALYs estimated for PAD and cell salvage are similar. If the time horizon is extended to 30 years, then the

probability that PAD is cost-effective compared with cell salvage increases to over 60%. The probability that ANH is cost-effective compared with cell salvage decreases over a 30-year time horizon to around 55%.

If the equipment for washed cell salvage is used for only 50 operations per year rather than the estimated 100, then cell salvage is less cost effective than FSs, AFs and EPO unless decision-makers are prepared to pay £10,000 or more to gain an additional QALY.

Overall, cell salvage could result in net reductions in the volume of allogeneic blood transfused of between 6500 and 320,000 units per year, depending on the number of operations per year where cell salvage is feasible and appropriate and the extent to which cell salvage is used. This translates into annual savings to the NHS BTA of £0.73 million to £36 million. Cell salvage is associated with net savings and QALY gains to the NHS overall. These range from £0.44 million per year, with an associated gain of 28 QALYs, if cell salvage can be used in 5800 operations. This saving could increase to £3 million per year with a gain of 194 QALYs if cell salvage was used in 41,000 elective operations.

Strengths and weaknesses of the methodologies used

Choice of comparators

The transfusion strategies used as comparators to cell salvage and included in the systematic reviews and economic model were chosen according to whether they were used or were likely to be used in routine practice in the UK, they were independent of surgical procedure and there was evidence about their effectiveness from a systematic review. The intervention had to comply with all of the above criteria to be included. These criteria were used to minimise the chance of including transfusion strategies that were not relevant to practice in the UK. The third criterion was applied to minimise the number of assumptions and associated uncertainty about the clinical evidence used in the economic model.

A number of possible interventions or transfusion strategies were identified but were not included in the systematic reviews or economic model. These included platelet-rich plasmapheresis, iron, patient (body) warmers, new surgical equipment (e.g. cut and coagulate at the same time), near-patient testing (e.g. Hb and thromboelastography), haemostatic agents (e.g. vitamin K and recombinant factor VIIa), preoperative clinics to prepare patients for surgery and combinations of transfusion strategies such as cell salvage combined with ANH. The main reason for exclusion of these interventions was that no systematic review of evidence to support them was identified. Patient (body) warmers and near-patient testing were identified as interventions used for purposes other than minimising allogeneic blood transfusion. Platelet-rich plasmapheresis and vitamin K were excluded since they are not appropriate for all kinds of elective surgery with moderate to high blood loss. Recombinant factor VIIa was excluded because it was not fully licensed for use in routine practice in UK. This means that this study does not provide evidence about the relative effectiveness or cost-effectiveness of cell salvage compared with the excluded interventions. This limits the relevance of the results to settings where cell salvage is a possible replacement or addition to the transfusion strategies evaluated in this study.

Systematic review

The clinical evidence was primarily assessed using systematic review methods. All the included systematic reviews were of high quality, and the updated systematic reviews of cell salvage and PAD followed the criteria specified by the Cochrane Library.[39] Broad and comprehensive electronic search strategies were used to update two existing systematic reviews of cell salvage and PAD. A focused search strategy was used to identify systematic reviews of other transfusion strategies in the Cochrane Library. Only if no reviews were found in the Cochrane Library was an electronic search conducted in other databases. This means that some systematic reviews and data may have been excluded from the analysis. However, it was beyond the scope of this evaluation to undertake a comprehensive search for systematic reviews of the other transfusion strategies.

Both the updates of the cell salvage and PAD systematic reviews and the systematic reviews of the other transfusion strategies were restricted to studies using an RCT design. Often the setting, treatment protocol and patients in clinical trials are atypical of those in routine practice. This may mean that the level of effectiveness found in a clinical trial may not be replicated in routine practice. However, well-designed clinical trials may have greater internal validity than other study designs. One of the systematic reviews included in this review did separately analyse the results of observational studies to assess the effectiveness of

autologous blood transfusion strategies. Overall, a comparison of the results from analysis of the clinical trials did not differ substantively from the results from analysis of the observational studies.[29] This suggests that the data from the systematic reviews have some level of external validity and are relevant to routine practice.

However, the quality of the individual trials included in each of the systematic reviews varied considerably. Overall, the researchers conducting the reviews concluded that the methodological quality of the trials was poor.[13,21,29–33] Key criticisms were that: many trials were unblinded; inadequate methods of concealing treatment allocation were used, which may result in observer-induced bias; many of the trials had a small sample size with the consequent possibility of publication bias; trials used subjective outcome measures, such as the need for allogeneic transfusion, which may lead to reporting bias; and there was significant heterogeneity between and within trials. All of these factors tend to increase the chance that the treatment effect of the comparator treatment (in this case the transfusion strategy used as an alternative to allogeneic blood transfusion) is overestimated. This increases the level of uncertainty about whether the alternative transfusion strategies have a statistically significant effect on the primary outcome measure: exposure to allogeneic blood transfusion. Analyses of the data within each of the systematic reviews, to test for the effects of these factors, suggested that the estimate of RR of exposure to allogeneic blood was lower when these factors were controlled for. There was also some limited evidence of publication bias, in the form of missing small negative studies.

A further issue is that evidence is needed regarding the actual clinical value of avoiding allogeneic blood transfusion. This requires evidence about the incidence of complications associated with allogeneic blood transfusion strategies and strategies to minimise allogeneic blood transfusion. In particular, a range of transfusion-related complications that are deemed serious hazards of transfusion in the UK were not reported in the trials or the systematic reviews. In addition, the incidence of serious transfusion-transmitted infections has declined over the last decade with improvements in screening and treatment of allogeneic blood. This reduces the clinical value of exposure to allogeneic blood as a primary outcome measure. There is a lack of evidence regarding the long-term clinical benefit of avoiding allogeneic blood transfusion and indeed receiving autologous blood transfusion.[13,21,29–33]

Economic model

The economic model compared cell salvage with allogeneic blood transfusion only, PAD with and without EPO, ANH and allogeneic blood transfusion with FSs, AFs or EPO to minimise blood loss or the need for a transfusion. The use of transfusion protocols was also explored in the secondary analyses.

The model was static in nature and based on a short timeframe of 1 month for the primary analysis, and the lifetime costs and outcomes associated with transfusion were not included in the model. The time horizon was extended up to 30 years in the secondary analyses. The static structure of the model was based on the assumption that the values of the variables included would not change significantly over time. There is no evidence to suggest that this is an unreasonable assumption for the timeframes considered in the primary and secondary analyses.

The model included short-term changes in the outcomes and costs associated with the adverse events included in the model. However, the costs and outcomes associated with adverse events that are chronic in nature and have an impact on lifetime use of healthcare and on outcomes are likely to change over time. For example, the costs and consequences of transfusion-transmitted infections are likely to increase over time. These are not incorporated in the model structure or time horizon for the primary analysis. The likelihood of transfusion-transmitted infections and adverse events related to transfusion only were very low (less than 0.1%). In addition, the systematic reviews indicated that there were no statistically significant differences in the rates of other adverse events that could have been caused by surgery or transfusion. The review of published economic evaluations (which generally included higher estimates of the incidence of transfusion-transmitted infections than those included in this model) indicated that transfusion-transmitted viral infections such as hepatitis and HIV have a limited impact on the relative long-term costs and benefits of alternative transfusion strategies.[60,61] This is because the probabilities of transfusion-transmitted viral infection in the study settings used were extremely low. In addition, adverse events with higher probabilities of occurrence and short-term impacts, such as bacterial infection, are more likely to affect the relative cost-effectiveness of alternative transfusion strategies.[60,61] These factors suggest that the static structure and short timeframes used for this model were unlikely to

affect substantially the overall conclusions. In addition, the static structure of the model and the timeframe of analysis are likely to bias the results in favour of transfusion strategies associated with higher rates of allogeneic blood transfusion. This favours the allogeneic blood transfusion strategy, ANH, FSs, AFs and EPO rather than cell salvage.

To test the potential impact of incorporating longer time horizons, the secondary analyses included use of 10- and 30-year timeframes. These indicated that as in the primary analysis, cell salvage was likely to be more cost-effective than allogeneic blood only, PAD plus EPO and allogeneic blood transfusion with FSs, AFs or EPO. However, the longer time horizons suggested that PAD may be more cost-effective than cell salvage. This was due to the potential impact of stroke, an adverse event that could be due to either surgery or transfusion. Transfusion-transmitted viral infections did not affect the relative cost-effectiveness of cell salvage. The systematic reviews of clinical evidence indicated that although there were differences in the number of strokes between allogeneic and autologous transfusion techniques, these were not statistically significant. Therefore, it is not clear whether the differences observed in the rates of this event were due to transfusion, surgery or the underlying health of the patient. Problems and uncertainty associated with the adverse event data are discussed in more detail below. These factors indicate that longer term studies are required to evaluate the occurrence of adverse chronic events and the long-term health and mortality of transfusion patients.

The structure of the model was developed from the reviews of clinical and economic evidence discussed above and discussion with experts in transfusion in both the project team and the expert panel. However, lack of data meant that the range of events included in the model was constrained to those for which data were available on the rate or likelihood of occurrence from either the systematic reviews of published effectiveness literature or were reported in the Serious Hazards of Transfusion Annual reports.[6,68,69] This meant that the analysis was restricted to serious events associated with blood transfusion. In addition, a number of potentially serious events were excluded that may have an impact on both resources and costs and overall quality of life. These include some of the possible transfusion-transmitted infections (syphilis, *T. cruzi*, cytomegalovirus), which may bias the analysis in favour of strategies that are associated with higher rates of allogeneic blood transfusion. The fact that these infections are not reported in either the SHOT Annual Reports or systematic reviews does not necessarily mean that the incidence of the infections is zero. However, it is likely that the incidence of these infections in the UK blood transfusion system is very low, given improved methods to reduce the incidence of transfusion-transmitted infection in the UK setting. These include the use of leucodepletion for all blood products to be used for transfusion. Leucodepletion reduces the theoretical risk of vCJD and the risk of cytomegalovirus. In addition, a number of other events were excluded owing to lack of information about the likely incidence or probability that they would occur. These include transfusion-related complications (gastrointestinal symptoms, hypersensitivity, phlebitis, platelet refractoriness, non-fatal air embolism) and complications where the cause could be surgical or transfusion related (e.g. multi-organ failure, bacterial infection due to immunosuppression).

The primary and secondary analyses used QALYs as the outcome measure to estimate ICERs, net benefit and CEACs. QALYs take into account differences in potential survival and the impact of adverse events on overall HRQoL. QALYs potentially provide a method to weight the impact of differences in the morbidity of adverse events by the impact of the adverse event on health status and overall HRQoL. QALYs tend to be weighted by mortality and may be less sensitive to adverse events that have a short or relatively low impact on quality of life. This may bias the analysis if one or more interventions are associated with high rates of adverse events that individually have a relatively low impact on health, but cumulatively could have a significant impact on health and HRQoL. Overall, the estimates of expected QALYs followed the estimates of number of lives with adverse events and the differences between cell salvage and other transfusion strategies was similar between the two measures of outcome. Additionally, the estimate of QALYs also took into account the utility associated with surgery and inpatient hospital stay, which is not captured by the measure of lives with no adverse event. These factors suggest that the QALY is a reasonable measure for the economic analysis. The use of QALYs in the economic analysis also makes the evaluation consistent with the approach used for reports to the National Institute for Health and Clinical Excellence.

Strengths and weaknesses of the data

Systematic review

None of the included transfusion strategies appeared to have an effect on the incidence of adverse events. However, the data were insufficient to draw conclusions of the effect of any of the transfusion strategies on important clinical events. Many of the adverse events were reported in an *ad hoc* manner, so that a clear set of adverse events was not reported consistently between the individual studies. These factors mean that it is not possible to assess whether there was sufficient power to detect clinically and statistically important differences in the occurrence of adverse events.

Some of the transfusion strategies were not specifically assessed in cardiac or orthopaedic surgery settings. This meant that additional assumptions had to be made about the benefits of alternative transfusion strategies in the economic model (discussed further below).

The cell salvage systematic review included a subgroup analysis that compared cell salvage to allogeneic blood according to whether the active and control groups also included an active treatment or not. The treatment effect excluding the trials with an additional active treatment effect in both arms was slightly lower, with a wider CI (RR 0.59, 95% CI 0.48 to 0.73) than that for all trials (RR 0.61, 95% CI 0.52 to 0.71). The impact of additional active treatments in the comparator and control arms was not assessed in the systematic reviews of the other transfusion strategies. The fact that many participants may have received other active treatments (albeit in both arms) makes it difficult to ascertain the independent effects of the transfusion strategies.

There were no direct comparisons of cell salvage with transfusion strategies other than allogeneic transfusion alone. This means that only indirect comparisons can be made of the differences in RR compared with allogeneic blood. The lack of direct comparisons means that it is not possible to ascertain whether differences in the RR of exposure to allogeneic blood are due to differences in effect or differences in the samples of participants studied. The lack of direct comparisons combined with inconsistent reporting on adverse outcomes means that any assessment of the effectiveness of cell salvage, compared with transfusion strategies other than allogeneic blood transfusion alone, can only be exploratory of potential differences and is therefore uncertain.

The majority of the trials included in the systematic reviews were not conducted in the UK, which may reduce the relevance of the results to a UK setting if there are differences in transfusion or surgical practice, or the clinical, social or demographic characteristics of participants, that could affect the need for transfusion with allogeneic or autologous blood, or the use of pharmacotherapy to minimise blood loss.

Economic model

The data used to estimate the probability of transfusion-related complications and some of the transfusion-transmitted infections were estimated from surveys of the serious hazards of transfusion in UK practice.[6,68,69] These surveys relied on self-report of serious hazards of transfusion to obtain data on the annual number of these events in the UK. This may lead to under-reporting of these adverse events. The SHOT report for 2003 noted that 85% of hospitals reported participating in the serious hazards of transfusion scheme, yet only 47% of hospitals reported any adverse event.[6] The surveys also reported that there were very few reports of adverse events as a consequence of autologous transfusion and noted that systems to report and collect these data systematically were not in place.[6] The serious hazards of transfusion reports did not include denominator data on the annual number of transfusions to estimate the probability of an adverse event per allogeneic or autologous transfusion. These data were not available from the National Blood Service or national statistics. Therefore, the number of allogeneic transfusions was estimated from a national audit report of the performance of the UK blood service.[4] The number of autologous transfusions was estimated from a survey of transfusion practice in the UK.[26] The accuracy of these sources of data is not clear. It is not clear whether, overall, the combination of these factors leads to under- or overestimation of adverse events related to transfusion only.

In addition, the data used to estimate the likelihood of adverse events associated with allogeneic blood transfusions gave numbers of people having a transfusion with an event. There was insufficient information to estimate the likelihood of events by the number of units of allogeneic blood transfused. If the likelihood of adverse events increases with the volume of allogeneic blood transfused, this means that these data will be underestimates. This would bias the analysis in favour of those transfusion strategies that are associated with higher volumes of allogeneic blood transfused.

The results of the primary analysis were tested in secondary analyses to explore the impact of subsets of data. Overall, the secondary analyses supported the results of the primary analysis. However, it should be noted that these secondary analyses were based on smaller numbers of trials and patients than used in the primary analysis. This could magnify the uncertainty associated with the data from the systematic reviews and reduce the robustness of the economic analysis still further. The secondary analyses should therefore be treated with caution and considered as indicative of potential differences between alternative methods of transfusion.

As noted above, the clinical evidence used in the model was judged by the systematic reviews to be of generally low quality. In addition, the lack of systematic collection and analysis of data from direct comparisons of cell salvage with transfusion strategies other than allogeneic blood transfusion alone meant that a number of assumptions were required for the economic model. It was assumed that combining the allogeneic control arm data across all the trials included in all the systematic reviews would provide a baseline population that provided an accurate estimate of the need for allogeneic transfusion and associated units of allogeneic blood transfused, length of hospital inpatient stay and adverse events. The estimates of these variables seem to be consistent with the range of estimates produced in the systematic reviews of the alternative transfusion strategies[13,21,29–33] and with the range of estimates used in previous economic evaluations[36–38,57–65] and data for the UK.[71,72]

A second assumption made was that applying estimates of transfusion strategy-specific absolute risk differences and absolute WMDs to the allogeneic strategy estimates provided accurate and robust estimates of (a) the differences between the alternative transfusion strategies and allogeneic blood only and (b) the differences between the alternative transfusion strategies to minimise exposure to allogeneic blood. This requires the further assumptions that (a) the absolute risk differences found for the patient samples used in the clinical trials do not differ from those that would be found for a pooled patient sample (i.e. the only difference from the trial patient samples and the pooled patient samples is the baseline need for transfusion) and (b) the estimates of events derived by applying these absolute differences to the pooled sample accurately reflect the relative differences between the alternative transfusion strategies to minimise allogeneic blood transfusion. Inspection of the few trials where the active transfusion strategy was compared with the allogeneic blood transfusion plus an alternative active transfusion strategy suggests that these assumptions provide similar estimates of differences. However, the validity of these assumptions and associated uncertainty can only be fully explored with additional data from prospective direct comparisons of cell salvage with the alternative transfusion strategies to minimise exposure to allogeneic blood.

Generally, there was a lack of UK-specific resource use data from prospective randomised trials or well-controlled observational studies. However, two key variables for the model were the number of units of allogeneic blood transfused and length of hospital stay for the index admission. These were taken from the systematic reviews of clinical evidence. As noted above, the data for these variables seem to compare well with available UK data from national statistics and surveys for blood transfusion and elective surgical procedures.[71,72] In addition, the data from the trials indicate that when cell salvage was compared with allogeneic blood transfusion only, it was associated with statistically significant reductions in the units of allogeneic blood transfused per transfusion and average length of stay in hospital. This supports the finding of lower expected costs for cell salvage. The cost per unit of allogeneic blood was derived from national prices. The costs of resources for the operation, the cost per inpatient day and the cost of transfusion-related services were taken from SMUHT. This may limit the generalisability of the cost data and therefore the results of the economic model to other settings.

There was a lack of data in either published studies or national statistical databases about the use of resources to estimate the costs of adverse events and transfusion-transmitted infections in the UK. The same lack of data was found for estimates of the impact of these adverse events on health status and the utility or HRQoL of these adverse events. Again, a number of assumptions were required to estimate the costs and consequences of these events. However, the extremely low probabilities associated with the adverse events mean that the impact of these variables on total expected costs and outcomes was also very low.

For the primary analysis, the model uses pooled data for all types of cell salvage. The costs of cell salvage are based on the costs of washed cell salvage, which are higher than those of unwashed

cell salvage. However, washed cell salvage is associated with a slightly higher level of effectiveness than unwashed cell salvage. This biases the primary analysis against cell salvage. The secondary analyses suggest that the results varied according to surgical procedure, timing and technique of cell salvage. The probability of allogeneic blood transfusion, units of blood transfused and average length of stay all vary according to the elective surgical procedure. The impact of surgical procedure on the relative cost-effectiveness of cell salvage was tested in the secondary analysis. This indicated that overall, the relative cost-effectiveness of cell salvage did not differ by surgical procedure. The impact of both surgical procedure and timing and technique of cell salvage was also explored in the secondary analyses. These indicated that cell salvage could still be cost-effective if washed intraoperative cell salvage was used in cardiac procedures and unwashed postoperative cell salvage was used in orthopaedic procedures. However, it should be noted that these analyses used subsets of data, with smaller numbers of trials and patients.

Data were not directly available on the number of cases that can be treated with one cell salvage machine and associated equipment and staff. This meant that the costs of cell salvage were based on estimates of activity levels derived from (a) a survey of UK practice that included data on the number of units of autologous blood transfused by different methods of autologous transfusion practice and (b) estimates of the units of autologous blood transfused from the trials included in the systematic reviews. However, the secondary and budgetary impact analyses indicated that the relative cost-effectiveness of cell salvage estimated by this economic model was not substantially affected by estimates of activity levels.

Comparison of the economic model with other studies

The review of published economic evaluations of different transfusion strategies indicated wide variations in the conclusions about the relative cost-effectiveness of autologous blood transfusion in general and cell salvage in particular. The results of the economic model for this study are consistent with five studies that found autologous transfusion techniques to be cost-effective compared with allogeneic blood transfusion alone.[37,59–61,63] The results of this study are not consistent with those that found autologous transfusion was not cost-effective.[36,38,57,58,62,64,65] Only two studies evaluated cell salvage, which was compared with allogeneic blood transfusion alone. One of these found that cell salvage was cost-effective[63] and the other did not.[62] There were no economic evaluations that compared cell salvage with the other alternative transfusion strategies evaluated in this study. The differences in findings between this study and previous economic evaluations are likely to be due to a number of factors. First, differences in the estimates of the rates of adverse events: the rates of transfusion-transmitted infection used for this study are lower than those used in previous evaluations, reflecting improvements in blood safety over recent years. Second, differences in the estimates of resource use and unit cost associated with allogeneic blood and autologous transfusion: the length of inpatient stay used in this study was estimated directly from the trials included in the systematic reviews of the alternative transfusion strategies, and found a small reduction in inpatient stay. In contrast, several of the previously published economic evaluations did not include length of inpatient stay as a variable. In addition, the cost per unit of allogeneic blood used in this study is higher and closer to the cost per unit of autologous blood, again reflecting changes in the processing and supply of allogeneic blood to improve blood safety. The main additional cost of autologous blood is that the cost per unit of autologous blood is incurred for all patients having surgery, irrespective of whether they have a transfusion. This is offset by small differences in the length of hospital stay for the index hospital admission for elective surgery.

Limitations

The model used data from clinical trials that were mostly conducted outside the UK. These data were synthesised with UK-specific resource use, costs and utility values. Estimates for key resource use and cost variables were derived from the systematic reviews and associated clinical trials, and so may not be generalisable to UK practice. However, as discussed above, these estimates appear similar to data for the UK overall. This suggests that the results of the economic model are applicable to the UK setting and current practice. Data on the resources required pre- and perioperatively for both allogeneic and autologous transfusions were derived from activity data and trial datasets held by one hospital trust. There is a lack of data to assess the extent to which these data are an accurate representation for other settings in the UK. Again, this adds to the level of

uncertainty about the extent to which the results can be applied to UK practice.

Additionally, it should be noted that transfusion practice is changing rapidly, which raises two limitations to the results reported here. First, the data on the likelihood of events and some items of resource use were estimated from systematic reviews that included clinical trials published between 1979 and 2004. The costs of the transfusion strategies were estimated from current practice and technology. This means that the effectiveness of the transfusion strategies includes older technologies that may be less effective than the newer technologies used to estimate costs. This may underestimate the relative cost-effectiveness of transfusion strategies where there have been rapid changes in technology. The equipment used for cell salvage has changed over the last 10–20 years and the costs of the equipment are still changing. Hence the relative cost-effectiveness of cell salvage may be higher than that estimated in this study, if there have been no substantial changes to the technologies used for the alternative transfusion strategies. The second limitation is that of rapidly changing technologies so that the lifespan of the results of this study may be limited to a few years, if the estimates of effectiveness and costs also change.

The use of UK-specific resource use, unit cost and utility data and probabilities of transfusion-related complications and transfusion-transmitted infections limit the extent to which the results can be generalised to settings with different values for these variables. In particular, the results of this analysis may not be applicable to countries with higher rates of transfusion complications and transfusion-transmitted infections.

For the purposes of the systematic review and economic modelling, cell salvage was categorised on the basis of timing (intra- or postoperative) and technique (washed or unwashed). These classifications were assigned on the basis of the individual studies and their descriptions of the techniques used. In some cases it was difficult to determine the exact mode of the intervention as inadequate details were given.

In clinical practice, the timing of cell salvage (intra- or postoperative) relates to the expected dynamics of blood loss for a given procedure. For example, in abdominal aortic aneurysm repair, the majority of the blood loss would be expected to occur during surgery, whereas in total knee replacement under tourniquet, surgical bleeding is only initiated at the end of the procedure when the tourniquet is released. Similarly, there are also surgical procedures in which blood loss occurs both during and after the operation.

The earliest of the studies included in this study dates back to 1979, and the majority of the trials are at least 10 years old. Some of the cell salvage devices used are now obsolete as technology has become more sophisticated and transfusion practice has changed. Although some studies used unwashed systems intraoperatively, it is unlikely that this practice would be currently appropriate or acceptable for intraoperative cell salvage in the UK. This is because the quality of unwashed salvaged blood is highly variable and could contain potentially dangerous contaminants that would not necessarily be removed by filtration. Current transfusion guidelines refer explicitly to the use of washed rather than unwashed cell salvage.[82] Devices currently available for intraoperative cell salvage all have a washing function, with unwashed systems being reserved exclusively for postoperative salvage where blood is lost into wound drains. New machines have also been developed to enable both intra- and postoperative blood loss to be collected continuously, providing washed cell salvage for the majority of the blood loss experienced.

The effectiveness of cell salvage is limited to the amount of blood that can be successfully scavenged: if there is no significant blood loss the patient will not receive a transfusion of autologous blood. In postoperative cell salvage from wound drains, manufacturers recommend that autotransfusion should only proceed following a minimum loss of 200 ml. Similarly, most cell washing devices generally require a minimum blood volume, dictated by the processing set bowl size, to ensure adequate washing and safety of the product. The studies reported in the systematic review of cell salvage showed that only 64% of patients received a transfusion of autologous blood, reflecting the variability of blood loss in these procedures. In any given group of patients undergoing the same surgical procedure there will always be inconsistencies in the amount of blood loss experienced relating to clinical characteristics of the individual patients and sometimes to the surgeon performing the operation. When blood loss is highly variable, the cost of intraoperative cell salvage can be reduced by performing a partial set-up to collect blood into the reservoir only, reserving the decision to process as appropriate.

In intraoperative cell salvage, the efficiency of red cell recovery in cell salvage is not widely reported. There is always the potential for haemolysis if vacuum pressures are too high or if blood is aspirated by surface skimming as opposed to pools of blood. Sometimes, however, the nature of the surgical bleeding dictates that the blood–air interface which causes cellular damage may be inevitable, irrespective of vacuum pressures. In those surgical cases were blood loss oozes from a large surface area, swabs are often used to remove the blood from the field. Washing surgical swabs to recover red cells can increase the efficiency of the process by around 30%.[85]

This evaluation indicates that there are number of blood transfusion strategies that individually are effective in reducing allogeneic blood transfusion requirements. The systematic reviews and economic model focused on the need for and volume of allogeneic RBC transfusion. However, some of the transfusion strategies included in the study may also impact on the need for other allogeneic blood products such as fresh frozen plasma and platelets. Interventions which address coagulopathy, such as AF drugs, will not only reduce red cell requirements but may also influence the need for blood products. The advent of near-patient testing devices, such as thromboelastographs, to detect developing coagulopathies allows a timelier and appropriate intervention.

Good transfusion practice should consider all of the interventions included in this study. In the UK, Better Blood Transfusion initiatives have directed clinicians to a culture of 'appropriate' blood transfusion. Concerns over falling blood stocks, particularly in relation to the potential impact of a vCJD test, have also led to the development of integrated plans for dealing with blood shortages. Blood conservation and the need for education, preoperative planning and alternative transfusion strategies are central to this strategy.

A recent pilot of cell salvage (in the Trent region) gave rise to a number of recommendations, including the need for hospitals to identify the staff they wish to use the intraoperative cell salvage equipment, the need for certificated training in the use of cell salvage equipment and a documented record of training and assessment of ongoing competency kept by each hospital. Until recently, users were largely reliant on machine manufacturers to provide specialised training with competencies determined locally. The advent of national occupational standards, via the Skills for Health organisation, has improved this situation.

The analysis indicates that cell salvage may result in reduced demand for and use of allogeneic blood in elective surgery. Such savings could contribute to the overall effort to conserve and manage the current and future allogeneic blood stock. The need for blood conservation is further strengthened by the practical difficulties in facilitating PAD in the UK. The EU Directive 2002/98/EC, which was adopted into UK law in February 2005, demands that PAD blood be treated in exactly the same way as allogeneic blood. This means that locally organised PAD schemes will have to meet the same stringent quality control and assurance procedures set in place for the NHS BTA, will potentially require accreditation and will be open to inspection. It is likely, therefore, that the future of PAD is limited to a small number of cases which can be dealt with directly by the NHS BTA. These will include patients with rare blood types or combinations of red cell antibodies, patients donating bone marrow and patients who refuse their surgery without it.

This study has focused on the use of cell salvage and alternative transfusion strategies in elective surgery. The use of these methods to conserve blood in emergency surgery was not considered. In emergency surgical procedures, where the need for blood transfusion and volume of blood transfused is high, the benefits of cell salvage and other methods of minimising allogeneic blood use are likely to be enhanced.

Chapter 9
Conclusions

Implications for healthcare

The overall aims of this review were to compare patient outcomes, resource use and costs to the NHS and NHS BTA associated with cell salvage. The available evidence indicates a number of conclusions. However, it should be noted that these are subject to a number of caveats discussed in Chapter 7, about the quality and reliability of the data used, which may affect the reliability and robustness of the results. Many of the trials included in the clinical review of data were conducted outside the UK. In addition, the results of the economic model for this study are based on indirect comparisons of effectiveness data from different studies, which may under- or overestimate the relative effectiveness of cell salvage. It should also be noted that the evidence from which these conclusions are drawn relates to a specific population, that is, those people undergoing elective surgery that involves moderate to major blood loss. All of these factors may limit the extent to which the results are generalisable to different populations for elective surgery in the UK. The implications for the use of cell salvage in the UK are summarised below.

1. The analysis indicates that cell salvage may be an effective and cost-effective alternative to the allogeneic blood transfusion strategy. This applies to patients for whom there is no clinical reason to avoid allogeneic blood completely and transfusion of allogeneic blood is acceptable to the patient.
2. The analysis indicates that for a patient for whom there is no clinical reason to avoid allogeneic blood completely and transfusion of allogeneic blood is acceptable to the patient, cell salvage is likely to be more cost-effective than PAD (plus or minus EPO), but not ANH, in the short term. If the predicted life expectancy of the patient is greater than 5 years, PAD and ANH may be more cost-effective than cell salvage. However, the results for the longer term analysis are driven primarily by stroke, an adverse event that may be due to either surgery or transfusion. The review of clinical evidence suggested that there were no statistically significant differences in the rate of stroke between allogeneic and autologous transfusion techniques.
3. The analysis indicates that for patients for whom there is no clinical reason to avoid allogeneic blood completely and transfusion of allogeneic blood is acceptable to the patient, cell salvage is likely to be more cost-effective than allogeneic blood transfusion plus AFs, FSs or EPO.
4. The analysis indicates that washed intraoperative cell salvage may be more cost-effective than postoperative cell salvage in cardiac procedures. However, this analysis is based on a subset of trials from the systematic reviews. This increases the level of uncertainty associated with the data and reduces the robustness of the results.
5. The analysis indicates that unwashed postoperative cell salvage may be more cost-effective than intraoperative cell salvage in orthopaedic procedures. However, this analysis is based on a subset of trials from the systematic reviews. This increases the level of uncertainty associated with the data and reduces the robustness of the results. In addition, there are risks attached to the use of unwashed cell salvage that mean it is not appropriate or acceptable for intraoperative procedures and washed cell salvage may be more acceptable for postoperative procedures.
6. The analysis indicates that for patients for whom there is no clinical reason to avoid allogeneic blood completely and transfusion of allogeneic blood is acceptable to the patient, ANH is more likely to be cost-effective than cell salvage. The analysis did not directly compare ANH with any of the other blood transfusion strategies. This means that it is not appropriate to draw conclusions about the cost-effectiveness of ANH overall. However, the results do indicate that further research may be appropriate to assess the relative cost-effectiveness of ANH compared with the other blood transfusion strategies (discussed further below).
7. The analysis indicates that, on average, cell salvage could halve the volume of allogeneic blood used in each operation. If blood transfusion is required in 1% of all elective

surgery each year, and cell salvage was used in 10% of these (58,000 operations), then cell salvage would reduce the annual allogeneic blood requirement for elective surgery by 6500 units. If blood transfusion is required in 7% of all elective surgery and cell salvage is used in 50% of these operations (350,000), then cell salvage would reduce the annual allogeneic blood requirement for elective surgery by 229,000 units. This equates to approximately 10% of the units of allogeneic blood issued by the NHS BTA in 2003. If cell salvage is used for a lower proportion of operations, or is effective in reducing allogeneic blood requirement in fewer operations, then other measures may be required if the demand for allogeneic blood increases faster than supply.

8. Adopting cell salvage more widely within NHS hospitals may have significant organisational and management implications. Hospital Trusts will have to decide who will operate cell salvage devices and whether it is possible to accommodate these activities within their existing establishment. Currently throughout the UK, cell salvage machines are operated by a range of healthcare staff, such as nurses, perfusionists and anaesthetists, each centre having devised a solution that meets their individual circumstances. Without a coordinated approach, providing specialist resources and training, uptake is likely to be variable. There still exist some areas of controversy surrounding the use of cell salvage techniques in particular clinical situations. The National Blood Conservation Strategy, produced by the National Blood Transfusion Committee and NHS BTA in 2004,[24] suggested the following measures to promote the introduction of cell salvage: appropriate use of cell salvage as an achievable target for trusts; a website-based 'tool kit'; review of budget allocation; training initiatives; and template protocols. As yet, these recommendations have been slow to be implemented. Without the necessary support, it is probable that the impact of cell salvage and appropriate transfusion alternatives will continue to be muted.

Recommendations for further research

1. Adequately powered high-quality RCTs that report short- and long-term patient outcomes are needed to allow the assessment of the clinical and patient value of avoiding allogeneic blood transfusion and indeed receiving autologous blood transfusion. This review has identified a lack of data relating to short-term adverse events that may be due to either the surgical procedure, the process of transfusion or whether allogeneic or autologous blood was transfused. The outcome measures used in further clinical evaluations should concentrate on these events and their impact on the health status and HRQoL of the patient. Patient preferences for alternative transfusion strategies also need to be assessed.
2. Adequately powered high-quality RCTs to confirm or reject potential differences between cell salvage and alternative transfusion strategies according to surgical procedure, timing and technique of cell salvage are required. These need to include the short- and long-term patient outcomes discussed above.
3. The results of the analysis indicate possible differences in the likely cost-effectiveness of cell salvage compared with other techniques to minimise blood loss (i.e. ANH, PAD with or without EPO, EPO, AFs, FSs and EPO alone). However, these results were based on indirect comparisons of the clinical effectiveness of technologies. RCTs are needed that are adequately powered to detect important differences in adverse events such as stroke and the patient-related outcomes outlined above. Such RCTs should aim to provide direct head-to-head comparisons of cell salvage with alternative methods of minimising allogeneic blood use. These trials should be powered and designed to test whether cell salvage is more or less effective and cost-effective than the alternatives.
4. The increased effectiveness and lower costs of ANH compared with cell salvage suggested by this analysis also require confirmation by a well-designed RCT.
5. In addition, the analysis reported here did not include comparison of cell salvage versus ANH plus cell salvage, or other possible combinations of autologous techniques. This was because of a lack of robust clinical evidence of the effectiveness of these strategies. These combinations could include PAD plus cell salvage, PAD plus ANH, PAD followed by ANH, followed by intraoperative and/or postoperative cell salvage. Additional pilot studies and RCTs are required to assess the feasibility, effectiveness and cost-effectiveness of combinations of autologous strategies.
6. Observational and tracking studies are needed to document the number of adverse events and

infections as a consequence of transfusion. Such studies are required to produce reliable estimates of the incidence of these adverse events and infections transmitted during blood transfusion. Most of the current evidence about the incidence of the serious hazards of transfusion in the UK relies on self-report of their occurrence by participating hospitals. Although participation in the scheme is high, it is not clear whether all events are reported, particularly for adverse events related to autologous transfusion. In addition, there are no denominator data about the number of transfusions over which these events occurred. The new European Union Blood Directive[86] will require a centralised system of reporting adverse events relating to blood transfusion, and this, coupled with the European network on haemovigilance (www.ehn-org.net), should aid systematic reporting. Further research should classify the incidence of serious hazards of transfusion by whether the transfusion was for surgical or medical treatment. Again, pilot and audit studies are required to inform the design of large-scale studies and haemovigilance assessment.

7. The review of the clinical and economic literature for this study identified that there was little evidence about long-term survival associated with transfusion and with the serious hazards of transfusion. Further research about the long-term effects of transfusion on survival and the long-term effects of the serious hazards of transfusion on survival, health status and HRQoL is required. However, such studies need to be designed with care, since the effects of transfusion are likely to be confounded by the underlying age and morbidity of the population transfused.
8. Further research should also include documentation of the need for and use of health and social care services and costs. The economic model indicates that the long-term costs and outcomes are potentially important determinants of the relative costs and benefits of the alternative autologous techniques. As further data become available about the long-term costs and outcomes, these should be used to extend the time horizon for the economic model reported here. The systematic collection of transparent costing data coupled with long-term clinical outcome data and the incorporation into future economic models would have the potential to improve greatly the robustness of economic models of the cost-effectiveness of various transfusion strategies.

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Linda Davies (Reader and Director of Health Economics Research) was involved in designing, coordinating and securing funding for the review and economic analysis, screening economic search results, appraising the quality of the economic evaluations, abstracting data from primary resources and other sources, carrying out the economic analysis, designing a decision analytic model, synthesising clinical and economic data to generate probabilistic cost-effectiveness ratios, CEACs, sensitivity analysis of the model, writing of the economic chapters of the review, incorporating edits, final editing of the report and providing an economic perspective. Tamara Brown (Research Associate) was involved in developing the protocol, designing and running the electronic search strategies, screening search results, organising retrieval of papers, appraising quality of studies, abstracting data, contacting authors for additional information, performing meta-analysis and subgroup analyses of RRs, synthesis of data for the economic model including obtaining absolute risk reductions, interpretation of the data, project management including liaison with external advisors, writing of the first draft of the report on the systematic review and the review of economic evaluations, incorporating the edits of others, final editing of the report, writing two Cochrane updates of existing systematic reviews and providing a methodological perspective. Sarah Haynes (Autologous Transfusion Coordinator/Lecturer in Transfusion Medicine) provided expert knowledge of practical and technical aspects of blood transfusion and alternatives, assisted in determining relevance of studies for potential inclusion in the updates of the two systematic reviews, provided primary resource data, attended project team meetings and contributed to and edited the final report. Katherine Payne (Research Fellow) was involved in designing, coordinating and securing funding for the review and economic analysis, designing electronic search strategies, editing the systematic review and economic analysis, final editing of the report and providing an economic perspective. Rachel Elliott (Clinical Senior Lecturer) was involved in designing, coordinating and securing funding for the review and economic analysis, designing electronic search strategies, editing the systematic review and economic analysis, final editing of the report and providing an economic perspective. Charles McCollum (Professor of Surgery) was involved in designing, coordinating and securing funding for the review and economic analysis, advised on the clinical issues concerning blood transfusion in surgery and commented on the study protocol and the draft reports and final report.

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Appendix 1

Search strategies for the update of the Cochrane systematic reviews of cell salvage and preoperative autologous donation

Cell salvage search in MEDLINE (via OVID)

1. cell$ sav$.mp.
2. cell$ salvage.mp.
3. blood transfusion, autologous/
4. autotransfusion$.mp.
5. auto-transfusion$.mp.
6. blood salvage.mp.
7. autovac.mp.
8. solcotrans system.mp.
9. constavac.mp.
10. solcotrans.mp.
11. hemovac.mp.
12. BRAT.mp.
13. fresenius.mp.
14. consta vac.mp.
15. cell saver.mp.
16. dideco.mp.
17. electromedic.mp.
18. electromedics.mp.
19. gish biomedical.mp.
20. haemonetics.mp.
21. orth-evac.mp.
22. pleur-evac.mp.
23. sorenson.mp.
24. reinfusion system.mp.
25. sorin biomedical.mp.
26. or/1-25
27. exp blood transfusion/
28. exp hemorrhage/
29. exp anesthesia/
30. transfusion$.mp.
31. bleed$.mp.
32. blood loss$.mp.
33. hemorrhag$.mp.
34. haemorrhag$.mp.
35. or/27-34
36. 26 and 35
37. randomized controlled trial.pt.
38. controlled clinical trial.pt.
39. randomized controlled trials.sh.
40. random allocation.sh.
41. double blind method.sh.
42. single blind method.sh.
43. or/37-42
44. clinical trial.pt.
45. exp Clinical trials/
46. (clin$ adj25 trial$).ti,ab.
47. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
48. placebos.sh.
49. placebo$.ti,ab.
50. random$.ti,ab.
51. research design.sh.
52. or/44-51
53. comparative study.sh.
54. exp Evaluation studies/
55. follow up studies.sh.
56. prospective studies.sh.
57. (control$ or prospectiv$ or volunteer$).ti,ab.
58. or/53-57
59. 43 or 52 or 58
60. 36 and 59
61. animal/ not human/
62. 60 not 61
63. limit 62 to yr=2002-2004

Cell salvage search in EMBASE (via OVID)

1. cell$ sav$.mp.
2. cell$ salvage.mp.
3. blood transfusion, autologous/
4. autotransfusion$.mp.
5. auto-transfusion$.mp.
6. blood salvage.mp.
7. autovac.mp.
8. solcotrans system.mp.
9. constavac.mp.
10. solcotrans.mp.
11. hemovac.mp.
12. BRAT.mp.
13. fresenius.mp.
14. consta vac.mp.
15. cell saver.mp.
16. dideco.mp.
17. electromedic.mp.
18. electromedics.mp.
19. gish biomedical.mp.
20. haemonetics.mp.

21. orth-evac.mp.
22. pleur-evac.mp.
23. sorenson.mp.
24. reinfusion system.mp.
25. sorin biomedical.mp.
26. or/1-25
27. exp blood transfusion/
28. exp Bleeding/
29. exp anesthesia/
30. transfusion$.mp.
31. bleed$.mp.
32. blood loss$.mp.
33. hemorrhag$.mp.
34. haemorrhag$.mp.
35. or/27-34
36. 26 and 35
37. exp clinical trial/
38. controlled study/
39. randomized controlled trial/
40. randomization/
41. major clinical study/
42. double blind procedure/
43. single blind procedure/
44. crossover procedure/
45. clinical study/
46. prospective study/
47. longitudinal study/
48. comparative study/
49. evaluation/
50. "evaluation and follow up"/
51. evaluation stud$.tw.
52. comparative stud$.tw.
53. follow?up.mp.
54. placebo$.mp.
55. random$.tw.
56. cross?over$.tw.
57. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
58. (clin$ adj25 trial$).tw.
59. (control$ or prospectiv$ or volunteer$).tw.
60. or/37-59
61. 36 and 60
62. exp animal/
63. nonhuman/
64. human/
65. 62 or 63
66. 65 not 64
67. 61 not 66
68. limit 67 to yr=2002-2004

Cell salvage search in Web of Science (via OVID)

TS = ((CELL SAV* OR CELL SALVAGE OR AUTO?TRANSFUSION OR BLOOD SALVAGE) AND (TRANSFUSION OR BLEED* OR AN?ESTHESIA OR BLOOD LOS* OR H?EMORRHAG*))

Cell salvage search in Cochrane Central Register of Controlled Trials (via National Electronic Library for Health)

#1. (cell* next sav*)
#2. (cell* next salvage)
#3. BLOOD TRANSFUSION AUTOLOGOUS single term (MeSH)
#4. autotransfusion
#5. (auto next transfusion)
#6. (blood next salvage)
#7. (#1 or #2 or #3 or #4 or #5 or #6)
#8. BLOOD TRANSFUSION explode tree 1 (MeSH)
#9. HEMORRHAGE explode tree 1 (MeSH)
#10. ANESTHESIA explode tree 1 (MeSH)
#11. transfusion*
#12. bleed*
#13. (blood next loss*)
#14. hemorrhag*
#15. haemorrhag*
#16. (#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15)
#17. (#7 and #16)
#18. (#7 and #16) (2002 to current date)

PAD search in MEDLINE (via OVID)

1. Blood Transfusion, Autologous/
2. pre-operative autologous donat$.mp.
3. autologous blood donat$.mp.
4. autologous blood transfus$.mp.
5. autologous predonat$.mp.
6. or/1-5
7. exp Blood Transfusion/
8. exp Hemorrhage/
9. exp Anesthesia/
10. transfusion$.mp.
11. bleed$.mp.
12. blood loss$.mp.
13. hemorrhag$.mp.
14. haemorrhag$.mp.
15. or/7-14
16. 6 and 15
17. randomized controlled trial.pt.
18. controlled clinical trial.pt.
19. randomized controlled trials.sh.
20. random allocation.sh.
21. double blind method.sh.

22. single blind method.sh.
23. or/17-22
24. clinical trial.pt.
25. exp Clinical trials/
26. (clin$ adj25 trial$).ti,ab.
27. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
28. placebos.sh.
29. placebo$.ti,ab.
30. random$.ti,ab.
31. research design.sh.
32. or/24-31
33. comparative study.sh.
34. exp Evaluation studies/
35. follow up studies.sh.
36. prospective studies.sh.
37. (control$ or prospectiv$ or volunteer$).ti,ab.
38. or/33-37
39. 23 or 32 or 38
40. 16 and 39
41. animal/ not human/
42. 40 not 41
43. limit 42 to yr=2001-2004

PAD search in EMBASE (via OVID)

1. Blood Transfusion, Autologous/
2. pre-operative autologous donat$.mp.
3. autologous blood donat$.mp.
4. autologous blood transfus$.mp.
5. autologous predonat$.mp.
6. or/1-5
7. exp Blood Transfusion/
8. exp Bleeding/
9. exp Anesthesia/
10. transfusion$.mp.
11. bleed$.mp.
12. blood loss$.mp.
13. hemorrhag$.mp.
14. haemorrhag$.mp.
15. or/7-14
16. 6 and 15
17. exp clinical trial/
18. controlled study/
19. randomized controlled trial/
20. randomization/
21. major clinical study/
22. double blind procedure/
23. single blind procedure/
24. crossover procedure/
25. clinical study/
26. prospective study/
27. longitudinal study/
28. comparative study/
29. evaluation/
30. "evaluation and follow up"/
31. evaluation stud$.tw.
32. comparative stud$.tw.
33. follow?up.mp.
34. placebo$.mp.
35. random$.tw.
36. cross?over$.tw.
37. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).tw.
38. (clin$ adj25 trial$).tw.
39. (control$ or prospectiv$ or volunteer$).tw.
40. or/17-39
41. 16 and 40
42. exp animal/
43. nonhuman/
44. human/
45. 42 or 43
46. 45 not 44
47. 41 not 46
48. limit 47 to yr=2001-2004

PAD search in Web of Science (via OVID)

TS = ((PRE?OPERATIVE AUTOLOGOUS DONAT* OR AUTOLOGOUS BLOOD DONAT* OR AUTOLOGOUS BLOOD TRANSFUS* OR AUTOLOGOUS PRE?DONAT*) AND (TRANSFUSION OR BLEED* OR AN?ESTHESIA OR BLOOD LOS* OR H?EMORRHAG*))

PAD search in Cochrane Central Register of Controlled Trials (via National Electronic Library for Health)

#1. BLOOD TRANSFUSION AUTOLOGOUS single term (MeSH)
#2. (pre-operative next autologous next donat*)
#3. (autologous next blood next donat*)
#4. (autologous next blood next transfus*)
#5. (autologous next predonat*)
#6. (#1 or #2 or #3 or #4 or #5)
#7. BLOOD TRANSFUSION explode tree 1 (MeSH)
#8. HEMORRHAGE explode tree 1 (MeSH)
#9. ANESTHESIA explode tree 1 (MeSH)
#10. transfusion*
#11. bleed*
#12. (blood next loss*)
#13. hemorrhag*
#14. haemorrhag*
#15. (#7 or #8 or #9 or #10 or #11 or #12 or #13 or #14)

#16. (#6 and #15)
#17. (#6 and #15) (2001 to current date)

International Network of Agencies of Health Technology Assessment (HTA database via http://www.inahta.org/ on 26 February 2004)

Blood-transfusion – Subject headings OR Blood transfusion – Titles and Abstracts IN HTA reports or HTA projects

Text words were omitted if they would be picked up by another broader text word for example, 'autotransfusion$.mp' cancels the need for any other text word terms that incorporated 'autotransfusion$.mp'. The text words 'blood salvage' were used without the word 'intra-operative' so as to include studies that used postoperative blood salvage or did not specify.

Appendix 2

Inclusion/exclusion screening form for the cell salvage and PAD systematic review update

Trial author and date (e.g. Smith, 2003)	**Refman No.**		**NL/TB (circle)**
	Yes	**No**	**Unclear**
A. A randomised controlled trial?			
B. In adults (mean age equal to or more than 18 yrs) requiring major elective surgery?			
C. Including one of the following comparisons? (If YES please tick which comparison, if NO please give details of intervention provided in "other" row.) i) Cell salvage vs control ii) CS plus co-intervention vs identical co-intervention iii) Pre-operative autologous donation vs control iv) Pre-operative autologous donation plus co-intervention vs identical co-intervention			
Other:			
D. Including at least one of the following primary outcomes? Number of patients transfused with allogeneic blood and/or number of patients transfused with autologous blood Volume of allogeneic blood transfused and/or amount of autologous blood transfused Including any of the following secondary outcomes? Post-op complications (infections, thrombosis, non-fatal MI, renal failure); adverse transfusion reactions; re-operation for bleeding; pre-operative morbidity, pre-operative haemoglobin level; mortality; length of hospital stay, any other resource use or cost data;			

In / out / unclear (circle)

Appendix 3

Quality assessment forms for the cell salvage and PAD systematic review update

Form 1

Systematic review details	Score
1. Was the study described as randomised? (This includes the use of words such as randomly, random, and randomisation)	
2. Was the study described as double blind?	
3. Was there a description of withdrawals and dropouts?	

Scoring the items:
Either give a score of 1 point for each "yes" or 0 points for each "no". There are no in-between marks.

Give 1 additional point if:
For question 1, the method to generate the sequence of randomisation was described **and** it was appropriate (table of random numbers, computer generated, etc.)

and/or: If for question 2 the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)

Deduct 1 point if:
For question 1, the method to generate the sequence of randomisation was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)

and/or: For question 2, the study was described as double-blind but the method of blinding was inappropriate (e.g. comparison of tablet vs. injection with no double dummy)

Guidelines for Assessment
1. Randomisation
A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should be not regarded as appropriate.

2. Double blinding
A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and dropouts
Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Form 2

RCT details	Score
Selection bias (Randomisation procedure): Allocation concealment* A. Adequate concealment B. Concealment unclear C. Inadequate concealment D. Allocation concealment was not used	

***Notes on allocation concealment**

Adequate methods to ensure allocation concealment include:

- Centralised (e.g. allocation by a central office unaware of subject characteristics)
- Pre-numbered or coded treatments which are administered serially to participants
- On-site computer system combined with allocations kept in a locked unreadable computer file that can be accessed only after the characteristics of an enrolled participant have been entered
- Sequentially numbered, sealed, opaque envelopes
- Similar approaches along with reassurance that the person who generated the allocation scheme did not administer it.

Inadequate approaches to allocation concealment include:

- Alternation,
- Use of case record numbers,
- Dates of birth or day of the week, and
- Any procedure that is entirely transparent before allocation, such as an open list of random numbers.

Unclear concealment approaches include:

- Stating that a list or table was used,
- Only specifying that sealed envelopes were used, and
- Reporting an apparently adequate concealment scheme in combination with other information that leads the reviewer to be suspicious.

When studies do not report any concealment approach, adequacy should be considered unclear.

Appendix 4

Data extraction form for the cell salvage and PAD systematic review update

Author, date and Reference Manager ID	Reviewer ID:
Period of study	
Country/setting/ Number of centres	
Type of elective surgery:	
Comparison arm(s)	
Recruitment and randomisation details	
Primary outcome of study	
Power calculation reported?	
General description of study population (age, sex, baseline disease status, type of surgery):	
Selection criteria for entry into trial	
Inclusion criteria	Exclusion criteria
See Pages: (Highlight relevant section(s) in paper)	

DETAILS OF INTERVENTION	**Group A CONTROL (please name)**	**Group B (please name)**	**Group C (please name)**
Description of intervention (include following details if available/applicable) (a) Model/type of machine (b) Timing of autologous blood collection/donation (c) Storage (including duration) of autologous blood (d) Volume of blood collected/donated (e) Type of elective surgery and duration of operation (f) Use of transfusion threshold protocol (g) Any other active intervention given to all arms (e.g. iron supplementation – include drug/dose/ frequency/duration)			
Maximum length of study from randomisation to follow-up			
Number and frequency of visits from randomisation			

BASELINE CHARACTERISTICS **Please asterisk any significant differences**	**Group A (please name)**	**Group B (please name)**	**Group C (please name)**	**TOTAL**
Male: female (n/n)				
Age (years, mean, SD or range if no SD)				
Weight (kg, mean, SD or range if no SD)				
Hb/Hct (baseline)				
Hb/Hct (pre-op)				
Blood pressure (mm/Hg)				
Anticipated degree of blood loss				
Left ventricular impairment				
Renal impairment				
Other co-morbidities				
Other risk factors for requiring blood transfusion				
PARTICIPANT FLOW FOR STUDIES PRIMARY OUTCOME	**Group A CONTROL (please name)**	**Group B (please name)**	**Group C (please name)**	**TOTAL**
Number eligible (n)				
Number randomised to each group (n)				
Number excluded from initial sample (n, reason)				
Number assessed pre-op				
Number assessed intra-op				
Number assessed post-op				
Number assessed between post-op and discharge (give times)				
Number assessed at follow-up/end of study				
Number completed (n)				
Total number of dropouts at end of study (n)				
Number dead at end of study (n)				
How were the patients analysed for studies primary outcome? (ITT, APP, Completer)				

OUTCOME	**Use a different page for each time of assessment**		**Timing =**
	Group A CONTROL (n/N) please name	**Group B (n/N) please name**	**Group C (n/N) please name**
Number exposed to allogeneic blood (n/N)			
Volume of allogeneic blood transfused (units) FFP, platelets, whole blood or packed RBC (buffy coat poor, leucocyte depleted)			
Number exposed to autologous blood (n/N)			
Volume of autologous blood re-transfused (units) FFP, platelets, whole blood or packed RBC (buffy coat poor, leucocyte depleted)			
Blood loss (mls/units)			
Thrombosis (CABG)			
Thrombosis (other arterial)			
DVT			
Pulmonary embolus			
Stroke			
MI			
Renal failure			
Mortality			
Transfusion reaction			
Haemorrhage			
Re-op for bleeding			
Post-op infection			
Wound complication			
Post-op Hb/Hct			
Compliance			
Quality of life			
Length of stay			
Wastage of autologous blood			
Other economic data			

Study conclusions:

Other comments:			
Who funded the study?			
Subgroup analysis performed? (give details)			
Who made the decision to transfuse? (Anaesthetist, surgeon, were they blinded to patients' status?)			
Checklist:	Tick when completed	Date and signature	Tick when completed
Data extracted			Table of included studies
Data duplicate extracted			Results in Revman
References checked			Revman checked

Appendix 5

Inclusion/exclusion form for the review of systematic reviews

Trial author and date (e.g. Smith, 2003)	**Reference Manager ID**		**NL/TB (circle)**
	Yes	**No**	**Unclear**
A. A systematic review of individually randomised controlled trials?			
B. In adults (mean age equal to or more than 18 yrs) requiring major elective surgery?			
C. Including one of the following comparisons?			
PAD plus EPO			
EPO			
ANH			
Antifibrinolytics (aprotinin, tranexamic acid, epsilon aminocaproic acid)			
Fibrin sealants			
Restrictive transfusion thresholds			
D. Including at least one of the following primary outcomes? Number of patients transfused with allogeneic blood and/or volume of allogeneic blood transfused Note if review also included any of the following secondary outcomes: Post-op complications (infections, thrombosis, non-fatal MI, renal failure); adverse transfusion reactions; re-operation for bleeding; pre-operative morbidity, pre-operative haemoglobin level; mortality; length of hospital stay; any other resource use or cost data			

In / out / unclear (circle)

Appendix 6

Search strategy for the economic data

1. exp blood transfusion/
2. exp hemorrhage/
3. exp anesthesia/
4. transfusion$.mp.
5. bleed$.mp.
6. blood loss$.mp.
7. hemorrhag$.mp.
8. haemorrhag$.mp.
9. or/1-8
10. Economics/
11. Exp "costs and cost analysis"/
12. Economic value of life/
13. Exp "economics, hospital"/
14. Economics, medical/
15. Economics, nursing/
16. Economics, pharmaceutical/
17. Or/10-16
18. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).tw
19. (expenditure$ not energy).tw
20. (value adj1 money).tw
21. budget$.tw
22. or/18-21
23. 17 or 22
24. letter.pt
25. editorial.pt
26. historical article.pt
27. or/24-26
28. 23 not 27
29. animal/
30. human/
31. 29 not (29 and 30)
32. 28 not 31
33. (metabolic adj cost).ti,ab,sh.
34. ((energy or oxygen) adj cost).ti,ab,sh
35. 32 not (33 or 34)
36. 9 and 35
37. limit 38 to yr=1994-2004

Appendix 7

Inclusion/exclusion form for the economic data

Trial author and date (e.g. Smith, 2003)		Refman No		
		Yes	**No**	**?**
1	**Based on primary data collection or systematic review?**			
2	**In adults (18 years plus) undergoing any of the following major elective surgery?** Primary joint replacement Revision joint replacement Coronary artery bypass grafting Valve replacement			
3	**Including at least two of the following interventions?** Intraoperative cell salvage Postoperative cell salvage Pre-operative autologous donation Pre-operative autologous donation plus erythropoietin Erythropoietin Acute normovolaemic haemodilution Antifibrinolytics (aprotinin, tranexamic acid, epsilon aminocaproic acid) Fibrin sealants Restrictive transfusion thresholds Allogeneic blood			
4	**Assessing any of the following outcomes?** Mortality Thrombosis Stroke MI Renal failure Wound complications Re-operation for bleeding Incorrect blood component transfused Acute haemolytic transfusion reaction Delayed haemolytic transfusion reaction Transfusion-related acute lung injury Post transfusion purpura Transfusion-related graft versus host disease Transfusion-transmitted infection Patient-based outcomes (HRQoL, satisfaction, preferences, utility values for health states)			
5	**Resource use and costs associated with transfusion strategies?**			
6	**Report resource use and cost separately?**			
7	**Report sufficient detail to extract costs and outcome data relevant to each alternative comparison of transfusion strategies?**			

Economic assessment **In / out / unclear**

For inclusion as economic evaluation of blood transfusion: requires YES for all 7 criteria

Appendix 8

Economic data extraction form

Economic Data Extraction Form

General Information

Paper Reference No.	Date:	Reviewer ID:
Author/Year:		
Title:		
Sub Title:		
Journal:		
Source of funding:		
Notes/Comments:		

Study Characteristics

Health Technology:

Comparator:

Type of Intervention		Economic Study Type		Perspective	
Primary prevention		Cost-effectiveness Analysis		NHS	
Secondary Prevention		Cost–utility Analysis		Societal	
Screening		Cost–benefit Analysis		Hospital	
Diagnosis		Cost–consequence Analysis		Not Stated	
Treatment		Cost study		Other (Please Specify)	
Rehabilitation		Not Reported			
Palliative Care				Setting:	
Other (Please Specify)					
Not Reported					

Hypothesis/Study Question:

Study Population:

Dates to which Data Relate		Modelling	
Effectiveness Evidence		Was a model used?	
Resource Use		Yes	
		No	
Price Year		If yes state purpose and type:	

Source of Data					
Source of Effectiveness Data Single Study ☐ Synthesis of Prev. Pub. ☐			Source of Cost Data Actual Source ☐ Literature Source ☐		
Link between Effectiveness and Costs					
Effectiveness data from a single study					
Study Sample:		Study design:			
Power calculation		RCT		Duration of follow-up:	
Number subjects in intervention group		Non RCT with concurrent controls		Loss to follow-up:	
Number subjects in control group		Cohort study		Any blinding for assessment of outcomes:	
Recruitment rate		Historical controls		Analysis of clinical study:	
Number excluded from study		Before and after study		Treatment completers	
Method of sample selection:		Case series		Intention to treat	
		Other (specify)		Effectiveness results:	
		Not reported			
		Number of centres			
Effectiveness data from a synthesis of previous studies (model)					
Study inclusion criteria:		Study designs included:		Number of primary studies included:	
Study exclusion criteria reported:		RCT		Method of combination of primary studies:	
Sources searched reported:		Non RCT with concurrent controls		Meta-analysis	
Criteria used to judge validity:		Cohort study		Narrative method	
Concealment of randomisation		Historical controls		Other (specify)	

Blind assessment		Before and after study		Results of the review:	
Low drop out rates		Case series			
Other (specify)		Other (specify)			
Not reported		Not reported			

Measure of Benefits used in the Economic Analysis No Measure of Benefit (*CCA* or *CMA*)			
Direct Costs: Health Service		Estimation of Direct Costs Based On:	
		A Guess	
		Actual Data	
		Derived using Modelling	
		Other	
		Not Reported	
Direct Costs: Patient		Estimation of Patient Direct Costs Based On:	
		A Guess	
		Actual Data	
		Derived using Modelling	
		Other	
		Not Reported	
Source of Direct Cost Data: Price Year:		Discounting Undertaken?	
		Yes	Discount Rate
		No	

Indirect Costs	Estimation of Indirect Costs Based On:
	A Guess ☐
	Actual Data ☐
	Derived using Modelling ☐
	Other ☐
	Not Reported ☐

Source of Indirect Cost Data Price Year:	Discounting Undertaken?
	Yes ☐ Discount Rate:
	No ☐

Currency:	Conversion Rates Used:

Statistical/Sensitivity Analyses

Statistical Tests Carried Out?		Types of test used in Analysis of Costs:
Yes	☐	
No	☐	

Type of Sensitivity Analysis:		Areas of Uncertainty Tested:
One-way Analysis	☐	
Two-way Analysis	☐	
Multi-way Analysis	☐	
Threshold Analysis	☐	
Analysis of Extremes	☐	
Probabilistic Analysis	☐	
Other	☐	
Not Reported	☐	
Not Carried out	☐	

Results				
Clinical Outcome/Benefit:				
Duration of Benefits:	Side Effects Considered?		Y	N
Cost results:				
Cost of Adverse Events Considered?		Y	N	Not Relevant
How were the Estimates of Costs and Benefits Combined?		Results of Synthesis of Costs and Benefits:		
Cost/Life Saved				
Cost/Life Gained				
Cost/QALY				
Net Benefit				
Incremental Net Benefit				
Other				
Not Combined				
Author's Conclusions:				
Reviewer's Conclusions:				
Overall assessment of study quality:				

Appendix 9

Table of characteristics of original cell salvage and PAD systematic reviews

Systematic reviews of interventions to minimise perioperative allogeneic blood transfusion

Author	Focus	Inclusion criteria	Methodological quality of included studies	Number of studies
Carless *et al*. 2003[30]	Effectiveness of cell salvage (CS), for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	Study design: RCTs with a concurrent control group Participants: adults (over 18 years) undergoing elective or non-urgent surgery Intervention: CS vs control group who did not receive CS [trials with a combination of active comparisons were included if both the intervention and the control groups were equally exposed to the active treatment (active plus CS versus active comparisons)] Primary outcomes: Number of patients transfused with allogeneic blood Amount of allogeneic blood transfused Other outcomes: adverse events, length of hospital stay Period: 1966–July 2002	Cochrane criterion for allocation concealment: 13 of 43 trials inadequately concealed treatment allocation (grade C) and 30 trials did not clearly describe allocation concealment (grade B). Schulz criteria (out of possible score of 7): 15 trials = 3, 18 trials = 2, 6 trials = 1, 4 trials = 0. Jadad criteria (out of possible score of 5): 3 trials = 3, 19 trials scored 2, 15 trials = 1, 6 trials = 0. 41 of 42 trials failed to report blinding, 32 of 43 trials failed to report or inadequately randomised participants, 25 trials reported no exclusions or used ITT analysis, 7 trials reported exclusions which were likely to cause bias κ = 0.65–1.0 for blinding, allocation concealment and method of randomisation)	26 RCTs compared CS alone with a control group which did not receive CS or any other active treatment, *n* = 1939 patients, CS = 973
Henry *et al*. 2001[13]	Effectiveness of PAD, for minimising perioperative allogeneic RBC transfusion and on clinical outcomes	Study design: RCTs with a concurrent control group Participants: adults (over 18 years) undergoing elective or non-urgent surgery, trials were included if participants aged less than 18 years were enrolled but the type of surgery was predominantly carried out in adult patients Intervention: PAD vs control group who did not receive PAD (trials of PAD vs another active intervention were excluded) Primary outcomes: Proportion of patients transfused with allogeneic RBCs Volume of blood transfused Adverse outcomes Period: 1966–January 2001	Cochrane criterion for allocation concealment: 2 of 8 trials inadequately concealed treatment allocation (grade C) and 6 trials did not clearly describe allocation concealment (grade B) Schulz criteria (out of possible score of 7): 7 trials = 2, 1 trial = 0 Jadad criteria (out of possible score of 5): 4 trials = 2, 4 trials = 1 Blinding was not reported in any trial, method of randomisation was inadequate or not reported in all trials, 6 trials reported no exclusions or used ITT analysis, 1 trial reported exclusions which were likely to cause bias (κ = 1.0 for blinding, allocation concealment and method of randomisation scores)	9 RCTS (4 orthopaedic, 4 cancer, 1 liver surgery)

Appendix 10

Cell salvage meta-analyses

Meta-analysis and subgroup analysis results for the cell salvage update – number of patients transfused with allogeneic blood[a]

Meta-analysis	No. of RCTs	No. of events/ No. of participants in cell salvage	No. of events/ No. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
All studies	***47***	***690/1952***	***1118/1905***	***0.61***	***0.52 to 0.71***	***p < 0.00001 I^2 = 87.2%***
Transfusion protocol	***38***	***584/1433***	***921/1434***	***0.63***	***0.54 to 0.73***	***p < 0.00001 I^2 = 86.8%***
No transfusion protocol	***9***	***106/519***	***197/471***	***0.44***	***0.22 to 0.88***	***p < 0.00001 I^2 = 87.6%***
Cardiac	***23***	***492/889***	***658/895***	***0.77***	***0.68 to 0.87***	***p < 0.00001 I^2 = 79.5%***
Orthopaedic	21	158/972	395/915	0.42	0.32 to 0.54	*p* = 0.005 I^2 = 58.7%
Vascular	3	40/91	65/95	0.55	0.13 to 2.36	*p* = 0.003 I^2 = 87.9%
Washed	***20***	***245/789***	***471/811***	***0.54***	***0.43 to 0.68***	***p < 0.00001 I^2 = 78.3%***
Unwashed	***26***	***444/1102***	***612/1072***	***0.71***	***0.60 to 0.84***	***p < 0.00001 I^2 = 84.7%***
Intraoperative	7	102/282	183/282	0.53	0.35 to 0.80	*p* = 0.0001 I^2 = 77.7%
Postoperative	***33***	***534/1448***	***788/1429***	***0.67***	***0.57 to 0.79***	***p < 0.00001 I^2 = 86.5%***
Intra- + postoperative	6	45/142	88/152	0.56	0.29 to 1.08	*p* < 0.00001 I^2 = 87.1%
Cardiac washed	***9***	***129/325***	***227/329***	***0.61***	***0.46 to 0.80***	***p < 0.00001 I^2 = 79.1%***
Cardiac unwashed	***14***	***363/564***	***431/566***	***0.87***	***0.78 to 0.97***	***p = 0.0001 I^2 = 67.6%***
Orthopaedic washed	9	76/373	179/387	0.46	0.34 to -.64	*p* = 0.03 I^2 = 52.5%
Orthopaedic unwashed	12	81/538	181/506	0.42	0.30 to 0.60	*p* = 0.04 I^2 = 48.1%
Vascular washed	3	40/91	65/95	0.55	0.13 to 2.36	*p* = 0.0003 I^2 = 87.9%
English	***42***	***639/1841***	***1043/1807***	***0.60***	***0.51 to 0.71***	***p < 0.00001 I^2 = 88.6%***
Non-English	4	39/91	55/78	0.62	0.47 to 0.80	*p* = 0.86 I^2 = 0%
Grade B	***35***	***609/1460***	***935/1414***	***0.64***	***0.55 to 0.76***	***p < 0.00001 I^2 = 87.7%***
Grade C	11	79/460	182/458	0.47	0.27 to 0.83	*p* < 0.00001 I^2 = 86.3%

continued

Meta-analysis	No. of RCTs	No. of events/ No. of participants in cell salvage	No. of events/ No. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
Active vs control	***28***	***405/1035***	***677/1029***	***0.59***	***0.48 to 0.73***	***p < 0.00001 I^2 = 90.6%***
Transfusion protocol	***24***	***349/841***	***551/833***	***0.63***	***0.51 to 0.77***	***p < 0.00001 I^2 = 89.1%***
No transfusion protocol	***4***	***56/194***	***126/196***	***0.27***	***0.02 to 4.08***	***p < 0.00001 I^2 = 95.8%***
Cardiac	***14***	***291/516***	***373/513***	***0.81***	***0.70 to 0.93***	***p < 0.00001 I^2 = 78.9%***
Orthopaedic	11	74/128	239/421	0.35	0.24 to 0.52	p = 0.0009 I^2 = 66.5%
Vascular	3	40/91	65/95	0.55	0.13 to 2.36	p = 0.0003 I^2 = 87.9%
Washed	***14***	***168/550***	***324/560***	***0.53***	***0.39 to 0.72***	***p < 0.00001 I^2 = 87.2%***
Unwashed	***13***	***236/425***	***318/409***	***0.73***	***0.58 to 0.91***	***p < 0.00001 I^2 = 88.4%***
Intraoperative	5	74/191	113/191	0.61	0.39 to 0.95	p = 0.01 I^2 = 68.9%
Postoperative	***18***	***287/738***	***473/724***	***0.60***	***0.45 to 0.79***	***p < 0.00001 I^2 = 93.1%***
Intra- + postoperative	5	44/106	91/114	0.52	0.26 to 1.01	p < 0.00001 I^2 = 90.8%

[a] Studies in bold italic indicate where data have been added as a result of the update of the cell salvage systematic review.

Meta-analysis and subgroup analysis results for the cell salvage update – units of allogeneic blood transfused[a]

Meta-analysis	No. of RCTs	No. of participants in cell salvage	No. of participants in control	WMD (random effects)	95% CI	Heterogeneity *p*-value
All studies	***27***	***974***	***963***	***–0.67***	***–0.89 to –0.45***	***p < 0.00001 I^2 = 74.1%***
Transfusion protocol	***23***	***771***	***773***	***–0.61***	***–0.84 to –0.37***	***p < 0.00001 I^2 = 75.7%***
No transfusion protocol	4	203	190	–1.26	–2.11 to –0.40	p = 0.04 I^2 = 64.0%
Cardiac	***17***	***691***	***677***	***–0.64***	***–0.90 to –0.39***	***p < 0.00001 I^2 = 69.9%***
Orthopaedic	7	190	193	–0.89	–1.40 to –0.39	p = 0.003 I^2 = 78.4%
Vascular	3	93	93	0.02	–0.34 to 0.38	p = 0.42 I^2 = 0%
Active vs control	***18***	***638***	***622***	***–0.90***	***–1.23 to –0.56***	***p < 0.00001 I^2 = 79.9%***
Transfusion protocol	***15***	***486***	***483***	***–0.81***	***–1.16 to –0.46***	***p < 0.00001 I^2 = 81.9%***

continued

Meta-analysis	No. of RCTs	No. of participants in cell salvage	No. of participants in control	WMD (random effects)	95% CI	Heterogeneity *p*-value
No transfusion protocol	3	152	139	–1.64	–2.96 to –0.33	$p = 0.05$ $I^2 = 66.7\%$
Cardiac	***11***	***442***	***424***	***–0.97***	***–1.40 to –0.55***	***p < 0.00001*** ***I^2 = 76.0%***
Orthopaedic	4	103	105	–1.13	–1.78 to –0.48	$p = 0.002$ $I^2 = 80.1\%$
Vascular	3	93	93	0.02	–0.34 to 0.38	$p = 0.42$ $I^2 = 0\%$

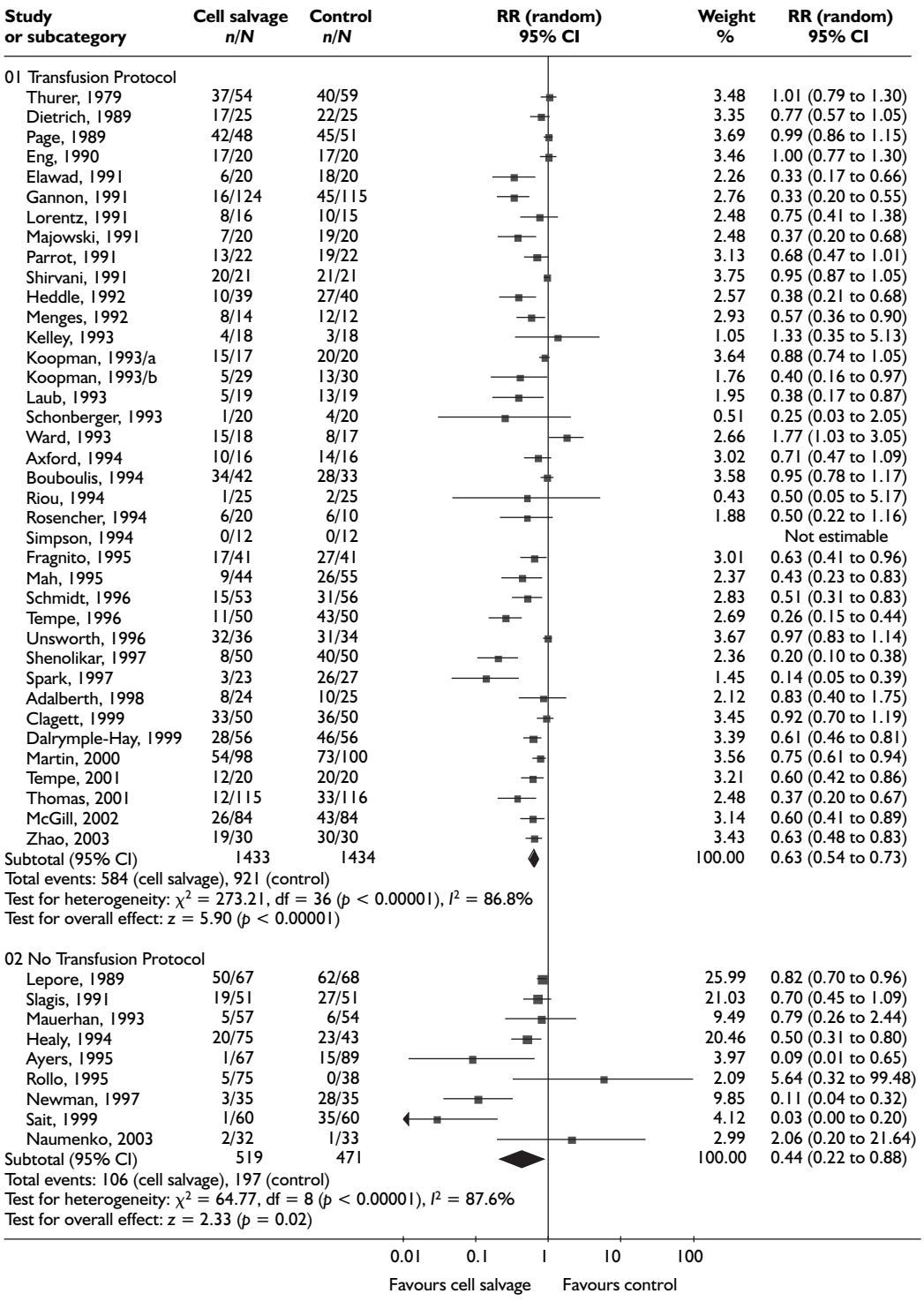
[a] Studies in bold italic indicate where data have been added as a result of the update of the cell salvage systematic review.

Meta-analysis and subgroup analysis results for the cell salvage update – adverse events and other outcomes

Outcome	Meta-analysis	No. of RCTs	No. of events/ No. of participants in cell salvage	No. of events/ No. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
Mortality	All studies	15	13/614	11/598	1.22	0.55 to 2.70	$p = 0.78$ $I^2 = 0\%$
	Active vs control	11	13/417	8/394	1.53	0.65 to 3.61	$p = 0.86$ $I^2 = 0\%$
Reoperation for bleeding	All studies	14	22/563	20/556	1.00	0.55 to 1.81	$p = 0.87$ $I^2 = 0\%$
	Active vs control	8	13/302	10/290	1.08	0.47 to 2.48	$p = 0.65$ $I^2 = 0\%$
Any infection	All studies	13	25/721	34/669	0.74	0.44 to 1.25	$p = 0.49$ $I^2 = 0\%$
	Active vs control	9	24/420	31/406	0.75	0.41 to 1.37	$p = 0.37$ $I^2 = 0\%$
Wound complication	All studies	9	17/392	15/338	0.91	0.46 to 1.81	$p = 0.79$ $I^2 = 0\%$
	Active vs control	7	14/263	14/241	0.88	0.42 to 1.81	$p = 0.75$ $I^2 = 0\%$
Any thrombosis	All studies	7	9/264	6/233	1.46	0.56 to 3.83	$p = 0.95$ $I^2 = 0\%$
	Active vs control	6	9/189	6/190	1.46	0.56 to 3.83	$p = 0.95$ $I^2 = 0\%$
Stroke	All studies	4	3/247	5/249	0.65	0.17 to 2.50	$p = 0.76$ $I^2 = 0\%$
	Active vs control	3	2/149	3/149	0.73	0.14 to 3.72	$p = 0.57$ $I^2 = 0\%$
Non-fatal MI	All studies	9	16/411	22/420	0.76	0.40 to 1.43	$p = 0.68$ $I^2 = 0\%$
	Active vs control	5	10/223	19/225	0.58	0.28 to 1.19	$p = 0.88$ $I^2 = 0\%$
DVT	Active vs control	4	6/124	7/125	0.93	0.31 to 2.77	$p = 0.54$ $I^2 = 0\%$
Hospital length of stay	Active vs control	5	203	194	–1.28	–2.65 to 0.08	$p = 0.13$ $I^2 = 0\%$

Relative risk of exposure to allogeneic blood, cell salvage versus control, transfusion protocol

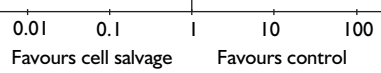
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 02 No. Exposed to Allogeneic Blood (Transfusion Protocol)



Relative risk of exposure to allogeneic blood, cell salvage versus control, type of surgery

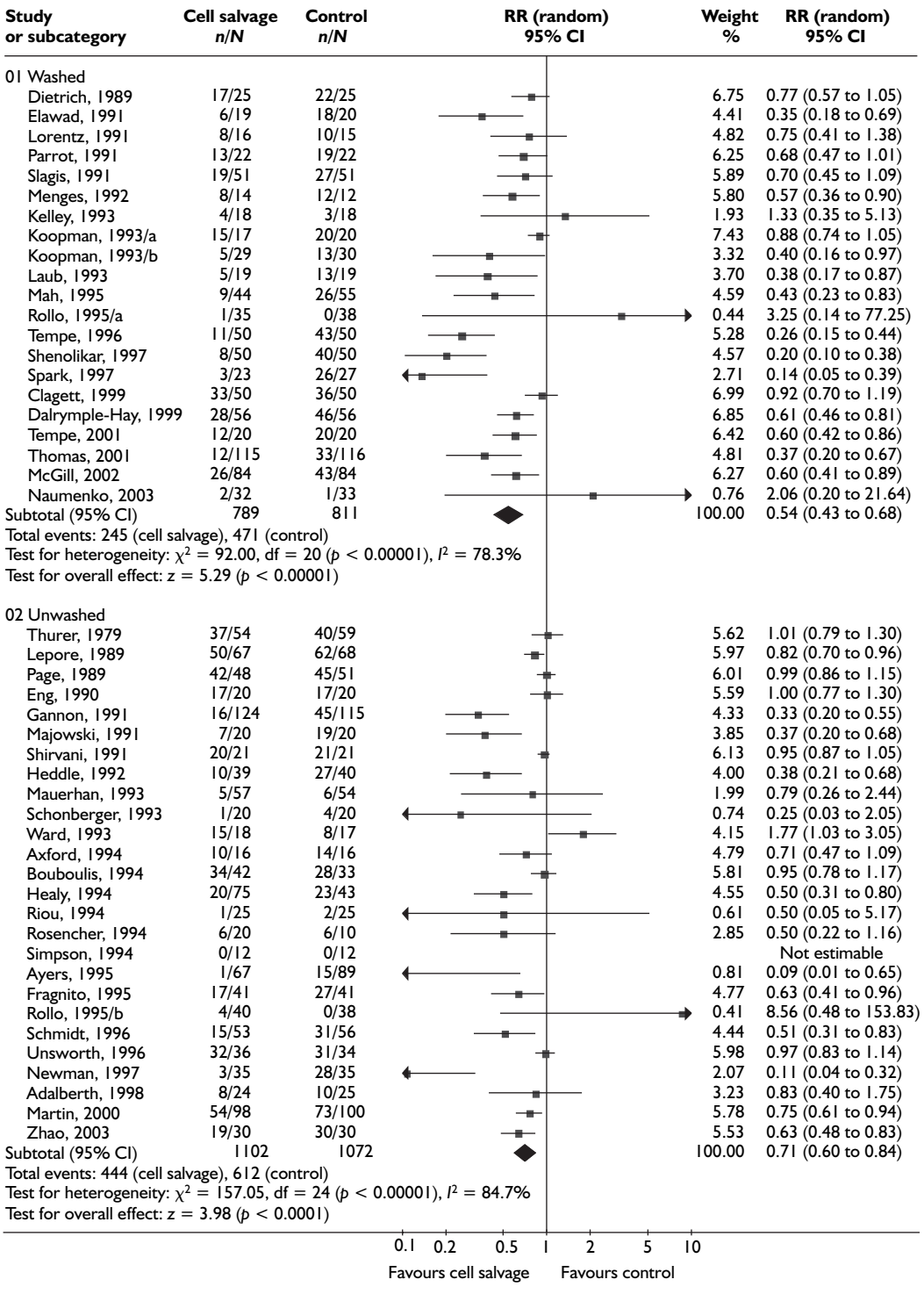
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 03 No. Exposed to Allogeneic Blood (Type of Surgery)

Study or subcategory	Cell salvage *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Cardiac					
Thurer, 1979	37/54	40/59		5.03	1.01 (0.79 to 1.30)
Dietrich, 1989	17/25	22/25		4.84	0.77 (0.57 to 1.05)
Lepore, 1989	50/67	62/68		5.30	0.82 (0.70 to 0.96)
Page, 1989	42/48	45/51		5.32	0.99 (0.86 to 1.15)
Eng, 1990	17/20	17/20		5.00	1.00 (0.77 to 1.30)
Parrot, 1991	13/22	19/22		4.52	0.68 (0.47 to 1.01)
Shirvani, 1991	20/21	21/21		5.42	0.95 (0.87 to 1.05)
Koopman, 1993/a	15/17	20/20		5.26	0.88 (0.74 to 1.05)
Laub, 1993	5/19	13/19		2.81	0.38 (0.17 to 0.87)
Schonberger, 1993	1/20	4/20		0.74	0.25 (0.03 to 2.05)
Ward, 1993	15/18	8/17		3.84	1.77 (1.03 to 3.05)
Axford, 1994	10/16	14/16		4.36	0.71 (0.47 to 1.09)
Bouboulis, 1994	34/42	28/33		5.17	0.95 (0.78 to 1.17)
Fragnito, 1995	17/41	27/41		4.35	0.63 (0.41 to 0.96)
Schmidt, 1996	15/53	31/56		4.08	0.51 (0.31 to 0.83)
Tempe, 1996	11/50	43/50		3.89	0.26 (0.15 to 0.44)
Unsworth, 1996	32/36	31/34		5.30	0.97 (0.83 to 1.14)
Dalrymple-Hay, 1999	28/56	46/56		4.90	0.61 (0.46 to 0.81)
Martin, 2000	54/98	73/100		5.15	0.75 (0.61 to 0.94)
Tempe, 2001	12/20	20/20		4.63	0.60 (0.42 to 0.86)
McGill, 2002	26/84	43/84		4.53	0.60 (0.41 to 0.89)
Naumenko, 2003	2/32	1/33		0.61	2.06 (0.20 to 21.64)
Zhao, 2003	19/30	30/30		4.96	0.63 (0.48 to 0.83)
Subtotal (95% CI)	889	895		100.00	0.77 (0.68 to 0.87)
Total events: 492 (cell salvage), 658 (control)					
Test for heterogeneity: $\chi^2 = 107.40$, df = 22 ($p < 0.00001$), $I^2 = 79.5\%$					
Test for overall effect: $z = 4.09$ ($p < 0.0001$)					
02 Orthopaedic					
Elawad, 1991	6/20	18/20		5.82	0.33 (0.17 to 0.66)
Gannon, 1991	16/124	45/115		7.09	0.33 (0.20 to 0.55)
Lorentz, 1991	8/16	10/15		6.38	0.75 (0.41 to 1.38)
Majowski, 1991	7/20	19/20		6.38	0.37 (0.20 to 0.68)
Slagis, 1991	19/51	27/51		7.63	0.70 (0.45 to 1.09)
Heddle, 1992	10/39	27/40		6.60	0.38 (0.21 to 0.68)
Menges, 1992	8/14	12/12		7.53	0.57 (0.36 to 0.90)
Koopman, 1993/b	5/29	13/30		4.52	0.40 (0.16 to 0.97)
Mauerhan, 1993	5/57	6/54		3.44	0.79 (0.26 to 2.44)
Healy, 1994	20/75	23/43		7.42	0.50 (0.31 to 0.80)
Riou, 1994	1/25	2/25		1.10	0.50 (0.05 to 5.17)
Rosencher, 1994	6/20	6/10		4.84	0.50 (0.22 to 1.16)
Simpson, 1994	0/12	0/12			Not estimable
Ayers, 1995	1/67	15/89		1.44	0.09 (0.01 to 0.65)
Mah, 1995	9/44	26/55		6.09	0.43 (0.23 to 0.83)
Rollo, 1995	5/75	0/38		0.76	5.64 (0.32 to 99.48)
Newman, 1997	3/35	28/35		3.58	0.11 (0.04 to 0.32)
Shenolikar, 1997	8/50	40/50		6.06	0.20 (0.10 to 0.38)
Adalberth, 1998	8/24	10/25		5.44	0.83 (0.40 to 1.75)
Sait, 1999	1/60	35/60		1.50	0.03 (0.00 to 0.20)
Thomas, 2001	12/115	33/116		6.37	0.37 (0.20 to 0.67)
Subtotal (95% CI)	972	915		100.00	0.42 (0.32 to 0.54)
Total events: 158 (cell salvage), 395 (control)					
Test for heterogeneity: $\chi^2 = 45.97$, df = 19 ($p = 0.0005$), $I^2 = 58.7\%$					
Test for overall effect: $z = 6.67$ ($p < 0.00001$)					
03 Vascular					
Kelley, 1993	4/18	3/18		17.62	1.33 (0.35 to 5.13)
Spark, 1997	3/23	26/27		24.38	0.14 (0.05 to 0.39)
Clagett, 1999	33/50	36/50		58.00	0.92 (0.70 to 1.19)
Subtotal (95% CI)	91	95		100.00	0.55 (0.13 to 2.36)
Total events: 40 (cell salvage), 65 (control)					
Test for heterogeneity: $\chi^2 = 16.58$, df = 2 ($p = 0.0003$), $I^2 = 87.9\%$					
Test for overall effect: $z = 0.80$ ($p = 0.42$)					



Relative risk of exposure to allogeneic blood, cell salvage versus control, type of cell salvage

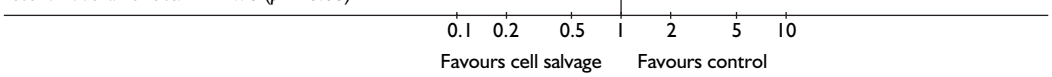
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 04 No.Exposed to Allogeneic Blood – (Washed vs Unwashed)



Relative risk of exposure to allogeneic blood, cell salvage versus control, timing of cell salvage

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 05 No.Exposed to Allogeneic Blood (Timing)

Study or subcategory	Cell salvage *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Intra-operative					
Elawad, 1991	6/20	18/20		12.71	0.33 (0.17 to 0.66)
Kelley, 1993	4/18	3/18		5.68	1.33 (0.35 to 5.13)
Laub, 1993	5/19	13/19		10.82	0.38 (0.17 to 0.87)
Fragnito, 1995	17/41	27/41		17.30	0.63 (0.41 to 0.96)
Tempe, 1996	11/50	43/50		15.30	0.26 (0.15 to 0.44)
Clagett, 1999	33/50	36/50		20.10	0.92 (0.70 to 1.19)
McGill, 2002	26/84	43/84		18.09	0.60 (0.41 to 0.89)
Subtotal (95% CI)	282	282		100.00	0.53 (0.35 to 0.80)
Total events: 102 (cell salvage), 183 (control)					
Test for heterogeneity: $\chi^2 = 26.93$, df = 6 ($p = 0.0001$), $I^2 = 77.7\%$					
Test for overall effect: $z = 3.00$ ($p = 0.003$)					
02 Post-operative					
Thurer, 1979	37/54	40/59		4.40	1.01 (0.79 to 1.30)
Dietrich, 1989	17/25	22/25		4.22	0.77 (0.57 to 1.05)
Lepore, 1989	50/67	62/68		4.66	0.82 (0.70 to 0.96)
Page, 1989	42/48	45/51		4.69	0.99 (0.86 to 1.15)
Eng, 1990	17/20	17/20		4.37	1.00 (0.77 to 1.30)
Gannon, 1991	16/124	45/115		3.41	0.33 (0.20 to 0.55)
Majowski, 1991	7/20	19/20		3.05	0.37 (0.20 to 0.68)
Shirvani, 1991	20/21	21/21		4.78	0.95 (0.87 to 1.05)
Slagis, 1991	19/51	27/51		3.69	0.70 (0.45 to 1.09)
Heddle, 1992	10/39	27/40		3.16	0.38 (0.21 to 0.68)
Menges, 1992	8/14	12/12		3.64	0.57 (0.36 to 0.90)
Mauerhan, 1993	5/57	6/54		1.59	0.79 (0.26 to 2.44)
Schonberger, 1993	1/20	4/20		0.60	0.25 (0.03 to 2.05)
Ward, 1993	15/18	8/17		3.28	1.77 (1.03 to 3.05)
Axford, 1994	14/16	10/16		3.77	1.40 (0.92 to 2.14)
Bouboulis, 1994	34/42	28/33		4.54	0.95 (0.78 to 1.17)
Healy, 1994	20/75	23/43		3.59	0.50 (0.31 to 0.80)
Riou, 1994	1/25	2/25		0.49	0.50 (0.05 to 5.17)
Rosencher, 1994	6/20	6/10		2.27	0.50 (0.22 to 1.16)
Simpson, 1994	0/12	0/12			Not estimable
Ayers, 1995	1/67	15/89		0.65	0.09 (0.01 to 0.65)
Mah, 1995	9/44	26/55		2.90	0.43 (0.23 to 0.83)
Rollo, 1995/b	4/40	0/38		0.33	8.56 (0.48 to 153.83)
Schmidt, 1996	15/53	31/56		3.50	0.51 (0.31 to 0.83)
Unsworth, 1996	32/36	31/34		4.67	0.97 (0.83 to 1.14)
Newman, 1997	3/35	28/35		1.65	0.11 (0.04 to 0.32)
Shenolikar, 1997	8/50	40/50		2.88	0.20 (0.10 to 0.38)
Adalberth, 1998	8/24	10/25		2.57	0.83 (0.40 to 1.75)
Dalrymple-Hay, 1999	28/56	46/56		4.28	0.61 (0.46 to 0.81)
Martin, 2000	54/98	73/100		4.52	0.75 (0.61 to 0.94)
Thomas, 2001	12/115	33/116		3.04	0.37 (0.20 to 0.67)
Naumenko, 2003	2/32	1/33		0.49	2.06 (0.20 to 21.64)
Zhao, 2003	19/30	30/30		4.33	0.63 (0.48 to 0.83)
Subtotal (95% CI)	1448	1429		100.00	0.67 (0.57 to 0.79)
Total events: 534 (cell salvage), 788 (control)					
Test for heterogeneity: $\chi^2 = 229.94$, df = 31 ($p < 0.00001$), $I^2 = 86.5\%$					
Test for overall effect: $z = 4.71$ ($p < 0.00001$)					
03 Both intra- and post-operative					
Lorentz, 1991	8/16	10/15		19.37	0.75 (0.41 to 1.38)
Parrot, 1991	13/22	19/22		24.92	0.68 (0.47 to 1.01)
Koopman, 1993/a	15/17	20/20		29.47	0.88 (0.74 to 1.05)
Koopman, 1993/b	5/29	13/30		13.44	0.40 (0.16 to 0.97)
Rollo, 1995/a	1/35	0/38		1.79	3.25 (0.14 to 77.25)
Spark, 1997	3/23	26/27		11.00	0.14 (0.05 to 0.39)
Subtotal (95% CI)	142	152		100.00	0.56 (0.29 to 1.08)
Total events: 45 (cell salvage), 88 (control)					
Test for heterogeneity: $\chi^2 = 38.75$, df = 5 ($p < 0.00001$), $I^2 = 87.1\%$					
Test for overall effect: $z = 1.73$ ($p = 0.08$)					

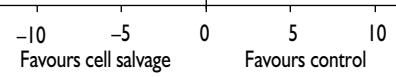


Units of allogeneic blood transfused, cell salvage versus control, all studies

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 06 Units of Allogeneic Blood Transfused (All Studies)

Study or subcategory	N	Cell salvage mean (SD)	N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
Schaff, 1978	63	2.40 (2.38)	51	4.80 (4.28)		2.02	–2.40 (–3.71 to –1.09)
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		0.64	–1.50 (–4.14 to 1.14)
Dietrich, 1989	25	1.36 (1.86)	25	2.78 (2.00)		2.65	–1.42 (–2.49 to –0.35)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		3.14	–0.60 (–1.53 to 0.33)
Page, 1989	48	3.15 (2.05)	51	3.83 (2.58)		3.19	–0.68 (–1.60 to 0.24)
Elawad, 1991	20	0.69 (0.87)	20	2.73 (0.88)		4.95	–2.04 (–2.58 to –1.50)
Parrot, 1991	22	1.38 (1.50)	22	2.18 (1.29)		3.55	–0.80 (–1.63 to 0.03)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		3.47	0.03 (–0.81 to 0.87)
Slagis, 1991	51	0.80 (1.15)	51	1.49 (1.44)		5.15	–0.69 (–1.20 to –0.18)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		5.74	–0.80 (–1.20 to –0.40)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		5.69	0.11 (–0.30 to 0.52)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		0.48	–1.30 (–4.39 to 1.79)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		4.75	–0.80 (–1.38 to –0.22)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		3.51	–0.66 (–1.49 to 0.17)
Schonberger, 1993	20	0.10 (1.34)	20	0.60 (1.34)		3.53	–0.50 (–1.33 to 0.33)
Axford, 1994	16	1.67 (1.95)	16	2.19 (2.25)		1.73	–0.52 (–1.98 to 0.94)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		3.58	–0.32 (–1.14 to 0.50)
Simpson, 1994	12	0.00 (0.00)	12	0.00 (0.00)			Not estimable
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		2.95	–0.80 (–1.78 to 0.18)
Fragnito, 1995	41	2.43 (0.80)	41	2.47 (0.90)		5.90	–0.04 (–0.41 to 0.33)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		1.21	–2.30 (–4.13 to –0.47)
Adalberth, 1998	24	0.75 (1.11)	25	0.88 (1.27)		4.29	–0.13 (–0.80 to 0.54)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		3.56	–0.20 (–1.02 to 0.62)
Dalrymple-Hay, 1999	56	0.99 (1.22)	56	1.69 (1.22)		5.45	–0.70 (–1.15 to –0.25)
Martin, 2000	98	1.80 (0.70)	100	2.20 (0.50)		6.78	–0.40 (–0.57 to –0.23)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		5.35	–0.39 (–0.86 to 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		6.77	–1.02 (–1.19 to –0.85)
Total (95% CI)	974		963			100.00	–0.67 (–0.89 to –0.45)

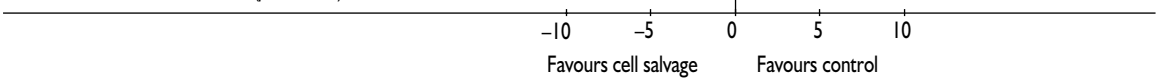
Test for heterogeneity: $\chi^2 = 96.60$, df = 25 ($p < 0.00001$), $I^2 = 74.1\%$
Test for overall effect: $z = 5.92$ ($p < 0.00001$)



Units of allogeneic blood transfused, cell salvage versus control, transfusion protocol

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 07 Units of Allogeneic Blood Transfused (Transfusion Protocol)

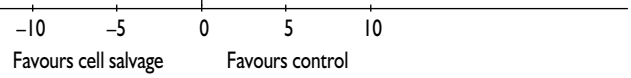
Study or subcategory	Cell salvage N	Cell salvage mean (SD)	Control N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Transfusion Protocol							
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		0.72	–1.50 (–4.14 to 1.14)
Dietrich, 1989	25	1.36 (1.86)	25	2.78 (2.00)		2.99	–1.42 (–2.49 to –0.35)
Page, 1989	48	3.15 (2.05)	51	3.83 (2.58)		3.60	–0.68 (–1.60 to 0.24)
Elawad, 1991	20	0.69 (0.87)	20	2.73 (0.88)		5.59	–2.04 (–2.58 to –1.50)
Parrot, 1991	22	1.38 (1.50)	22	2.18 (1.29)		4.00	–0.80 (–1.63 to 0.03)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		3.92	0.03 (–0.81 to 0.87)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		6.48	–0.80 (–1.20 to –0.40)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		6.43	0.11 (–0.30 to 0.52)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		0.54	–1.30 (–4.39 to 1.79)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		5.36	–0.80 (–1.38 to –0.22)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		3.96	–0.66 (–1.49 to 0.17)
Schonberger, 1993	20	0.10 (1.34)	20	0.60 (1.34)		3.99	–0.50 (–1.33 to 0.33)
Axford, 1994	16	1.67 (1.95)	16	2.19 (2.25)		1.95	–0.52 (–1.98 to 0.94)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		4.04	–0.32 (–1.14 to 0.50)
Simpson, 1994	12	0.00 (0.00)	12	0.00 (0.00)			Not estimable
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		3.33	–0.80 (–1.78 to 0.18)
Fragnito, 1995	41	2.43 (0.80)	41	2.47 (0.90)		6.67	–0.04 (–0.41 to 0.33)
Adalberth, 1998	24	0.75 (1.11)	25	0.88 (1.27)		4.85	–0.13 (–0.80 to 0.54)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		4.02	–0.20 (–1.02 to 0.62)
Dalrymple-Hay, 1999	56	0.99 (1.20)	56	1.69 (1.20)		6.20	–0.70 (–1.14 to –0.26)
Martin, 2000	98	1.80 (0.70)	100	2.20 (0.50)		7.66	–0.40 (–0.57 to –0.23)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		6.04	–0.39 (–0.86 to 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		7.65	–1.02 (–1.19 to –0.85)
Subtotal (95% CI)	771		773			100.00	–0.61 (–0.84 to –0.37)
Test for heterogeneity: $\chi^2 = 86.44$, df = 21 ($p < 0.00001$), $I^2 = 75.7\%$							
Test for overall effect: $z = 5.10$ ($p < 0.00001$)							
02 No Transfusion Protocol							
Schaff, 1978	63	2.40 (2.38)	51	4.80 (4.28)		17.50	–2.40 (–3.71 to –1.09)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		27.26	–0.60 (–1.53 to 0.33)
Slagis, 1991	51	0.80 (1.15)	51	1.49 (1.44)		44.74	–0.69 (–1.20 to –0.18)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		10.51	–2.30 (–4.13 to –0.47)
Subtotal (95% CI)	203		190			100.00	–1.26 (–2.11 to –0.40)
Test for heterogeneity: $\chi^2 = 8.32$, df = 3 ($p = 0.04$), $I^2 = 64.0\%$							
Test for overall effect: $z = 2.89$ ($p = 0.004$)							



Units of allogeneic blood transfused, cell salvage versus control, type of surgery

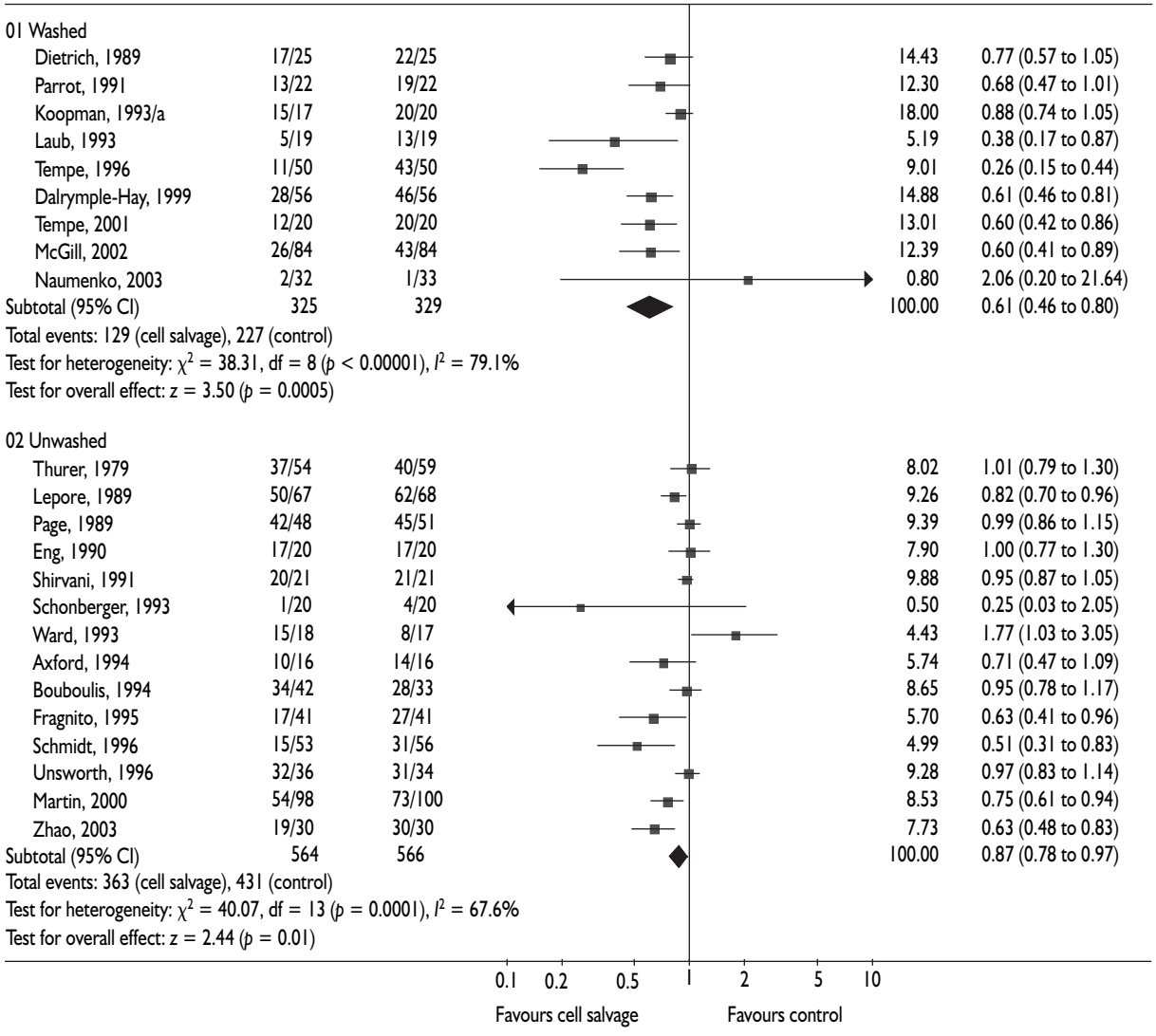
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 Cell Salvage – Blood Transfused (All studies)
Outcome: 08 Units of Allogeneic Blood Transfused (Type of Surgery)

Study or subcategory	N	Cell salvage mean (SD)	N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Cardiac							
Schaff, 1978	63	2.40 (2.38)	51	4.80 (4.28)		3.23	–2.40 (–3.71 to –1.09)
Dietrich, 1989	25	1.36 (1.86)	25	2.78 (2.00)		4.25	–1.42 (–2.49 to –0.35)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		5.04	–0.60 (–1.53 to 0.33)
Page, 1989	48	3.15 (2.05)	51	3.83 (2.58)		5.11	–0.68 (–1.60 to 0.24)
Parrot, 1991	22	1.38 (1.50)	22	2.18 (1.29)		5.69	–0.80 (–1.63 to 0.03)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		5.57	0.03 (–0.81 to 0.87)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		0.76	–1.30 (–4.39 to 1.79)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		5.63	–0.66 (–1.49 to 0.17)
Schonberger, 1993	20	0.10 (1.34)	20	0.60 (1.34)		5.66	–0.50 (–1.33 to 0.33)
Axford, 1994	16	1.67 (1.95)	16	2.19 (2.25)		2.77	–0.52 (–1.98 to 0.94)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		5.74	–0.32 (–1.14 to 0.50)
Fragnito, 1995	41	2.43 (0.80)	41	2.47 (0.90)		9.47	–0.04 (–0.41 to 0.33)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		1.94	–2.30 (–4.13 to –0.47)
Dalrymple-Hay, 1999	56	0.99 (1.20)	56	1.69 (1.20)		8.81	–0.70 (–1.14 to –0.26)
Martin, 2000	98	1.80 (0.70)	100	2.20 (0.50)		10.88	–0.40 (–0.57 to –0.23)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		8.58	–0.39 (–0.86 to 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		10.87	–1.02 (–1.19 to –0.85)
Subtotal (95% CI)	691		677			100.00	–0.64 (–0.90 to –0.39)
Test for heterogeneity: $\chi^2 = 53.21$, df = 16 ($p < 0.00001$), $I^2 = 69.9\%$							
Test for overall effect: $z = 4.92$ ($p < 0.00001$)							
02 Orthopaedic							
Elawad, 1991	20	0.69 (0.87)	20	2.73 (0.88)		17.79	–2.04 (–2.58 to –1.50)
Slagis, 1991	51	0.80 (1.15)	51	1.49 (1.44)		18.51	–0.69 (–1.20 to –0.18)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		20.62	–0.80 (–1.20 to –0.40)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		17.06	–0.80 (–1.38 to –0.22)
Simpson, 1994	12	0.00 (0.00)	12	0.00 (0.00)			Not estimable
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		10.60	–0.80 (–1.78 to 0.18)
Adalberth, 1998	24	0.75 (1.11)	25	0.88 (1.27)		15.42	–0.13 (–0.80 to 0.54)
Subtotal (95% CI)	190		193			100.00	–0.89 (–1.40 to –0.39)
Test for heterogeneity: $\chi^2 = 23.13$, df = 5 ($p = 0.0003$), $I^2 = 78.4\%$							
Test for overall effect: $z = 3.47$ ($p = 0.0005$)							
03 Vascular							
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		6.44	–1.50 (–4.14 to 1.14)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		57.55	0.11 (–0.30 to 0.52)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		36.00	–0.20 (–1.02 to 0.62)
Subtotal (95% CI)	93		93			100.00	0.02 (–0.34 to 0.38)
Test for heterogeneity: $\chi^2 = 1.74$, df = 2 ($p = 0.42$), $I^2 = 0\%$							
Test for overall effect: $z = 0.11$ ($p = 0.91$)							



Relative risk of exposure to allogeneic blood, cell salvage versus control, type of cell salvage, cardiac surgery

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 02 Cell Salvage – Blood Transfused (Washed vs Unwashed)
Outcome: 01 No. Exposed Allogeneic Blood (Cardiac)

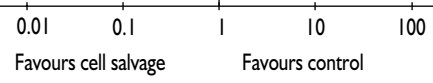


Relative risk of exposure to allogeneic blood, cell salvage versus control, active versus control, all studies

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 01 No. Exposed to Allogeneic Blood (Active vs Control)

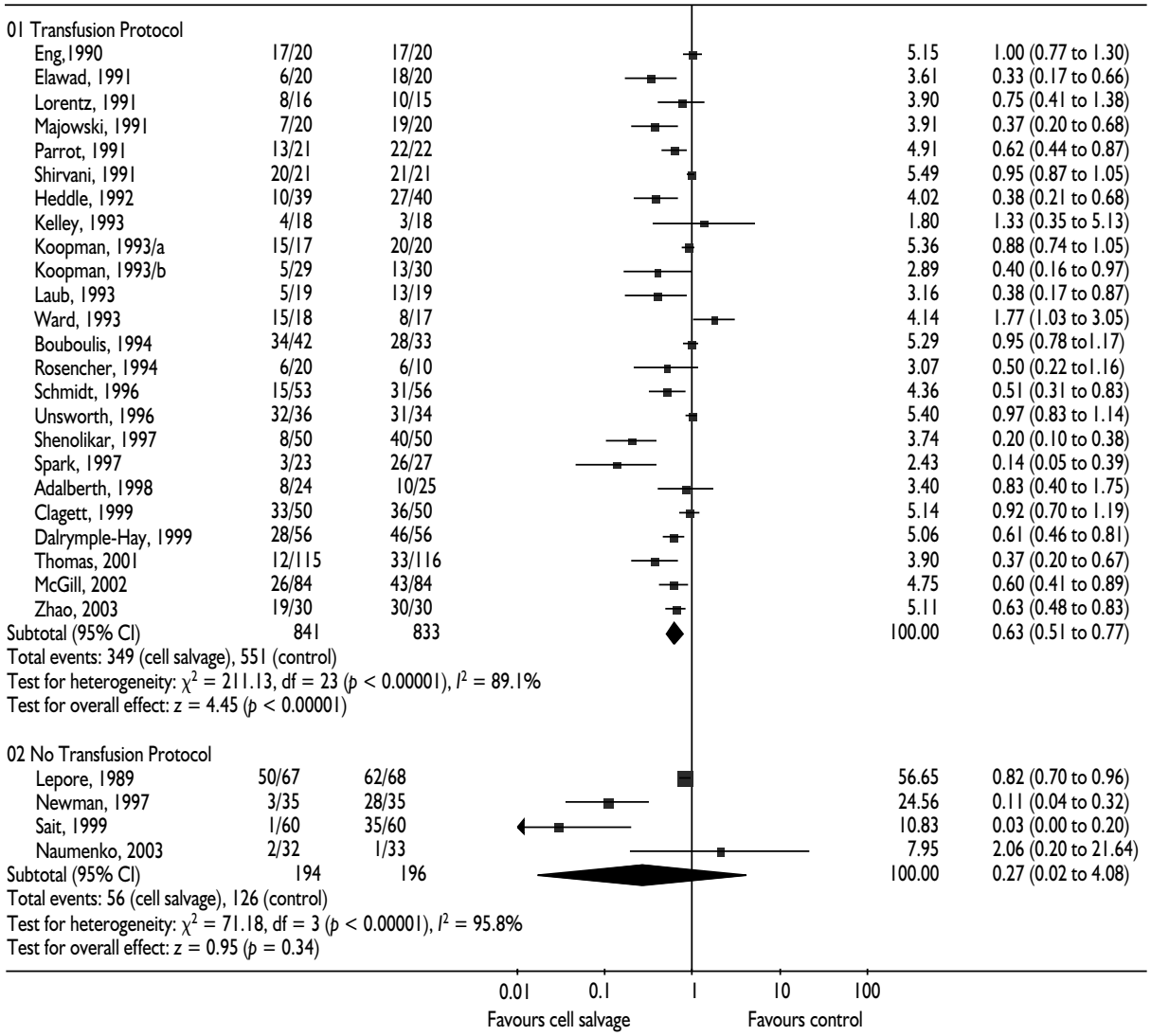
Study or subcategory	Cell salvage *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Cell Salvage vs Control					
Lepore, 1989	50/67	62/68		4.92	0.82 (0.70 to 0.96)
Eng 1990	17/20	17/20		4.70	1.00 (0.77 to 1.30)
Elawad, 1991	6/20	18/20		3.29	0.33 (0.17 to 0.66)
Lorentz, 1991	8/16	10/15		3.56	0.75 (0.41 to 1.38)
Majowski, 1991	7/20	19/20		3.57	0.37 (0.20 to 0.68)
Parrot, 1991	13/21	22/22		4.49	0.62 (0.44 to 0.87)
Shirvani, 1991	20/21	21/21		5.01	0.95 (0.87 to 1.05)
Heddle, 1992	10/39	27/40		3.67	0.38 (0.21 to 0.68)
Kelley, 1993	4/18	3/18		1.65	1.33 (0.35 to 5.13)
Koopman, 1993/a	15/17	20/20		4.90	0.88 (0.74 to 1.05)
Koopman, 1993/b	5/29	13/30		2.64	0.40 (0.16 to 0.97)
Laub, 1993	5/19	13/19		2.89	0.38 (0.17 to 0.87)
Ward, 1993	15/18	8/17		3.78	1.77 (1.03 to 3.05)
Bouboulis, 1994	34/42	28/33		4.83	0.95 (0.78 to 1.17)
Rosencher, 1994	6/20	6/10		2.80	0.50 (0.22 to 1.16)
Schmidt, 1996	15/53	31/56		3.98	0.51 (0.31 to 0.83)
Unsworth, 1996	32/36	31/34		4.93	0.97 (0.83 to 1.14)
Newman, 1997	3/35	28/35		2.14	0.11 (0.04 to 0.32)
Shenolikar, 1997	8/50	40/50		3.41	0.20 (0.10 to 0.38)
Spark, 1997	3/23	26/27		2.22	0.14 (0.05 to 0.39)
Adalberth, 1998	8/24	10/25		3.11	0.83 (0.40 to 1.75)
Clagett, 1999	33/50	36/50		4.69	0.92 (0.70 to 1.19)
Dalrymple-Hay, 1999	28/56	46/56		4.62	0.61 (0.46 to 0.81)
Sait, 1999	1/60	35/60		0.94	0.03 (0.00 to 0.20)
Thomas, 2001	12/115	33/116		3.56	0.37 (0.20 to 0.67)
McGill, 2002	26/84	43/84		4.34	0.60 (0.41 to 0.89)
Naumenko, 2003	2/32	1/33		0.69	2.06 (0.20 to 21.64)
Zhao, 2003	19/30	30/30		4.67	0.63 (0.48 to 0.83)
Subtotal (95% CI)	1035	1029		100.00	0.59 (0.48 to 0.73)

Total events: 405 (cell salvage), 677 (control)
Test for heterogeneity: $\chi^2 = 287.73$, df = 27 ($p < 0.00001$), $I^2 = 90.6\%$
Test for overall effect: $z = 4.84$ ($p < 0.00001$)



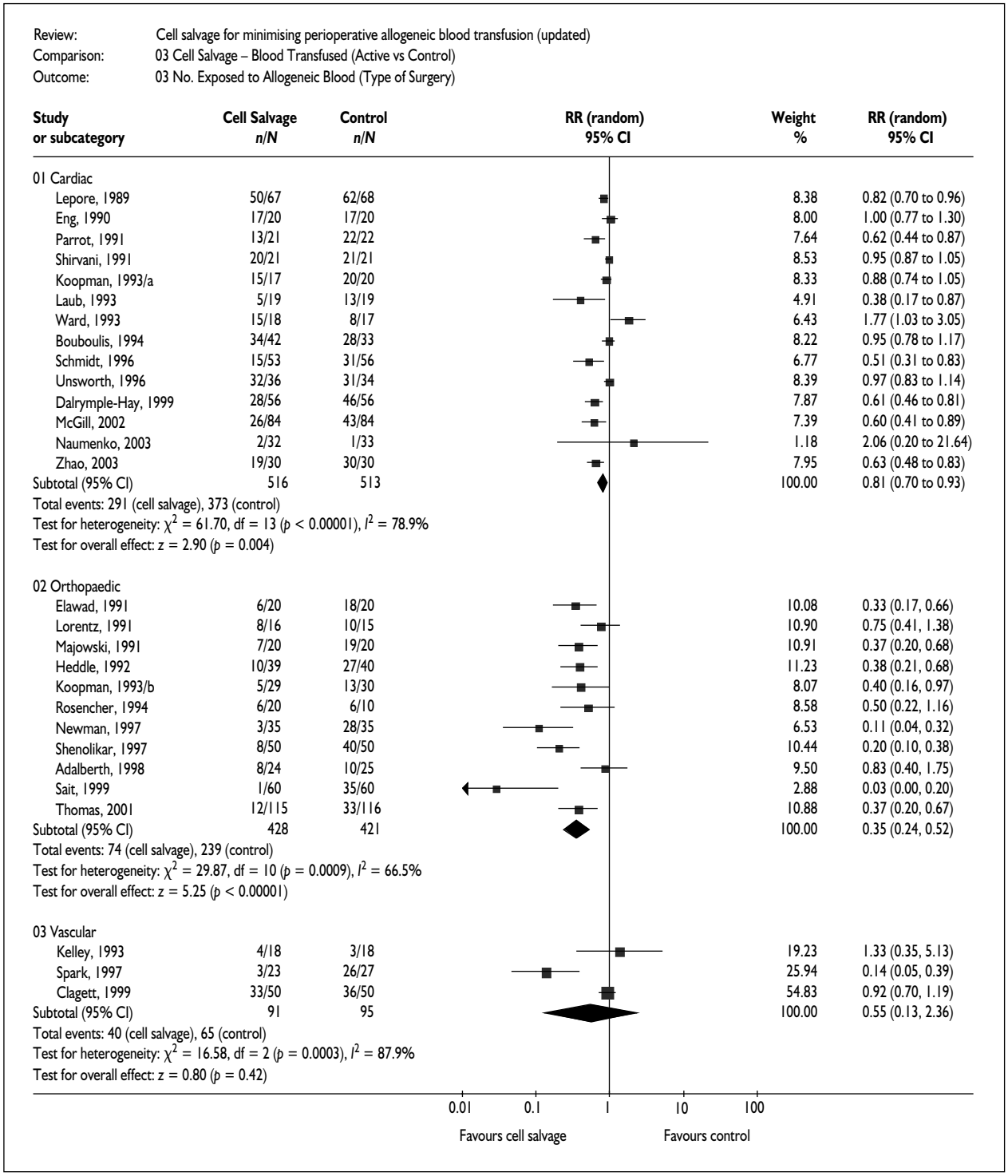
Relative risk of exposure to allogeneic blood, cell salvage versus control, active versus control, transfusion protocol

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 02 No. Exposed to Allogeneic Blood (Transfusion Protocol)



Relative risk of exposure to allogeneic blood, cell salvage versus control, active versus control, type of surgery

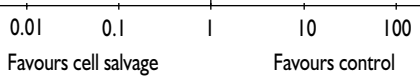
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 03 No. Exposed to Allogeneic Blood (Type of Surgery)



Relative risk of exposure to allogeneic blood, cell salvage versus control, active versus control, type of cell salvage

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 04 No. Exposed to Allogeneic Blood (Washed vs Unwashed)

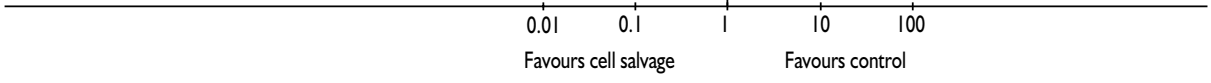
Study or subcategory	Cell Salvage *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Washed					
Elawad, 1991	6/20	18/20		6.85	0.33 (0.17 to 0.66)
Lorentz, 1991	8/16	10/15		7.50	0.75 (0.41 to 1.38)
Parrot, 1991	13/21	22/22		9.85	0.62 (0.44 to 0.87)
Kelley, 1993	4/18	3/18		3.19	1.33 (0.35 to 5.13)
Koopman, 1993/a	15/17	20/20		10.96	0.88 (0.74 to 1.05)
Koopman, 1993/b	5/29	13/30		5.33	0.40 (0.16 to 0.97)
Laub, 1993	5/19	13/19		5.90	0.38 (0.17 to 0.87)
Shenolikar, 1997	8/50	40/50		7.14	0.20 (0.10 to 0.38)
Spark, 1997	3/23	26/27		4.41	0.14 (0.05 to 0.39)
Clagett, 1999	33/50	36/50		10.40	0.92 (0.70 to 1.19)
Dalrymple-Hay, 1999	28/56	46/56		10.22	0.61 (0.46 to 0.81)
Thomas, 2001	12/115	33/116		7.49	0.37 (0.20 to 0.67)
McGill, 2002	26/84	43/84		9.47	0.60 (0.41 to 0.89)
Naumenko, 2003	2/32	1/33		1.29	2.06 (0.20 to 21.64)
Subtotal (95% CI)	550	560		100.00	0.53 (0.39 to 0.72)
Total events: 168 (cell salvage), 324 (control)					
Test for heterogeneity: $\chi^2 = 75.19$, df = 13 ($p < 0.00001$), $I^2 = 82.7\%$					
Test for overall effect: $z = 4.09$ ($p < 0.0001$)					
02 Unwashed					
Lepore, 1989	50/67	62/68		9.76	0.82 (0.70 to 0.96)
Eng, 1990	17/20	17/20		9.22	1.00 (0.77 to 1.30)
Majowski, 1991	7/20	19/20		6.64	0.37 (0.20 to 0.68)
Shirvani, 1991	20/21	21/21		9.98	0.95 (0.87 to 1.05)
Heddle, 1992	10/39	27/40		6.86	0.38 (0.21 to 0.68)
Ward, 1993	15/18	8/17		7.10	1.77 (1.03 to 3.05)
Bouboulis, 1994	34/42	28/33		9.53	0.95 (0.78 to 1.17)
Rosencher, 1994	6/20	6/10		5.05	0.50 (0.22 to 1.16)
Schmidt, 1996	15/53	31/56		7.54	0.51 (0.31 to 0.83)
Unsworth, 1996	32/36	31/34		9.77	0.97 (0.83 to 1.14)
Newman, 1997	3/35	28/35		3.74	0.11 (0.04 to 0.32)
Adalberth, 1998	8/24	10/25		5.67	0.83 (0.40 to 1.75)
Zhao, 2003	19/30	30/30		9.14	0.63 (0.48 to 0.83)
Subtotal (95% CI)	425	409		100.00	0.73 (0.58 to 0.91)
Total events: 236 (cell salvage), 318 (control)					
Test for heterogeneity: $\chi^2 = 103.26$, df = 12 ($p < 0.00001$), $I^2 = 88.4\%$					
Test for overall effect: $z = 2.77$ ($p = 0.006$)					



Relative risk of exposure to allogeneic blood, cell salvage versus control, active versus control, timing of cell salvage

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 05 No. Exposed to Allogeneic Blood (Timing)

Study or subcategory	Cell Salvage n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Intra-operative					
Elawad, 1991	6/20	18/20		19.54	0.33 (0.17 to 0.66)
Kelley, 1993	4/18	3/18		9.76	1.33 (0.35 to 5.13)
Laub, 1993	5/19	13/19		17.12	0.38 (0.17 to 0.87)
Clagett, 1999	33/50	36/50		27.83	0.92 (0.70 to 1.19)
McGill, 2002	26/84	43/84		25.75	0.60 (0.41 to 0.89)
Subtotal (95% CI)	191	191		100.00	0.61 (0.39 to 0.95)
Total events: 74 (cell salvage), 113 (control)					
Test for heterogeneity: χ^2 = 12.87, df = 4 (p = 0.01), I^2 = 68.9%					
Test for overall effect: z = 2.19 (p = 0.03)					
02 Post-operative					
Lepore, 1989	50/67	62/68		7.54	0.82 (0.70 to 0.96)
Eng, 1990	17/20	17/20		7.19	1.00 (0.77 to 1.30)
Majowski, 1991	7/20	19/20		5.46	0.37 (0.20 to 0.68)
Shirvani, 1991	20/21	21/21		7.67	0.95 (0.87 to 1.05)
Heddle, 1992	10/39	27/40		5.62	0.38 (0.21 to 0.68)
Ward, 1993	15/18	8/17		5.79	1.77 (1.03 to 3.05)
Bouboulis, 1994	34/42	28/33		7.39	0.95 (0.78 to 1.17)
Rosencher, 1994	6/20	6/10		4.29	0.50 (0.22 to 1.16)
Schmidt, 1996	15/53	31/56		6.09	0.51 (0.31 to 0.83)
Unsworth, 1996	32/36	31/34		7.54	0.97 (0.83 to 1.14)
Newman, 1997	3/35	28/35		3.27	0.11 (0.04 to 0.32)
Shenolikar, 1997	8/50	40/50		5.22	0.20 (0.10 to 0.38)
Adalberth, 1998	8/24	10/25		4.75	0.83 (0.40 to 1.75)
Dalrymple-Hay, 1999	28/56	46/56		7.08	0.61 (0.46 to 0.81)
Sait, 1999	1/60	35/60		1.44	0.03 (0.00 to 0.20)
Thomas, 2001	12/115	33/116		5.45	0.37 (0.20 to 0.67)
Naumenko, 2003	2/32	1/33		1.06	2.06 (0.20 to 21.64)
Zhao, 2003	19/30	30/30		7.15	0.63 (0.48 to 0.83)
Subtotal (95% CI)	738	724		100.00	0.60 (0.45 to 0.79)
Total events: 287 (cell salvage), 473 (control)					
Test for heterogeneity: χ^2 = 246.59, df = 17 (p < 0.00001), I^2 = 93.1%					
Test for overall effect: z = 3.61 (p = 0.0003)					
03 Both					
Lorentz, 1991	8/16	10/15		20.01	0.75 (0.41 to 1.38)
Parrot, 1991	13/21	22/22		25.20	0.62 (0.44 to 0.87)
Koopman, 1993/a	15/17	20/20		27.50	0.88 (0.74 to 1.05)
Koopman, 1993/b	5/29	13/30		14.82	0.40 (0.16 to 0.97)
Spark, 1997	3/23	26/27		12.47	0.14 (0.05 to 0.39)
Subtotal (95% CI)	106	114		100.00	0.52 (0.26 to 1.01)
Total events: 44 (cell salvage), 91 (control)					
Test for heterogeneity: χ^2 = 43.39, df = 4 (p < 0.00001), I^2 = 90.8%					
Test for overall effect: z = 1.94 (p = 0.05)					

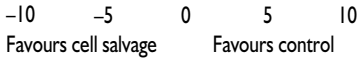


Units of allogeneic blood transfused, cell salvage versus control, transfusion protocol

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 06 Units Allogeneic Blood Transfused (Active vs Control)

Study or subcategory	N	Cell salvage mean (SD)	N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Cell Salvage vs Control							
Schaff,1978	63	2.40 (2.38)	51	4.80 (4.28)		3.70	–2.40 (–3.71 to –1.09)
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		1.34	–1.50 (–4.14 to 1.14)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		5.22	–0.60 (–1.53 to 0.33)
Elawad, 1991	20	0.69 (0.87)	20	2.70 (0.88)		7.15	–2.01 (–2.55 to –1.47)
Parrot, 1991	21	1.38 (1.50)	22	4.50 (1.75)		5.02	–3.12 (–4.09 to –2.15)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		5.62	0.03 (–0.81 to 0.87)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		7.84	–0.80 (–1.20 to –0.40)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		7.80	0.11 (–0.30 to 0.52)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		1.02	–1.30 (–4.39 to 1.79)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		6.96	–0.80 (–1.38 to –0.22)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		5.67	–0.66 (–1.49 to 0.17)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		5.74	–0.32 (–1.14 to 0.50)
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		4.99	–0.80 (–1.78 to 0.18)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		2.40	–2.30 (–4.13 to –0.47)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		5.72	–0.20 (–1.02 to 0.62)
Dalrymple-Hay, 1999	56	0.99 (1.20)	56	1.69 (1.20)		7.63	–0.70 (–1.14 to –0.26)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		7.51	–0.39 (–0.86 to 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		8.64	–1.02 (–1.19 to –0.85)
Subtotal (95% CI)	638		622			100.00	–0.90 (–1.23 to –0.56)

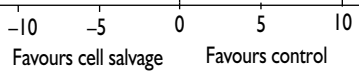
Test for heterogeneity: $\chi^2 = 84.44$, df = 17 ($p < 0.00001$), $I^2 = 79.9\%$
Test for overall effect: $z = 5.29$ ($p < 0.00001$)



Units of allogeneic blood transfused, cell salvage versus control, transfusion protocol

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 07 Units of Allogeneic Blood Transfused (Transfusion Protocol)

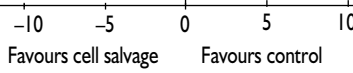
Study or subcategory	Cell salvage N	Cell salvage mean (SD)	Control N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Transfusion Protocol							
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		1.53	–1.50 (–4.14 to 1.14)
Elawad, 1991	20	0.69 (0.87)	20	2.73 (0.88)		8.06	–2.04 (–2.58 to –1.50)
Parrot, 1991	21	1.38 (1.50)	22	4.50 (1.75)		5.68	–3.12 (–4.09 to –2.15)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		6.35	0.03 (–0.81 to 0.87)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		8.83	–0.80 (–1.20 to –0.40)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		8.78	0.11 (–0.30 to 0.52)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		1.16	–1.30 (–4.39 to 1.79)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		7.85	–0.80 (–1.38 to –0.22)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		6.40	–0.66 (–1.49 to 0.17)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		6.49	–0.32 (–1.14 to 0.50)
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		5.64	–0.80 (–1.78 to 0.18)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		6.47	–0.20 (–1.02 to 0.62)
Dalrymple-Hay, 1999	56	0.99 (1.20)	56	1.69 (1.20)		8.59	–0.70 (–1.14 to –0.26)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		8.46	–0.39 (–0.86 to 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		9.71	–1.02 (–1.19 to –0.85)
Subtotal (95% CI)	486		483			100.00	–0.81 (–1.16 to –0.46)
Test for heterogeneity: $\chi^2 = 77.34$, df = 14 ($p < 0.00001$), $I^2 = 81.9\%$							
Test for overall effect: $z = 4.56$ ($p < 0.00001$)							
02 No Transfusion Protocol							
Schaff, 1978	63	2.40 (2.38)	51	4.80 (4.28)		32.71	–2.40 (–3.71 to –1.09)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		46.03	–0.60 (–1.53 to 0.33)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		21.27	–2.30 (–4.13 to –0.47)
Subtotal (95% CI)	152		139			100.00	–1.64 (–2.96 to –0.33)
Test for heterogeneity: $\chi^2 = 6.00$, df = 2 ($p = 0.05$), $I^2 = 66.7\%$							
Test for overall effect: $p = 2.45$ ($p = 0.01$)							



Units of allogeneic blood transfused, cell salvage versus control, transfusion protocol

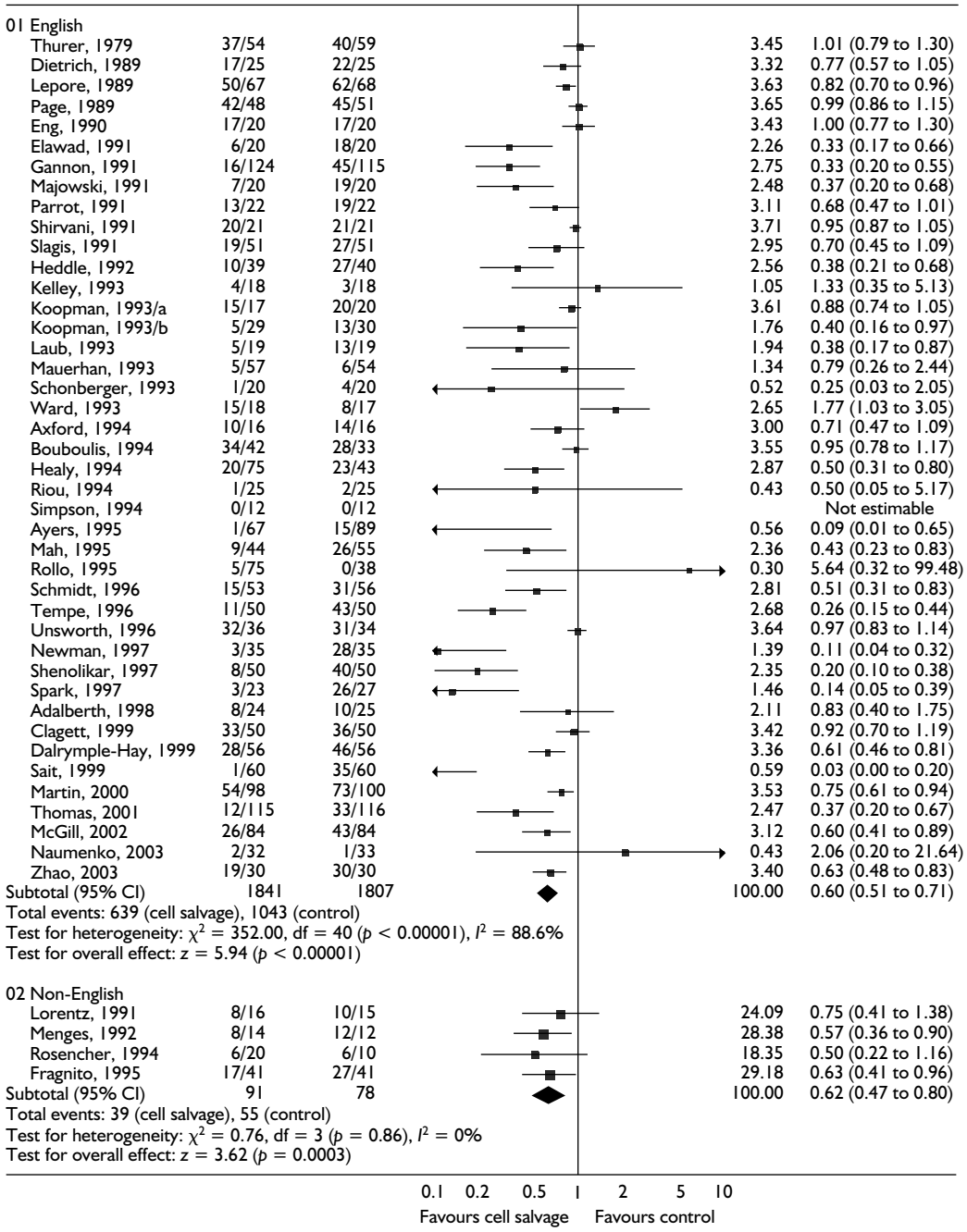
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 03 Cell Salvage – Blood Transfused (Active vs Control)
Outcome: 08 Units Allogeneic Blood Transfused (Type of Surgery)

Study or subcategory	Cell salvage N	Cell salvage mean (SD)	Control N	Control mean (SD)	WMD (random) 95% CI	Weight %	WMD (random) 95% CI
01 Cardiac							
Schaff, 1978	63	2.40 (2.38)	51	4.80 (4.28)		6.39	–2.40 (–3.71, –1.09)
Lepore, 1989	67	2.70 (2.80)	68	3.30 (2.70)		8.99	–0.60 (–1.53, 0.33)
Parrot, 1991	21	1.38 (1.50)	22	4.50 (1.75)		8.65	–3.12 (–4.09, –2.15)
Shirvani, 1991	21	2.57 (1.73)	21	2.54 (0.95)		9.67	0.03 (–0.81, 0.87)
Koopman, 1993/a	17	4.90 (3.40)	20	6.20 (6.00)		1.77	–1.30 (–4.39, 1.79)
Laub, 1993	19	0.64 (1.16)	19	1.30 (1.45)		9.75	–0.66 (–1.49, 0.17)
Bouboulis, 1994	42	1.88 (1.50)	33	2.20 (2.00)		9.88	–0.32 (–1.14, 0.50)
Zhao, 1996	22	3.60 (2.40)	20	5.90 (3.48)		4.16	–2.30 (–4.13, –0.47)
Dalrymple–Hay, 1999	56	0.99 (1.20)	56	1.69 (1.20)		13.09	–0.70 (–1.14, –0.26)
McGill, 2002	84	0.68 (1.55)	84	1.07 (1.56)		12.88	–0.39 (–0.86, 0.08)
Zhao, 2003	30	1.20 (0.27)	30	2.22 (0.40)		14.79	–1.02 (–1.19, –0.85)
Subtotal (95% CI)	442		424			100.00	–0.97 (–1.40, –0.55)
Test for heterogeneity: $\chi^2 = 41.62$, df = 10 ($p < 0.00001$), $I^2 = 76.0\%$							
Test for overall effect: $z = 4.51$ ($p < 0.00001$)							
02 Orthopaedic							
Elawad, 1991	20	0.69 (0.87)	20	2.73 (0.88)		26.53	–2.04 (–2.58, –1.50)
Heddle, 1992	39	0.40 (0.80)	40	1.20 (1.00)		29.05	–0.80 (–1.20, –0.40)
Koopman, 1993/b	29	0.30 (0.80)	30	1.10 (1.40)		25.84	–0.80 (–1.38, –0.22)
Ekback, 1995	15	1.90 (1.55)	15	2.70 (1.16)		18.58	–0.80 (–1.78, 0.18)
Subtotal (95% CI)	103		105			100.00	–1.13 (–1.78, –0.48)
Test for heterogeneity: $\chi^2 = 15.10$, df = 3 ($p = 0.002$), $I^2 = 80.1\%$							
Test for overall effect: $z = 3.40$ ($p = 0.0007$)							
03 Vascular							
Davies, 1987	25	4.00 (3.40)	25	5.50 (5.80)		9.10	–1.50 (–4.14, 1.14)
Kelley, 1993	18	0.33 (0.69)	18	0.22 (0.55)		52.36	0.11 (–0.30, 0.52)
Clagett, 1999	50	2.10 (2.10)	50	2.30 (2.10)		38.54	–0.20 (–1.02, 0.62)
Subtotal (95% CI)	93		93			100.00	0.02 (–0.34, 0.38)
Test for heterogeneity: $\chi^2 = 1.74$, df = 2 ($p = 0.42$), $I^2 = 0\%$							
Test for overall effect: $z = 0.11$ ($p = 0.91$)							



Relative risk of exposure to allogeneic blood, cell salvage versus control, language of publication

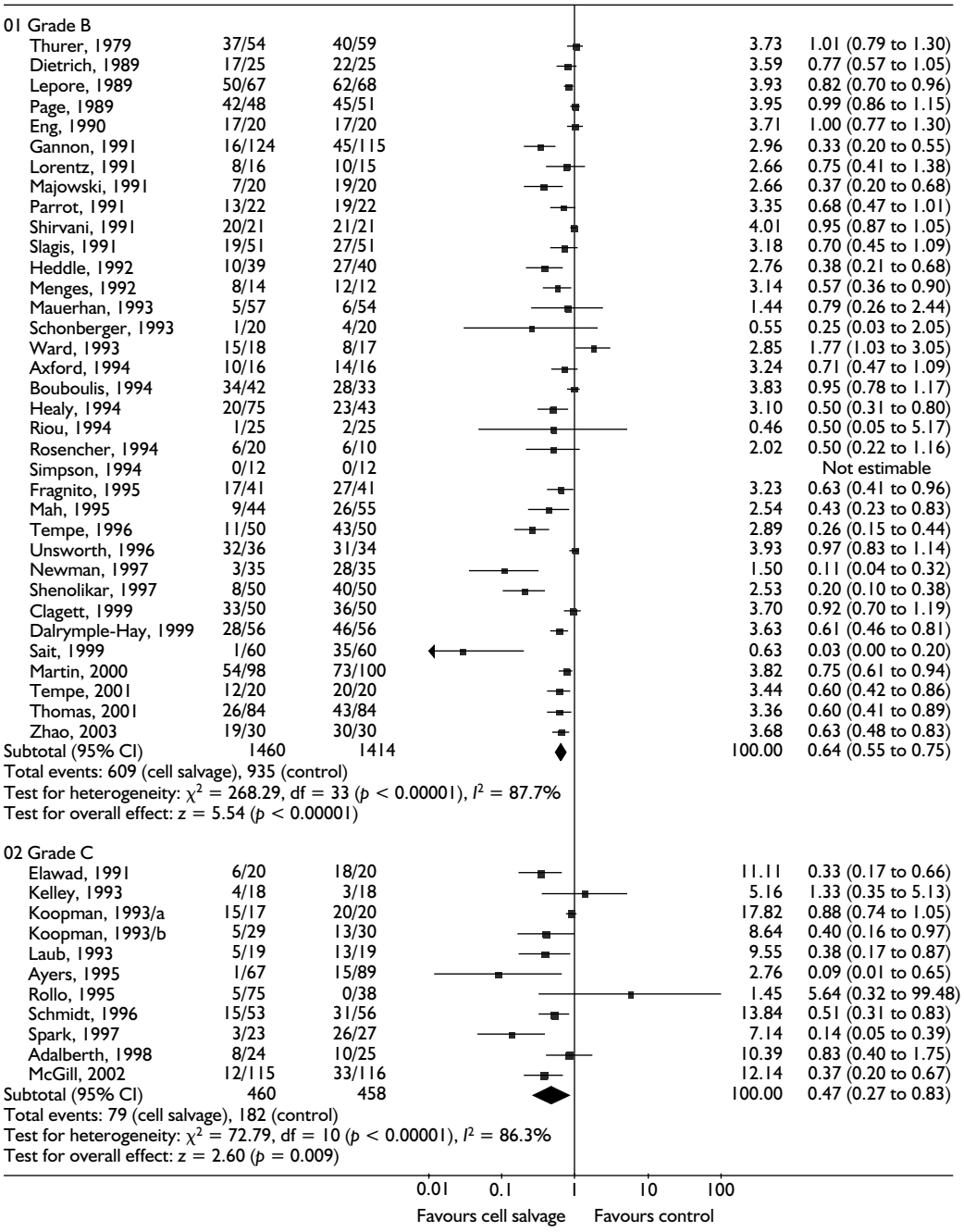
Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 06 Cell Salvage – Blood Transfused (Language & Methodological Quality)
Outcome: 01 Language of Publication (All Studies)



Study or subcategory	Cell salvage n/N	Control n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 English					
Thurer, 1979	37/54	40/59		3.45	1.01 (0.79 to 1.30)
Dietrich, 1989	17/25	22/25		3.32	0.77 (0.57 to 1.05)
Lepore, 1989	50/67	62/68		3.63	0.82 (0.70 to 0.96)
Page, 1989	42/48	45/51		3.65	0.99 (0.86 to 1.15)
Eng, 1990	17/20	17/20		3.43	1.00 (0.77 to 1.30)
Elawad, 1991	6/20	18/20		2.26	0.33 (0.17 to 0.66)
Gannon, 1991	16/124	45/115		2.75	0.33 (0.20 to 0.55)
Majowski, 1991	7/20	19/20		2.48	0.37 (0.20 to 0.68)
Parrot, 1991	13/22	19/22		3.11	0.68 (0.47 to 1.01)
Shirvani, 1991	20/21	21/21		3.71	0.95 (0.87 to 1.05)
Slagis, 1991	19/51	27/51		2.95	0.70 (0.45 to 1.09)
Heddle, 1992	10/39	27/40		2.56	0.38 (0.21 to 0.68)
Kelley, 1993	4/18	3/18		1.05	1.33 (0.35 to 5.13)
Koopman, 1993/a	15/17	20/20		3.61	0.88 (0.74 to 1.05)
Koopman, 1993/b	5/29	13/30		1.76	0.40 (0.16 to 0.97)
Laub, 1993	5/19	13/19		1.94	0.38 (0.17 to 0.87)
Mauerhan, 1993	5/57	6/54		1.34	0.79 (0.26 to 2.44)
Schonberger, 1993	1/20	4/20		0.52	0.25 (0.03 to 2.05)
Ward, 1993	15/18	8/17		2.65	1.77 (1.03 to 3.05)
Axford, 1994	10/16	14/16		3.00	0.71 (0.47 to 1.09)
Bouboulis, 1994	34/42	28/33		3.55	0.95 (0.78 to 1.17)
Healy, 1994	20/75	23/43		2.87	0.50 (0.31 to 0.80)
Riou, 1994	1/25	2/25		0.43	0.50 (0.05 to 5.17)
Simpson, 1994	0/12	0/12			Not estimable
Ayers, 1995	1/67	15/89		0.56	0.09 (0.01 to 0.65)
Mah, 1995	9/44	26/55		2.36	0.43 (0.23 to 0.83)
Rollo, 1995	5/75	0/38		0.30	5.64 (0.32 to 99.48)
Schmidt, 1996	15/53	31/56		2.81	0.51 (0.31 to 0.83)
Tempe, 1996	11/50	43/50		2.68	0.26 (0.15 to 0.44)
Unsworth, 1996	32/36	31/34		3.64	0.97 (0.83 to 1.14)
Newman, 1997	3/35	28/35		1.39	0.11 (0.04 to 0.32)
Shenolikar, 1997	8/50	40/50		2.35	0.20 (0.10 to 0.38)
Spark, 1997	3/23	26/27		1.46	0.14 (0.05 to 0.39)
Adalberth, 1998	8/24	10/25		2.11	0.83 (0.40 to 1.75)
Clagett, 1999	33/50	36/50		3.42	0.92 (0.70 to 1.19)
Dalrymple-Hay, 1999	28/56	46/56		3.36	0.61 (0.46 to 0.81)
Sait, 1999	1/60	35/60		0.59	0.03 (0.00 to 0.20)
Martin, 2000	54/98	73/100		3.53	0.75 (0.61 to 0.94)
Thomas, 2001	12/115	33/116		2.47	0.37 (0.20 to 0.67)
McGill, 2002	26/84	43/84		3.12	0.60 (0.41 to 0.89)
Naumenko, 2003	2/32	1/33		0.43	2.06 (0.20 to 21.64)
Zhao, 2003	19/30	30/30		3.40	0.63 (0.48 to 0.83)
Subtotal (95% CI)	1841	1807		100.00	0.60 (0.51 to 0.71)
Total events: 639 (cell salvage), 1043 (control)					
Test for heterogeneity: $\chi^2 = 352.00$, df = 40 ($p < 0.00001$), $I^2 = 88.6\%$					
Test for overall effect: $z = 5.94$ ($p < 0.00001$)					
02 Non-English					
Lorentz, 1991	8/16	10/15		24.09	0.75 (0.41 to 1.38)
Menges, 1992	8/14	12/12		28.38	0.57 (0.36 to 0.90)
Rosencher, 1994	6/20	6/10		18.35	0.50 (0.22 to 1.16)
Fragnito, 1995	17/41	27/41		29.18	0.63 (0.41 to 0.96)
Subtotal (95% CI)	91	78		100.00	0.62 (0.47 to 0.80)
Total events: 39 (cell salvage), 55 (control)					
Test for heterogeneity: $\chi^2 = 0.76$, df = 3 ($p = 0.86$), $I^2 = 0\%$					
Test for overall effect: $z = 3.62$ ($p = 0.0003$)					

Relative risk of exposure to allogeneic blood, cell salvage versus control, methodological quality

Review: Cell salvage for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 06 Cell Salvage – Blood Transfused (Language & Methodological Quality)
Outcome: 02 Methodological Quality (All Studies)



Appendix 11

PAD meta-analyses

Meta-analysis and subgroup analysis results for the PAD update[a]

Outcome	Meta-analysis	No. of RCTs	No. of events/ No. of participants in cell salvage	No. of events/ No. of participants in control	RR (random effects)	95% CI	Heterogeneity *p*-value
No. of patients transfused with allogeneic blood	***All studies***	***11***	***149/716***	***375/707***	***0.36***	***0.25 to 0.51***	***p = 0.0005 I^2 = 69.6%***
	Transfusion protocol	***7***	***138/585***	***299/611***	***0.48***	***0.38 to 0.60***	***p = 0.18 I^2 = 34.3%***
	No transfusion protocol	***4***	***11/121***	***76/96***	***0.12***	***0.04 to 0.33***	***p = 0.08 I^2 = 56.2%***
	Orthopaedic	***5***	***21/221***	***75/204***	***0.21***	***0.11 to 0.43***	***p = 0.07 I^2 = 56.9%***
	Oncology	5	128/467	280/483	0.49	0.38 to 0.63	*p* = 0.15 I^2 = 41.3%
	Oral	***1***	***0/28***	***20/20***	***0.02***	***0.00 to 0.28***	***NA***
No. of patients transfused with allogeneic/ autologous blood	***All studies***	***9***	***496/620***	***343/612***	***1.33***	***1.10 to 1.61***	***p < 0.00001 I^2 = 80.6%***
	Transfusion protocol	***5***	***384/499***	***267/516***	***1.48***	***1.16 to 1.89***	***p = 0.001 I^2 = 78.2%***
	No transfusion protocol	***4***	***112/121***	***76/96***	***1.10***	***0.95 to 1.29***	***p = 0.26 I^2 = 24.8%***
	Orthopaedic	***3***	***105/125***	***43/109***	***1.78***	***0.61 to 5.20***	***p < 0.00001 I^2 = 97.2%***
	Oncology	5	363/467	280/483	1.38	1.20 to 1.58	*p* = 0.13 I^2 = 44.5%
Any thrombosis	All studies	3	6/140	3/110	0.82	0.21 to 3.13	*p* = 0.53 I^2 = 0%
Any infection	All studies	3	74/309	81/312	0.70	0.34 to 1.43	*p* = 0.07 I^2 = 61.9%

[a] Studies in bold italic indicate where data have been added as a result of the update of the cell salvage systematic review.

Meta-analysis and subgroup analysis results for the PAD update[a]

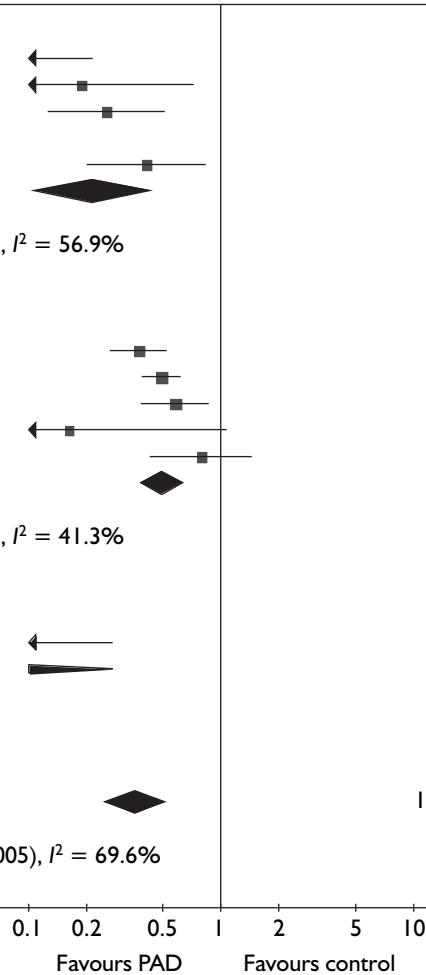
Outcome	Meta-analysis	No. of included RCTs	No. of participants in cell salvage	No. of participants in control	WMD (random effects)	95% CI	Heterogeneity *p*-value
Preoperative Hb levels (g/dl)	***All studies***	***5***	***267***	***267***	***–1.16***	***–1.60 to –0.73***	***p = 0.004 I^2 = 73.9%***

[a] Studies in bold italic indicate where data have been added as a result of the update of the cell salvage systematic review.

Relative risk of exposure to allogeneic blood, PAD versus control, type of surgery

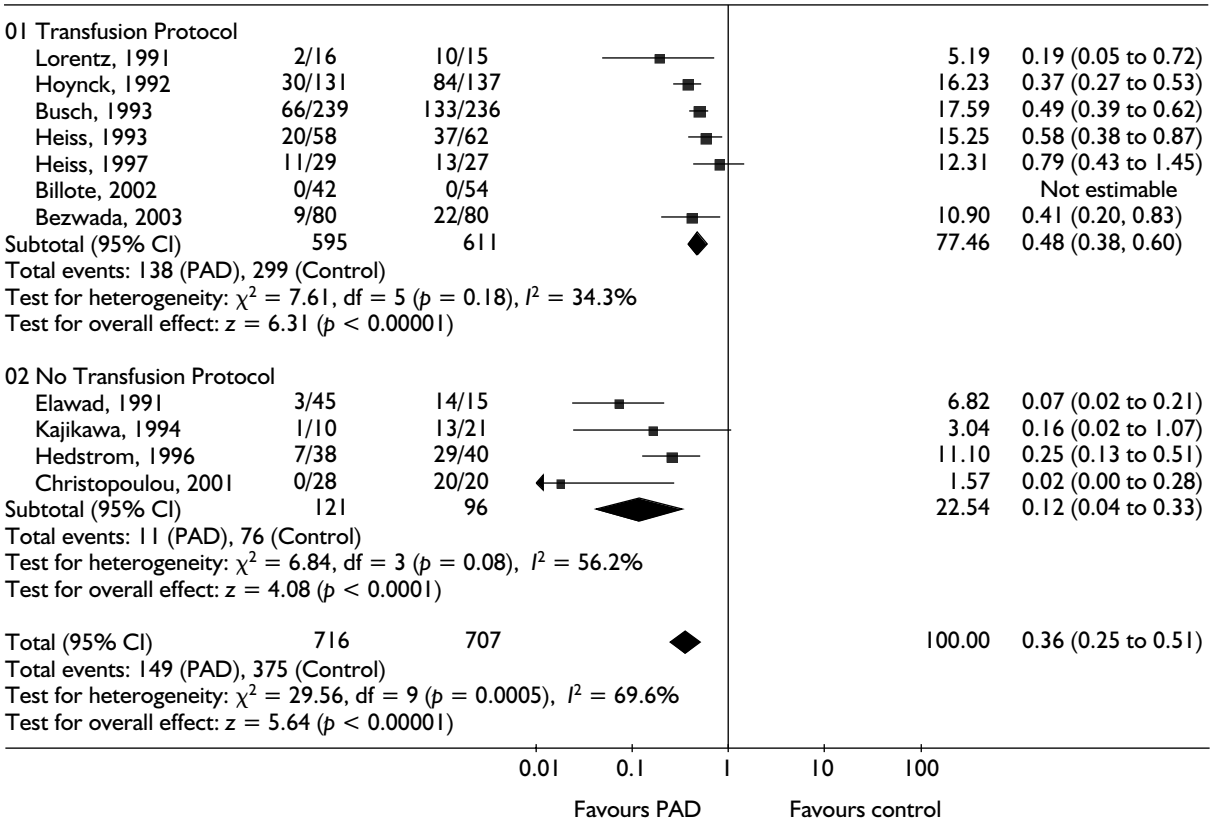
Review: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 PAD vs Control (Blood Transfused)
Outcome: 02 No. Exposed to Allogeneic Blood Transfusion (Operation Type)

Study or subcategory	PAD *n/N*	Control *n/N*	RR (random) 95% CI	Weight %	RR (random) 95% CI
01 Orthopaedic					
Elawad, 1991	3/45	14/15		6.82	0.07 (0.02 to 0.21)
Lorentz, 1991	2/16	10/15		5.19	0.19 (0.05 to 0.72)
Hedstrom, 1996	7/38	29/40		11.10	0.25 (0.13 to 0.51)
Billote, 2002	0/42	0/54			Not estimable
Bezwada, 2003	9/80	22/80		10.90	0.41 (0.20 to 0.83)
Subtotal (95% CI)	221	204		34.02	0.21 (0.11 to 0.43)
Total events: 21 (PAD), 75 (Control)					
Test for heterogeneity: χ^2 = 6.97, df = 3 (p = 0.07), I^2 = 56.9%					
Test for overall effect: z = 4.35 (p < 0.0001)					
02 Oncology					
Hoynck, 1992	30/131	84/137		16.23	0.37 (0.27 to 0.53)
Busch, 1993	66/239	133/236		17.59	0.49 (0.39 to 0.62)
Heiss, 1993	20/58	37/62		15.25	0.58 (0.38 to 0.87)
Kajikawa, 1994	1/10	13/21		3.04	0.16 (0.02 to 1.07)
Heiss, 1997	11/29	13/27		12.31	0.79 (0.43 to 1.45)
Subtotal (95% CI)	467	483		64.41	0.49 (0.38 to 0.63)
Total events: 128 (PAD), 280 (Control)					
Test for heterogeneity: χ^2 = 6.82, df = 4 (p = 0.15), I^2 = 41.3%					
Test for overall effect: z = 5.48 (p < 0.00001)					
03 Oral and maxilofacial					
Christopoulou, 2001	0/28	20/20		1.57	0.02 (0.00 to 0.28)
Subtotal (95% CI)	28	20		1.57	0.02 (0.00 to 0.28)
Total events: 0 (PAD), 20 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: z = 2.88 (p = 0.004)					
Total (95% CI)	716	707		100.00	0.36 (0.25 to 0.51)
Total events: 149 (PAD), 375 (Control)					
Test for heterogeneity: χ^2 = 29.56, df = 9 (p = 0.0005), I^2 = 69.6%					
Test for overall effect: z = 5.64 (p < 0.00001)					



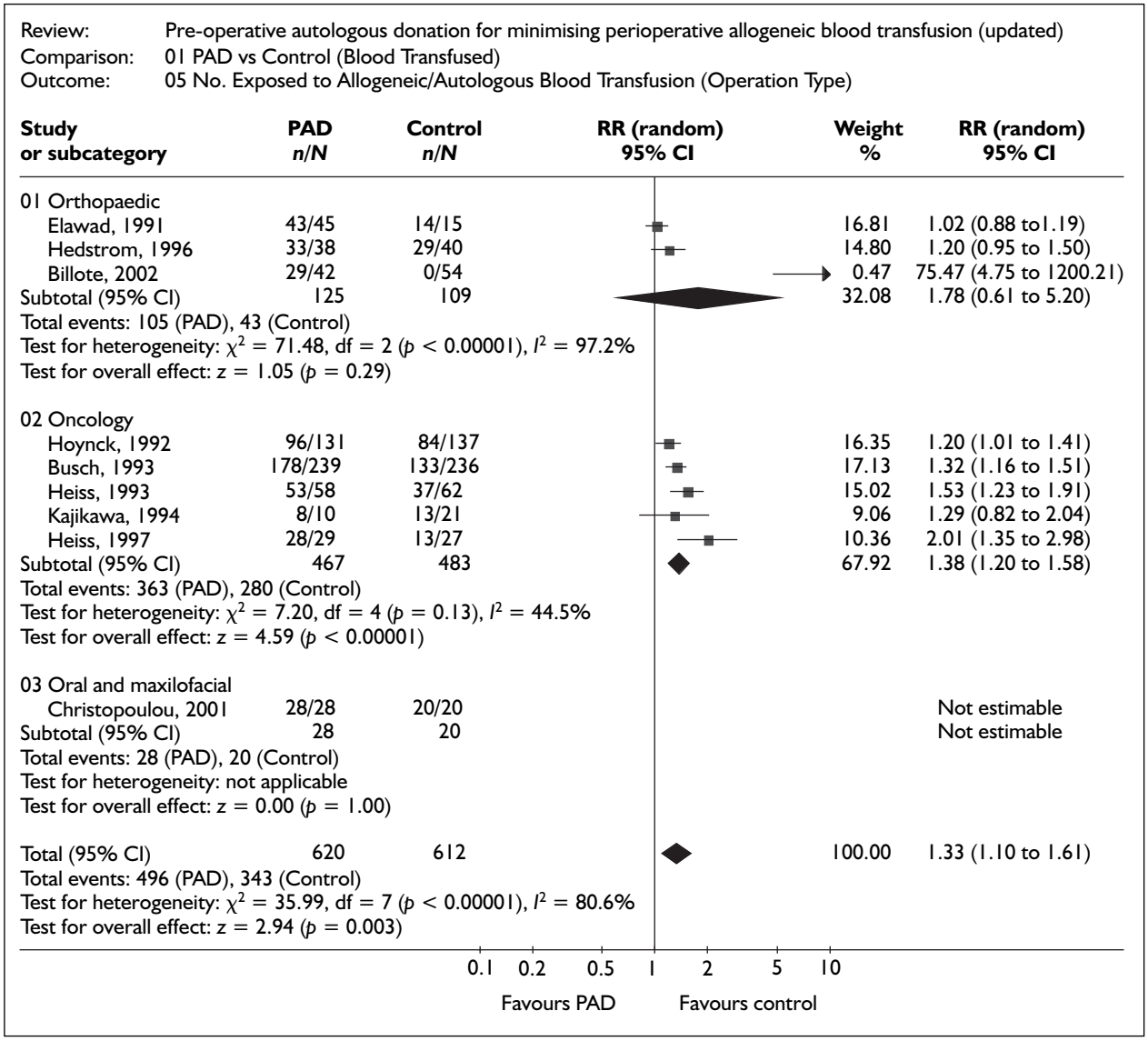
Relative risk of exposure to allogeneic blood, PAD versus control, transfusion protocol

Review: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 PAD vs Control (Blood Transfused)
Outcome: 03 No. Exposed to Allogeneic Blood Transfusion (Transfusion Protocol)



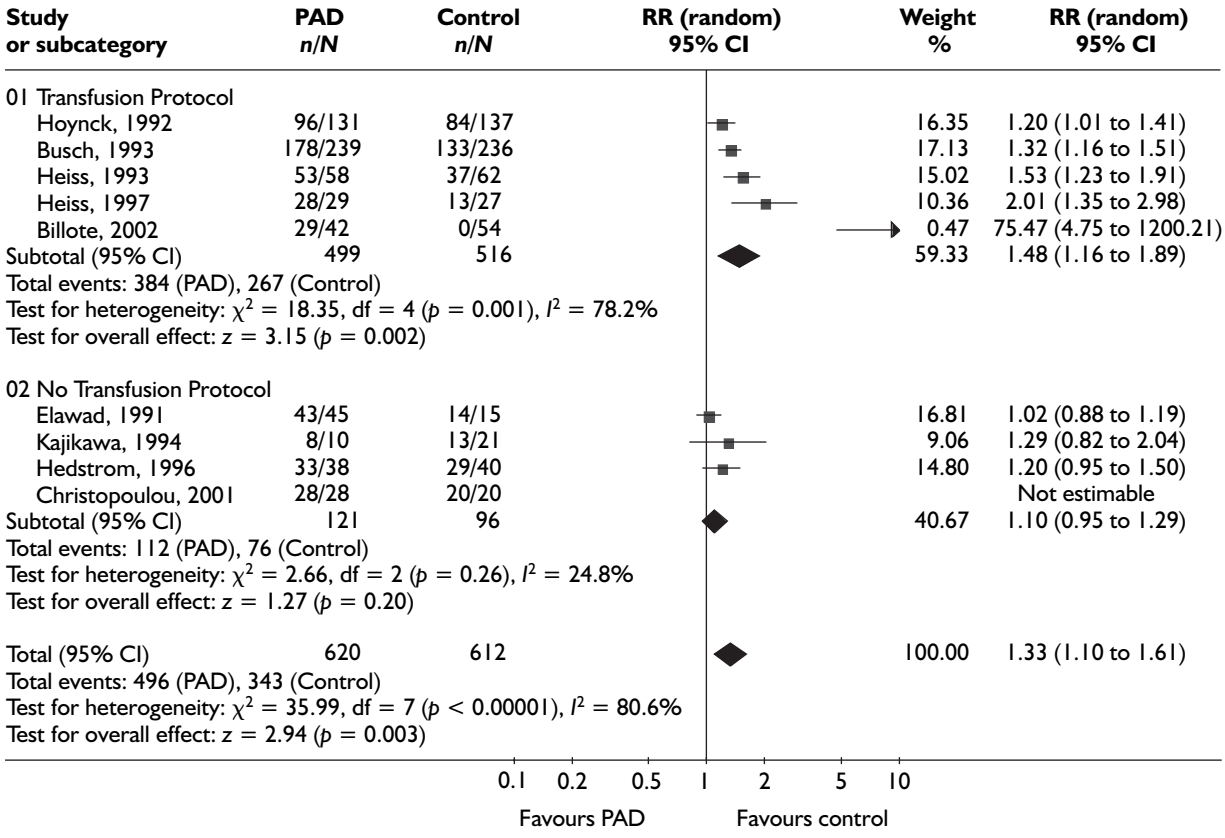
Relative risk of exposure to allogeneic/autologous blood, PAD versus control, type of surgery

Review: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 PAD vs Control (Blood Transfused)
Outcome: 05 No. Exposed to Allogeneic/Autologous Blood Transfusion (Operation Type)



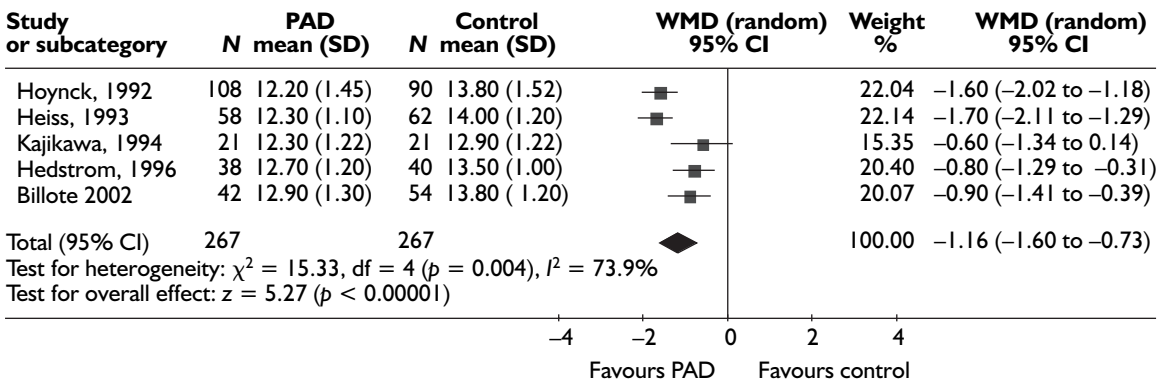
Relative risk of exposure to allogeneic/autologous blood, PAD versus control, transfusion protocol

Review: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 PAD vs Control (Blood Transfused)
Outcome: 06 No. Exposed to Allogeneic/Autologous Blood Transfusion (Transfusion Protocol)



Relative risk of exposure to allogeneic/autologous blood, PAD versus control, preoperative haemoglobin levels

Review: Pre-operative autologous donation for minimising perioperative allogeneic blood transfusion (updated)
Comparison: 01 PAD vs Control (Blood Transfused)
Outcome: 07 Pre-operative haemoglobin levels (g/dL)



Appendix 12

Table of included cost studies

Study characteristics	Comparators	Economic study type and population	Data
Name: Fung, 2004[87] **Setting:** hospital, USA **Perspective:** not stated **Funding:** leukofilters cost defrayed by support from Baxter Corporation	Leucoreduced (LR) blood products in open-heart surgery compared with no leukoreduced blood products	Cost study **Population:** primary or repeat CABG and/or valve, 645 patients received leucocyte reduced transfusion, 308 patients did not receive any allogeneic transfusion (also historical control of non-leucocyte reduced blood availability and patients who did and did not receive allogeneic non-LR transfusion-data not used)	**Dates:** **Effectiveness:** 2000–2 **Resource use:** 2000–2 **Price year:** not stated **Sources:** **Effectiveness:** prospective case–control single-centre study **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data
Name: Casati, 1999[88] **Setting:** hospital, Italy **Perspective:** hospital **Funding:** not reported	EACA and TXA versus aprotinin (AP)	Cost–consequence analysis **Population:** age 45–64 years, majority male, 10–11% predonated blood, undergoing primary elective cardiac surgery with cardiopulmonary bypass, excluded patients with ejection fraction less than 35%, impaired renal function, active chronic hepatitis, cirrhosis, previous haematological disorders, need for ventricular assistance device for weaning from CPB; 68 patients EACA arm, 72 patients TXA arm and 70 patients AP arm	**Dates:** **Effectiveness:** no dates reported **Resource use:** no dates reported **Price year:** not reported **Sources:** **Effectiveness:** RCT in single centre **Direct costs:** yes **Indirect costs:** not included **Currency:** US$; the conversion rate from Italian currency to US$ was not stated **Link between effectiveness and costs:** costs for same patient sample collected prospectively
Name: Thomas, 2001[89] **Setting:** hospital, UK **Perspective:** healthcare provider **Funding:** Welsh Office for Research and Development in Health and Social Care	Washed postoperative red cell salvage and a haemoglobin transfusion trigger (9 g/dl) compared with allogeneic blood transfusion	Cost-effectiveness analysis **Population:** mean age 67–71 years, 132 females, 99 males undergoing total knee replacement, 115 patients cell salvage group and 116 allogeneic group	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** 1998 **Sources:** **Effectiveness:** single RCT **Direct costs:** yes **Indirect costs:** not included **Currency:** UK£ **Link between effectiveness and costs:** costing done prospectively and reported as cost per patient so not clear if same patient sample for effectiveness and costing

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Huber, 1997[90] **Setting:** hospital, USA **Perspective:** health service **Funding:** not stated	Intraoperative autologous transfusion device, Haemonetics Cell Saver, compared with no use of the device	Cost–utility analysis **Population:** patients undergoing elective infrarenal aortic reconstruction for both abdominal aortic aneurysm (AAA) and aortoiliac occlusive disease (AIOD). Cell salvage was used in 138 of the 168 reconstructions (82.1%) during the study period (1991–95). mean age for AAA = 71 years and 75% male; mean age for AIOD = 64 years and 52% male	**Dates:** **Effectiveness:** 1980–95 **Resource use:** 1996 for complications **Price year:** 1996 **Sources:** **Effectiveness:** Two retrospective studies designed by the authors and a review of previously completed studies, 10 primary studies included, DEALE and US Vital Statistics used to determine life expectancy, the operative mortality rates were determined by a previous retrospective review of all 722 elective infrarenal aortic reconstructions performed in the authors' institution over a 12-year period. **Direct costs:** yes **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** retrospective review of hospital costs in part based on actual hospital data but not clear if any cost based on same patient sample
Name: Goodnough, 1996[91] **Setting:** hospital, USA **Perspective:** hospital **Funding:** not reported	Intra-operative cell salvage	Cost-effectiveness analysis **Population:** 184 consecutive patients who underwent AAA (infrarenal *n* = 165, suprarenal *n* = 19), 22% female, mean age 69 years, 42% coronary artery disease, 14% previous coronary bypass	**Dates:** **Effectiveness:** 1992–4 **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** 3-year retrospective hospital chart review of 184 patients and prospective audit of 100 consecutive patients (to estimate RBC mass only) **Direct costs:** yes **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costs based on actual data but not on same patient sample as effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Lazzara, 1997[92] **Setting:** community hospital, USA **Perspective:** patient and third-party payer **Funding:** not reported	Full-dose aprotinin vs half-dose aprotinin vs no aprotinin	Cost–consequence analysis **Population:** patients undergoing open-heart surgery (89 men, 44 women, mean age 67.4 years), no aprotinin $n = 52$, full dose aprotinin $n = 50$, half-dose aprotinin $n = 31$ (21, 35 and 21 had intraoperative salvage of shed mediastinal blood with Cell-Saver-5, respectively)	**Dates:** **Effectiveness:** 1994–January 1995 **Resource use:** 1994–January 1995 **Price year:** not stated **Sources:** **Effectiveness:** single-centre controlled study carried out prospectively and unmasked **Direct costs:** yes **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costing carried out on same patient sample as the effectiveness data
Name: Guerra, 1995[93] **Setting:** hospital, USA **Perspective:** patient **Funding:** not reported	Intraoperative filtered and washed cell salvage	Cost–consequence analysis **Population:** patients undergoing total hip arthroplasty (THA), cell salvage group (Haemonetic Cell-Saver I) $n = 45$, mean age 62 years; control group $n = 45$, mean age 63 years; 25 patients in control and 35 patients in cell salvage group also underwent PAD, which was not routinely retransfused	**Dates:** **Effectiveness:** 1987–January 1991 **Resource use:** 1987–January 1991 **Price year:** not stated **Sources:** **Effectiveness:** single-centre retrospective cohort of 45 consecutive patients who underwent THA before introduction of cell salvage and 45 patients after introduction of cell salvage **Direct costs:** yes **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costing retrospectively based on flat rate for intraoperative autotransfusion regardless of amount of blood salvaged and the charge for a unit of blood in the study institution
Name: Crowe, 2003[94] **Setting:** hospital, USA **Perspective:** hospital **Funding:** not stated	Actual costs and reimbursements to hospital for stratified group of patients having revision total hip arthroplasty based on severity index	Cost study **Population:** 49 patients having 51 revision total hip arthroplasty; 30 women and 19 men; mean age 66 years (range 32–93 years)	**Dates:** **Effectiveness:** 1995–9 **Resource use:** 1995–9 **Price year:** not stated **Sources:** **Effectiveness:** clinical records reviewed of uncontrolled single-centre cohort **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Bottner, 2003[95] **Setting:** hospital, USA **Perspective:** **Funding:** not stated	Blood management in patients who underwent bilateral total knee arthroplasty	Cost study **Population:** 461 patients who had bilateral one-stage total knee replacements	**Dates:** **Effectiveness:** 1995–2000 **Resource use:** 1995–2000 **Price year:** not stated **Sources:** **Effectiveness:** retrospective review of clinical records **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data
Name: Chew, 2003[96] **Setting:** hospital, Canada **Perspective:** **Funding:** not stated	Direct costs of elective AAA to emergency AAA in Canada, and to compare direct plus overhead costs of EAAA and RAAA to US direct plus overhead costs	Cost study **Population:** 48 EAAA patients (mean age 71 years) and 41 RAAA patients (mean age 75 years)	**Dates:** **Effectiveness:** 1997–8 **Resource use:** 1997–8 **Price year:** 1998 **Sources:** **Effectiveness:** retrospective review of hospital records **Direct costs:** yes **Indirect costs:** no **Currency:** Can$, costs converted using currency conversion of 1.41 Can$ to 1.00 US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data
Name: Postma, 2003[97] **Setting:** hospital, The Netherlands **Perspective:** healthcare perspective **Funding:** Landsteiner Foundation for Blood Transfusion Research in Amsterdam	Leucocyte depletion of red-cell transfusion compared with non-leucodepleted transfusion in patients undergoing cardiac surgery	Cost-effectiveness analysis **Population:** 48 EAAA patients (mean age 71 years) and 41 RAAA patients (mean age 75 years)	**Dates:** **Effectiveness:** 1992–4 **Resource use:** 1992–4 **Price year:** 1999 **Sources:** **Effectiveness:** RCT, Dutch National Bureau of Statistics for life expectancy data **Direct costs:** yes **Indirect costs:** no **Currency:** US$, US$1 = 1.03 euros exchange rate for 1999 **Link between effectiveness and costs:** costs for same patient sample as effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Volkova, 2002[98] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Totally white blood cell reduced blood supply compared with a non-reduced white blood cell supply in patients undergoing CABG	Cost–consequences analysis **Population:** all patients undergoing CABG (including elective, emergent, primary, redo, single or multiple grafts; patients receiving transfusion before WBC reduction, $n = 416$; patients not transfused $n = 152$; patients receiving WBC reduced transfusion, $n = 484$; patients not transfused $n = 182$; patients transfused with non-WBC reduced blood after policy of WBC reduction, $n = 317$; patients not transfused $n = 174$ Control patients who did not receive transfusion were more likely to be younger and male	**Dates:** **Effectiveness:** 1991–4 **Resource use:** 1991–4 **Price year:** **Sources:** **Effectiveness:** retrospective case–control study in single centre **Direct costs:** yes **Indirect costs:** no Currency: US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data
Name: Blumberg, 2002[99] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Leucocyte-reduced transfusions in cardiac surgery	Cost–consequences analysis **Population:** adults undergoing primary CABG, primary valve replacement or both; $n = 171$ for not leucocyte reduced, $n = 159$ for leucocyte reduced; also compared with those who did not receive transfusion, 11% not leucocyte reduced patients and 14% leucocyte reduced patients were emergency cases	**Dates:** **Effectiveness:** 1997–8 **Resource use:** 1997–8 **Price year:** 1998 **Sources:** **Effectiveness:** retrospective cohort with historical control in single centre, transfusion service, hospital finance office, laboratory information system, hospital medical records, cardiothoracic service **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Haynes, 2002[100] **Setting:** 8 hospitals, UK **Perspective:** NHS **Funding:** NHS Executive North West Research and Development Directorate	Acute ANH and intraoperative cell salvage (CS) versus allogeneic blood transfusion in aortic surgery	Cost minimisation analysis **Population:** adults undergoing elective infrarenal aortic reconstruction, aged between 30 and 80 years, Hb >11 g/dl and platelet count of >150,000/l. Exclusion criteria were: MI in last 6 months, severe angina, myocardial ischaemia, aortic stenosis, left ventricular ejection fraction (LVEF) <40%, preoperative creatinine >200 mmol/l, aspartate aminotransferase level >100 units/l, refusal of allogeneic blood, haematological disorders, severe pulmonary disease; ANH + CS $n = 74$ (median age 72 years, 56 males), allogeneic group $n = 71$, median age 69 years, 60 males)	**Dates:** **Effectiveness:** 1997–9 **Resource use:** 1997–9 **Price year:** 1999–2000 **Sources:** **Effectiveness:** prospective single study (multi-centred), patient-blinded and randomised (stratified), independent physician made decision to transfuse allogeneic blood based on rigid protocol (Hb fell below 8g/dl) **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** costs collected prospectively for same patient sample as effectiveness data
Name: Breakwell, 2000[101] **Setting:** hospital, UK **Perspective:** not stated **Funding:** not stated	Postoperative cell salvage (8 hours, ConstVac) reinfusion in patients undergoing simultaneous bilateral total knee arthroplasty compared with allogeneic blood	Cost study **Population:** adults with osteoarthritis or rheumatoid arthritis (RA) undergoing simultaneous bilateral total knee arthroplasty; $n = 14$ for CS (8 male, mean age 66.8 years, 6 = RA), $n = 19$ for control (8 males, mean age 73.7 years, 3 = RA)	**Dates:** **Effectiveness:** 1999 **Resource use:** 1999 **Price year:** 1999 **Sources:** **Effectiveness:** prospective randomised controlled single-centre study, consecutive patients, patients received allogeneic blood if Hb fell below 9 g/dl, length of follow-up = 3 days post-operative **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** costs collected prospectively for same patient sample as effectiveness data
Name: Capraro 2001[102] **Setting:** tertiary care hospital, Finland **Perspective:** not stated **Funding:** not stated	Transfusion practices in CABG operations in a Finnish University hospital	Cost study **Population:** uncombined CABG patients, $n = 2363$ (1763 males, mean age 63 years)	**Dates:** **Effectiveness:** 1997–9 **Resource use:** 1997–9 **Price year:** 1999 **Sources:** **Effectiveness:** register-based cohort 1997–9 compared with multicentre nationwide survey of surgical transfusion practices in Finland from 1993 to 1994 (including 93 patients from study hospital) **Direct costs:** yes **Indirect costs:** no **Currency:** euros **Link between effectiveness and costs:** costs collected prospectively for same patient sample as effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Carson, 1999[103] **Setting:** 20 hospitals in 4 metropolitan areas, USA **Perspective:** not stated **Funding:** Ortho Biotech Inc. and Agency for Health Care Policy and Research	Allogeneic red cell blood transfusion (majority packed RBC) on the risk and cost of postoperative bacterial infection in patients undergoing hip fracture repair	Cost–effectiveness analysis **Population:** consecutive hip fracture patients aged 60 years or older, excluded if refused blood transfusion or had metastatic cancer or if hip fractures result of trauma that caused multiple injuries requiring surgery, $n = 9598$, mean age 80.3 years (SD 8.7), 79% women	**Dates:** **Effectiveness:** 1983–93 **Resource use:** 1983–93 **Price year:** 1995 **Sources:** **Effectiveness:** retrospective cohort chart review **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected retrospectively for same patient sample as effectiveness data
Name: Casati, 2000[104] **Setting:** hospital, Italy **Perspective:** not stated **Funding:** not stated	Haemostatic effects of aprotinin compared with TXA in adults undergoing primary elective cardiac surgery	Cost–consequences analysis **Population:** adults undergoing primary elective cardiac surgery necessitating cardiopulmonary bypass, aprotinin, $n = 518$ (mean age 62 years), TXA $n = 522$ (mean age 61 years), exclusion criteria were impaired renal function, advanced hepatic dysfunction and haematologic diseases; threshold for transfusion of packed RBCs was haematocrit <18% and Hb <6g/dl during cardiopulmonary bypass (CPB), 24% and 8 g/dl accompanied by signs or symptoms of hypovolaemia after CPB and during the ICU	**Dates:** **Effectiveness:** 1996–7 **Resource use:** 1996–7 **Price year:** **Sources:** **Effectiveness:** unblinded prospective RCT in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected on different patient sample
Name: Christenson, 1996[105] **Setting:** hospital, Switzerland **Perspective:** not stated **Funding:** Fumedica AG, Medtronic Europe SA	Platelet sequestration on postoperative blood transfusion requirement in patients undergoing revision CABG	Cost–benefit analysis **Population:** adults undergoing revision CABG, total preoperative platelet-rich plasma (PRP), harvest aim was 20% or more of total estimated circulating platelets, exclusion criteria were transfusion of any blood products ≤7 days preoperatively, preoperative platelet count <150,000/μl, preoperative haematocrit <35%, body weight <50 kg, unstable angina at time of operation or induction anaesthesia patients requiring rethoracotomy due to postoperative surgical bleeding, patients in whom PRP contained <20% estimated circulating platelets, transfusion algorithm used for FFP and platelets, PRP $n = 20$, control $n = 20$; mean age 63.4 years (range 42–80), 83% male, 8% operations were urgent, all patients had triple vessel coronary artery disease, 85% taking 100 mg daily aspirin	**Dates:** **Effectiveness:** 1995–6 **Resource use:** 1995–6 **Price year:** **Sources:** **Effectiveness:** prospective RCT in single centre **Direct costs:** no **Indirect costs:** no **Currency:** Swiss francs with equivalent US$ reported **Link between effectiveness and costs:** costs collected on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Gardner, 2000[106] **Setting:** public teaching hospital, Western Australia **Perspective:** hospital **Funding:** no external support	Autologous red cell salvage and allogeneic red cell transfusion during infrarenal abdominal aortic aneurysm repair	Cost study **Population:** elective and emergency infrarenal abdominal aortic aneurysm repair, processing of cell salvage blood required minimum 1000 ml scavenged blood, elective AAA $n = 90$, 51 (56%) patients had sufficient scavenged blood for processing, mean age 72.6 years (range 51–86 years)	**Dates:** **Effectiveness:** 1995–8 **Resource use:** 1995–8 **Price year:** 1999 **Sources:** **Effectiveness:** prospective consecutive patients undergoing elective or emergency AAA repair in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** Australian$ **Link between effectiveness and costs:** costs collected on same patient sample
Name: Gower, 1998[107] **Setting:** hospital, UK **Perspective:** not stated **Funding:** not stated	Preoperative cross-match versus a group, screen and save only policy for all primary total hip and knee arthroplasty patients	Cost–consequences analysis **Population:** all primary total hip and knee arthroplasty patients, maximum surgical blood ordering schedule (MSBOS) $n = 73$ (38 THAs and 35 TKAs), mean age 69.2 years (range 45–88), 26 male vs group, screen and save (G&S) $n = 67$ (33 THAs and 34 TKAs), mean age 67.2 years (range 40–84), 31 male	**Dates:** **Effectiveness:** 1995–6 **Resource use:** 1995–6 **Price year:** **Sources:** **Effectiveness:** prospective before and after study using two separate cohorts of patients (audit of MSBOS then audit repeated after G&S policy introduced) **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** costs collected prospectively on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Helm, 1998[108] **Setting:** hospital, USA **Perspective:** hospital **Funding:** Bayer Inc.	Multi-modality blood conservation programme (MMD) applied algorithmically on basis of bleeding and transfusion risk compared with the use of an identical set of transfusion guidelines but in a more limited set of blood conservation measures, in patients undergoing CABG	Cost-effectiveness analysis **Population:** 100 CABG patients in MMD group, 90 patients in control group; exclusions were reoperative procedure, operation other than CABG, aged over 80 years, haematocrit <33%, creatinine level >2.5 mg/dl, documented bleeding disorder, emergent procedure, operation within 4 h of admission or first evaluation, Jehovah's Witnesses or patients refusing allogeneic transfusion; MMD included intraoperative cell salvage, retrograde autologous priming, EPO, iron, aprotinin plus more	**Dates:** **Effectiveness:** 1994–5 **Resource use:** 1995 **Price year:** 1995 **Sources:** **Effectiveness:** prospective single-centred non-randomised trial with historical controls **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected on same patient sample for MMD group but costing of control undertaken on different group than used in the effectiveness analysis, costing on consecutive series of diagnostic-related group-matched patients 3 months prior to initiation of MMD protocol
Name: Nuttall, 2000[109] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Bayer Corp. research grant and Mayo Foundation for medical education and research	Aprotinin, TXA, TXA and intraoperative blood donation, compared with placebo (sham blood draw) for reduction of bleeding, transfusion requirements and transfusion-related costs associated with cardiac surgical procedures placing patients at high risk for bleeding	Cost-effectiveness study **Population:** elective revision sternotomy for CABG or cardiac valve surgery or combination; patients excluded if history of bleeding, platelet disorder, prothrombin time more than 15.0 s, blood urea nitrogen level >100 mg/dl, recent history of thrombolytic, warfarin or heparin therapy, taking ≥325 mg daily aspirin, bleeding time more than 8.0 minutes, congenital heart disease, weight <45 kg, preoperative Hb <12.5 g/dl; allogeneic erythrocytes transfused when Hb was <8 g/dl after discontinuation CPB and <7 g/dl during CPB if intraoperative autologous blood not available; TXA $n = 45$, placebo $n = 43$, aprotinin $n = 40$, TXA plus intraoperative blood donation (12.5% blood volume collected prior to CPB) $n = 32$	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** 1997 **Sources:** **Effectiveness:** prospective single-centred patient and provider-blind RCT **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected prospectively on same patient sample as the effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Renton, 1997[110] **Setting:** hospital, UK **Perspective:** not stated **Funding:** not stated	Present perioperative usage of blood products in a cardiothoracic unit	Cost study **Population:** elective cardiac surgery, routine blood order was 8 units, transfusion threshold was Hb <7 g/dl during CPB and <10 g/dl postoperatively, *n* = 74 patients, mean age 58.3 years	**Dates:** **Effectiveness:** August 1993 **Resource use:** August 1993 **Price year:** not stated **Sources:** **Effectiveness:** clinical and blood bank records for blood usage (audit) **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** costs collected prospectively on same patient sample as the effectiveness data
Name: Rizzi, 1998[111] **Setting:** hospital, Italy **Perspective:** not stated **Funding:** not stated	Postoperative blood salvage in hip and knee arthroplasty	Cost study **Population:** hip and knee arthroplasty, patients who had malignant lesions in vicinity of operative site or infections were excluded, average age 65 years (39–83), 133 THA (23 = revisions), 28 TKA, total = 161 (113 women), PAD performed in 156 patients (97%), reinfusion carried out if quantity drained in initial 4 h was at least 250 ml, transfusion threshold Hb = 8.5 g/dl	**Dates:** **Effectiveness:** 1994–5 **Resource use:** 1994–5 **Price year:** not stated **Sources:** **Effectiveness:** single centre, consecutive cohort **Direct costs:** yes **Indirect costs:** no **Currency:** US$, conversion rate not reported **Link between effectiveness and costs:** costs collected prospectively on same patient sample as the effectiveness data
Name: Rosengart, 1997[112] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Bayer Inc.	Comprehensive multimodality blood conservation programme to minimise risk of blood transfusion in open-heart surgery	Cost study **Population:** 50 Jehovah's Witnesses who underwent open-heart operations Blood conservation programme included high-dose EPO, aprotinin, intraoperative autologous blood donation and cell salvage, continuous shed blood reinfusion, 26 patients also received retrograde autologous priming, mean age 61 years, male to female ratio 2:3, 30 of these patients who were first-time coronary bypass patients were compared with 30 control patients undergoing first-time coronary bypass and not Jehovah's Witnesses and received standard blood conservation protocol (intraoperative autologous donation plus intraoperative cell salvage)	**Dates:** **Effectiveness:** 1992–5 **Resource use:** 1992–5 **Price year:** not stated **Sources:** **Effectiveness:** single centre, consecutive cohort **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected prospectively on same patient sample as the effectiveness data

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Sans, 1996[113] **Setting:** hospital, Spain **Perspective:** not stated **Funding:** Biomet?	Subcutaneous administration of 100 IU/kg rHuEPO in facilitating the donation over 2 weeks of 4 units of blood and in preventing sharp decreases in haematocrit levels	Cost–consequences analysis **Population:** patients undergoing hip or knee replacement, age 45–78 years with 3 or more units blood requested; exclusion criteria were overweight, hypertension, history of blood loss, Hb <11 g/dl, infectious or neoplastic disease, history of seizures, kidney or liver dysfunction, previous medication known to affect EPO production; of 75 patients, 23 excluded regarding exclusion criteria and 6 failed to complete the protocol; all patients had PAD, placebo $n = 13$, rHuEPO 30 IU/kg $n = 11$, rHuEPO 60 IU/kg $n = 11$, rHuEPO 100 IU/kg $n = 11$; twice per week for 2 weeks prior to surgery to facilitate collection of 4 units PAD blood, mean age 66–69 years across groups	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** prospective, single-centre, consecutive, randomised and double-blind study **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:**
Name: Shulman, 2002[114] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Intraoperative autologous donation plus normovolaemic haemodilution plus red cell salvage versus red cell salvage alone (normovolaemic haemodilution declined by patients) in patients undergoing primary or revision total hip replacement	Cost-effectiveness analysis **Population:** patients undergoing primary or revision total hip replacement; inclusion criteria were projected blood loss ≥800 ml, minimum preoperative haematocrit 35%, minimum platelet count 150,000/ul; patients who had donated autologous blood by PAD and those with pre-existing coagulopathy were excluded Intraoperative autologous donation goal of 660 ml packed red cell mass with haematocrit of 85% (as many as 3 red cell equivalents) and a similar volume of plasma and plateletpheresis product with a full transfusion dose; minimum haematocrit of 24% was used as threshold; 1 unit autologous red cells was calculated to be the volume that yielded red cell mass 200 ml, which is same volume as average allogeneic unit of RBCs; intraoperative autologous donation plus normovolaemic haemodilution plus red cell salvage $n = 40$, mean age 43 years vs red cell salvage alone $n = 40$, mean age 44 years	**Dates:** **Effectiveness:** not stated, 11 months **Resource use:** not stated, 4 years **Price year:** not stated **Sources:** **Effectiveness:** prospective, single-centre, consecutive, case-controlled study **Direct costs:** no **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs calculated over a period of 4 years so unclear if included same patient sample as effectiveness data

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Study characteristics	Comparators	Economic study type and population	Data
Name: Singbartl, 2002[115] **Setting:** hospital, Germany **Perspective:** not stated **Funding:** not stated	PAD + preoperative autologous plasmapheresis + perioperative blood salvage (concept 1) vs PAD + perioperative blood salvage (concept 2) when an increase of RBC mass of at least 1 RBC unit (190 ml) was expected in patients undergoing elective major bone and joint surgery	Cost comparison **Population:** patients undergoing elective major bone and joint surgery	**Dates:** **Effectiveness:** 1999–2000 **Resource use:** 1999–2000 **Price year:** not stated **Sources:** **Effectiveness:** retrospective comparison of 2 cohorts: concept 1 (1999) and concept 2 (2000) **Direct costs:** yes **Indirect costs:** no **Currency:** €1 = DM2 **Link between effectiveness and costs:** costs calculated for same sample as effectiveness data for each cohort
Name: Wilhelmi, 2001[116] **Setting:** hospital, Germany **Perspective:** not stated **Funding:** not stated	Routine CABG without any transfusion of blood or blood products as compared with the administration of fresh frozen plasma (FFP)	Cost study **Population:** patients undergoing CABG, FFP [4 units FFP (250 ml each) after CPB] $n = 60$, mean age 63 years, male/female 43/17, control (1000 ml hydroxyethyl-starch for equivalent volume substitution) $n = 60$, mean age 65 years, male/female 44/16; exclusion criteria: previous thoracic surgical interventions, oral medication with thrombocyte aggregation inhibitors 72 h prior to surgery, history of coagulation disorders and LVEF <40%; 2 patients who underwent emergency surgery were included in the control group; all patients received 1,000,000 units aprotinine in priming solution, all patients had intraoperative cell salvage; patients in both groups received 4 units FFP if cumulative blood loss via chest tubes was >200 ml during first hour, 350 ml during first 2 h and 500 ml during first 5 h, packed RBC units (300 ml each) were transfused if Hb level decreased below 8.0 g/dl	**Dates:** **Effectiveness:** 1997–8 **Resource use:** 1997–8 **Price year:** not stated **Sources:** **Effectiveness:** prospective, consecutive block randomised single-centre study **Direct costs:** yes **Indirect costs:** no **Currency:** euro **Link between effectiveness and costs:**

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Study characteristics	Comparators	Economic study type and population	Data
Name: Woolson, 2003[117] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Stryker Corp.	PAD versus unwashed postoperative blood salvage in preventing the need for allogeneic blood transfusion after total knee arthroplasty	Cost study **Population:** patients undergoing primary tricompartmental total knee arthroplasty or revision total knee arthroplasty involving the exchange of the tibial component only; intervention = postoperative blood salvage in first 6 h *n* = 44 patients (47 knees), mean age 70.1 years (37–88), men/women 20/24, control group = predonation of 1 unit of autologous blood between 3 and 5 weeks prior to operation and routinely reinfused on day 1 or 2 postoperatively *n* = 41 patients (41 knees), mean age 69.4 years (47–84) male/female 19/22; threshold for autologous transfusion = 34% haematocrit, threshold for allogeneic transfusion = 30% haematocrit postoperatively and symptoms of acute anaemia	**Dates:** **Effectiveness:** 1996–2001 **Resource use:** 1996–2001 **Price year:** not stated **Sources:** **Effectiveness:** prospective, single-centre RCT **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:**
Name: Couvret, 2002[118] **Setting:** hospital, France **Perspective:** not stated **Funding:** not stated	PAD and indications for perioperative blood transfusion in patients undergoing total hip or knee arthroplasty	Cost study **Population:** patients undergoing total hip or knee arthroplasty, study 1 = 3 units PAD and liberal autologous transfusion (haematocrit <30%), knee arthroplasty had 6 h postoperative cell salvage (62/182) *n* = 182, mean age 67 years, 55% female, study 2 = 2 units PAD indicated if estimated RBC reserve <800 ml for hip and <1000 ml for knee, haematocrit >33% and life expectancy of >10 years, (haematocrit trigger <24%), knee arthroplasty had 6 hours postoperative cell salvage (81/182) *n* = 182, mean age 68 years, 52% female	**Dates:** **Effectiveness:** 1997–2000 **Resource use:** 1997–2000 **Price year:** not stated **Sources:** **Effectiveness:** 2 consecutive prospective observational cohorts in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:**
Name: Hadjianastassiou, 2002[119] **Setting:** district general hospital, UK **Perspective:** not stated **Funding:** not stated	Blood transfusion in primary unilateral total knee replacement arthroplasty	Cost study **Population:** patients undergoing elective primary unilateral total knee replacement; no specific protocol existed regarding indications for allogeneic blood transfusion, locally agreed maximum surgical blood ordering schedule (MSBOS) involved routine preoperative cross matching of 3 units red cells, compared data with suggested threshold of Hb <8 g/dl and minimum transfusion 2 units blood; mean age 68.7 years (SD 8.8), 66% female	**Dates:** **Effectiveness:** not stated **Resource use:** 1998–9 **Price year:** 1998–9 **Sources:** **Effectiveness:** retrospective survey of hospital casenotes in single centre of consecutive patients over 1 year **Direct costs:** yes **Indirect costs** no **Currency:** UK£ **Link between effectiveness and costs:**

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Study characteristics	Comparators	Economic study type and population	Data
Name: Hekmat, 2004[120] **Setting:** hospital, Germany **Perspective:** not stated **Funding:** not stated	Aprotinin (AP) versus TXA on drainage blood loss and transfusion requirements in patients undergoing primary CABG on CPB with intraoperative cell salvage	Cost–consequences analysis **Population:** patients undergoing primary CABG on CPB, age 40–70 years, body mass index 19–30, exclusions were concomitant non-coronary procedures, repeat CABG, history of bleeding diathesis, known coagulation factor deficiency, LVEF <40%, known allergy to study drugs; mean age 63 years, majority male; TXA = 58, AP = 60; 2 excluded from study who had re-exploration for bleeding; all patients has intraoperative cell salvage, during CPB allogeneic blood transfused if Hb <6 g/dl and after surgery if Hb <8 g/dl	**Dates:** **Effectiveness:** 2003 **Resource use:** 2003 **Price year:** 2003 **Sources:** **Effectiveness:** prospective double-blind randomised controlled single-centre study **Direct costs:** yes **Indirect costs:** no **Currency:** **Link between effectiveness and costs:** costs collected for patients at the same hospital undergoing same protocol for receiving study drugs
Name: Lester, 2000[121] **Setting:** private community hospital, USA **Perspective:** not stated **Funding:** not stated	Variability in costs (as measured by hospital charges) of total joint procedures where clinical outcome is expected to remain constant	Cost study **Population:** 796 total joint procedures	**Dates:** **Effectiveness:** 1993–5 **Resource use:** 1993–5 **Price year:** not stated **Sources:** **Effectiveness:** information services department of same hospital for retrospective analysis of cohort **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs based on same patient sample as effectiveness data
Name: Puskas, 1999[122] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Off-pump coronary bypass compared with CABG on cardiopulmonary bypass	Cost study **Population:** off-pump *n* = 125 (9 had minithoractotomy and 116 had median sternotomy incision), mean age 61 years, 69% male vs CABG *n* = 625, mean age 61.4 years, 72.5% male	**Dates:** **Effectiveness:** 1996–9 **Resource use:** 1996–9 **Price year:** not stated **Sources:** **Effectiveness:** retrospective single-centred study of 125 consecutive patients undergoing off-pump compared with contemporaneous computer-matched control group of 625 CABG patients **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample

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Study characteristics	Comparators	Economic study type and population	Data
Name: Puskas, 2001[123] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Off-pump CABG compared with conventional CABG	Cost study **Population:** off-pump $n = 200$ (median sternotomy), mean age 61.9 years, 69.5% male vs CABG $n = 1000$, mean age 62 years, 70.4% male; all patients received postoperative care in a single 'fast-track' protocol and looked after by a single group of nurses, residents and physicians' assistants	**Dates:** **Effectiveness:** 1997–9 **Resource use:** 1997–9 **Price year:** 1997 **Sources:** **Effectiveness:** retrospective single-centred study of 200 consecutive patients undergoing off-pump compared with contemporaneous computer-matched control group of 1000 CABG patients **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample
Name: Pingsmann, 1998[124] **Setting:** large university teaching hospital, Germany **Perspective:** not stated **Funding:** not stated	Primary total hip arthroplasty	Cost study **Population:** total hip arthroplasty, $n = 26$, 18 women, 8 men, average age 66 years (range 38–84)	**Dates:** **Effectiveness:** (1986–95 for complications data) not stated for actual 26 patients in sample **Resource use:** (1986–95 for complications data) not stated for actual 26 patients in sample **Price year:** **Sources:** **Effectiveness:** prospective single-centred study of 26 consecutive patients **Direct costs:** yes **Indirect costs:** no **Currency:** DM **Link between effectiveness and costs:** based on same patient sample except for perioperative complication cost
Name: Jeserschek, 2002[125] **Setting:** hospital, Austria **Perspective:** not stated **Funding:** no benefits received from commercial party	Aprotinin on blood loss and transfusion requirements in major orthopaedic operations with an expected high blood loss	Cost study **Population:** patients with aseptic or septic failure of hip or knee prosthesis or undergoing resection of soft tissue sarcoma, exclusion criteria were known or suspected allergy to aprotinin or previous treatment with aprotinin, $n = 17$ for aprotinin group, mean age 67 years, $n = 18$ for control group, mean age 73 years	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** prospective single-centred double-blind randomised study **Direct costs:** yes **Indirect costs:** no **Currency:** Austrian pounds, equivalent in euros **Link between effectiveness and costs:** based on same patient sample

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Study characteristics	Comparators	Economic study type and population	Data
Name: Billote, 2002[126] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Northwestern Memorial Intramural Fund, no benefits received from commercial party	PAD to decrease allogeneic transfusion among patients undergoing unilateral primary total hip replacement	Cost study **Population:** patients undergoing unilateral primary total hip replacement who had preoperative baseline Hb ≥120 g/dl; PAD (2 units 500 g whole blood collected per week no later than 2 weeks prior to surgery) *n* = 42, mean age 58 years, male: female 26:16, non-PAD *n* = 54, mean age 61 years, male: female 35:19; all patients had ferrous sulfate; exclusion criteria were unstable or severe cardiac disease, uncontrolled hypertension, symptomatic carotid or vertebral artery stenosis, bleeding diathesis or bacteraemia; transfusion threshold identical for allogeneic and autologous blood in operating room but differed postoperatively (Hb <70 g/dl in healthy patients for allogeneic transfusion, Hb same for autologous in then Hb <110 g/dl in recovery room, then Hb <100 g/dl postoperatively)	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** prospective single-centred RCT **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs based on same patient sample as effectiveness data
Name: Smith, 2003[127] **Setting:** hospital, USA **Perspective:** payer perspective **Funding:** Bayer Corp.	Aprotinin for primary and repeat CABG	Cost–benefit analysis **Population:** repeat or primary CABG, 695 = full dose aprotinin in primary CABG, 172 = full dose in repeat CABG, 188 = half dose aprotinin in primary CABG and 135 in repeat CABG, 690 = placebo in primary CABG and 177 in repeat CABG; allogeneic blood transfusion threshold = 21–25% postoperative haematocrit; intraoperative and postoperative blood conservation techniques varied between study sites; 85–91% males across arms of trials, mean age 61.5–63.7 years (range 33–89 years)	**Dates:** **Effectiveness:** 1990–5 **Resource use:** 1994–7 **Price year:** 2001 **Sources:** **Effectiveness:** all clinical trial data submitted by Bayer Pharmaceuticals to FDA supporting licensure of Trasylol (aprotinin injection) were supplied by Bayer for use in the economic analysis = 7 prospective randomised double-blind placebo controlled trials, *n* = 2057 **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** not based on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Shuhaiber, 2003[128] **Setting:** district general hospital, UK **Perspective:** not stated **Funding:** not stated	Autologous blood using an intraoperative cell salvage device during AAA surgery at a district general hospital	Cost study **Population:** patients undergoing elective infrarenal AAA, *n* = 96, mean age 72.1 years, male: female 84:9, postoperative transfusion trigger for allogeneic blood was Hb count < 10 g/dl or requiring relaparotomy	**Dates:** **Effectiveness:** 1992–9 **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** retrospective, single-centred case note review **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** cost derived from same patient sample as effectiveness data
Name: Long, 1999[129] **Setting:** hospital, Canada **Perspective:** not stated **Funding:** not stated	Cost and outcomes of HCV lookback studies in the province of Quebec	Cost study **Population:** patients who received blood transfusion between 1990 and 1997 from donor found to be seropositive for HCV	**Price year:** not stated **Sources:** **Effectiveness:** **Direct costs:** no **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** personnel costs to provide lookback study to Quebec Centre of the Canadian Red Cross, hospital costs of providing lookback at one hospital in Quebec, derived from same patient sample as effectiveness data
Name: Lorenze, 1998[130] **Setting:** community hospital, USA **Perspective:** hospital **Funding:** not stated	One-stage bilateral total hip replacements compared with two-stage bilateral total hip replacements	Cost-minimisation analysis **Population:** one-stage *n* = 40 and two-stage bilateral total hip replacements *n* = 40 in patients with osteoarthritis Assumed that each unilateral procedure was representative of one side of a two-stage total hip replacement; all patients had intra- and postoperative cell salvage	**Dates:** **Effectiveness:** 1991–3 **Resource use:** 1991–3 **Price year:** not stated **Sources:** **Effectiveness:** retrospective case note review of 2 matched cohorts in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** retrospective costing of same patient sample

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Study characteristics	Comparators	Economic study type and population	Data
Name: Zenati, 1997[131] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Minimally invasive direct coronary artery bypass grafting (MIDCABG) for selective patients with coronary artery disease compared with CABG	Cost-effectiveness analysis **Population:** MIDCABG group $n = 17$, mean age 64 years 23% female, CABG group (LVEF >50%) $n = 33$, mean age 65 years, 24% female; redo and concomitant cases were excluded; patients selected to undergo MIDCABG had to have single coronary artery disease with anticipated complete vascularisation by MIDCABG or double or triple coronary artery disease and exceedingly high risk for postoperative morbidity with conventional CABG with anticipated incomplete revascularisation after MIDCABG (functionally adequate or inadequate)	**Dates:** **Effectiveness:** 1996 **Resource use:** 1996 **Price year:** not stated **Sources:** **Effectiveness:** 2 prospective consecutive cohorts in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** on same patient sample
Name: Able, 1998[132] **Setting:** hospital, USA **Perspective:** healthcare provider of acute care hospital Funding: Bayer Corp.	Half-dose aprotinin with no aprotinin in first-time reoperative CABG surgery	Cost-effectiveness analysis **Population:** half-dose aprotinin, $n = 51$, mean age 69 years male: female 38:13 vs no aprotinin control, $n = 46$, median age 69 years, male: female 38:8; excluded in received other surgery in addition to first-time reoperative CABG, patient died, aprotinin use at other dose than half dose, patient transferred, all patients received intra- and postoperative cell salvage	**Dates:** **Effectiveness:** 1993–5 **Resource use:** 1993–5 **Price year:** 1996 **Sources:** **Effectiveness:** retrospective evaluation of medical records in single centre; historical controls prior to 1994 were used before aprotinin was introduced; risk of operative mortality calculated using Summit Medical Database, which uses risk model of mortality developed in Society of Thoracic Surgeons National Cardiac Surgery Database **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample as effectiveness data

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Study characteristics	Comparators	Economic study type and population	Data
Name: Bennett-Guerrero, 1997[133] **Setting:** hospital, USA and Argentina **Perspective:** hospital **Funding:** Society of Cardiovascular Anaesthesiologists Fellowship Award	High–dose aprotinin versus EACA for the reduction of bleeding in patients undergoing repeat CABG	Cost–benefit analysis **Population:** patients undergoing repeat CABG, valvular heart surgery or both; exclusion criteria were serum creatinine >2.5 mg/dl, <18 years old, history of allergy to aprotinin or protamine, thrombolytic therapy within 48 h of surgery, evidence of disseminated intravascular coagulation or significant upper urinary tract bleeding, undergoing repeated operation via thoracotomy, history of pre-existing coagulation disorder; aprotinin $n = 99$, mean age 62 years, 68% male vs EACA $n = 105$, mean age 63 years, 62% male; allogeneic erythrocytes transfusion threshold = haematocrit <0.18 during CPB and <0.25 after CPB	**Dates:** **Effectiveness:** 1994–6 **Resource use:** 1994–6 **Price year:** 1996 (certain costs taken from published estimates from 1991) **Sources:** **Effectiveness:** RCT based at 3 centres **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected prospectively for same patient sample as effectiveness data
Name: Cerveira, 1999[134] **Setting:** hospital, USA **Perspective:** not stated **Funding:** not stated	Minimal incision repair (MINI) versus laparoscopic-assisted (LAP) and standard open repair (OPEN) for patients undergoing elective repair of infrarenal AAA	Cost–consequences analysis **Population:** patients undergoing elective repair of infrarenal AAA who required a tube graft Selection for MINI included elective repair, infrarenal aneurysm, no iliac disease requiring bifurcated graft replacement and the ability to tolerate general anaesthesia; selection for LAP also included no contraindication to laparoscopy MINI $n = 11$, mean age 72.4 years 64% male; LAP $n = 17$, mean age 70.8 years, 59% male; OPEN $n = 37$, mean age 73 years, 73% male	**Dates:** **Effectiveness:** 1997–8 (MINI, OPEN), 1995–6 (LAP) **Resource use:** 1997–8 (MINI, OPEN), 1995–6 (LAP) **Price year:** not stated **Sources:** **Effectiveness:** non-randomised single study with concurrent and historical controls **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs collected retrospectively for same patient sample as effectiveness data
Name: Cook, 1999[135] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Health Care Financing Administration, Department of Health and Human Services	Current practice for RBC transfusion relative to the American College of Physicians guideline for RBC transfusion; to determine comparative rates and relative appropriateness of autologous versus allogeneic blood use	Cost study **Population:** Medicare beneficiaries who were hospitalised in 1993 for elective THA and TKA, $n = 2137$, $n = 467$ comprised the sample, mean age 74 years (32–95); 83% white, 72% female	**Dates:** **Effectiveness:** 1992–3 **Resource use:** 1992–3 **Price year:** not stated **Sources:** **Effectiveness:** computerised quality of care algorithm applied retrospectively to medical record and blood bank data, 26 hospitals in Colorado, Connecticut, Georgia, Oklahoma, Virginia **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Dignan, 2001[136] **Setting:** hospital, Australia and USA **Perspective:** not stated **Funding:** not stated	Ultra-low dose of aprotinin in routine (elective and urgent) CABG with left internal mammary artery	Cost–consequences analysis **Population:** patients undergoing CABG with left internal mammary artery harvested in combination with conduits other than the right internal mammary artery, exclusion criteria were refusal of blood transfusion, recent use antiplatelet agents other than aspirin, known or suspected allergy to aprotinin, previous sternotomy, known bleeding disorder, pregnancy; transfusion threshold = Hb <7 g/dl during CPB and <8 g/dl postoperatively or if patient's condition warranted transfusion; aprotinin $n = 101$, mean age 62.8 years, 26% female, 38% urgent cases, placebo $n = 99$, mean age 65.2 years, 22% female, 32% urgent case	**Dates:** **Effectiveness:** 1997–9 **Resource use:** 1997–9 **Price year:** **Sources:** **Effectiveness:** prospective randomised controlled double-blind trial in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample
Name: Goodnough, 2000[137] **Setting:** hospital, USA **Perspective:** not stated **Funding:** BJC Center for Quality Management, Innovations in Health Care Program	PAD versus ANH in patients scheduled for THA	Cost study **Population:** patients scheduled for THA, exclusion criteria were pregnancy, <18 years of age, MI in last 6 months or clinically significant myocardial disease, and/or uncontrolled hypertension (DBP ≥ 100 mmHg); PAD (up to 3 units blood donated 1–6 weeks prior to surgery) $n = 25$, mean age 67 years, 44% female vs ANH (haemodilution after induction anaesthesia to haematocrit 28%, maximum 3 units collected and replaced with hetastartch) $n = 23$, mean age 60 years, 47% female; all patients received 325 mg daily ferrous sulfate; blood transfused intraoperatively in both groups when Hb <8 g/dl	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** prospective RCT **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample
Name: Jha, 2001[138] **Setting:** General hospital, UK **Perspective:** not stated **Funding:** not stated	Obviating allogeneic blood by using a manual system of blood salvage (CBC ConstaVac) in prosthetic surgery of the knee	Cost–consequences analysis **Population:** patients undergoing primary prosthetic surgery of the knee, postoperative cell salvage (6 h) $n = 50$, mean age 72 years, 21 males, control $n = 50$, mean age 72 years, 25 males; no objective transfusion threshold used	**Dates:** **Effectiveness:** 1997–2000 **Resource use:** 1997–2000 **Price year:** not stated **Sources:** **Effectiveness:** retrospective review and comparison of case histories **Direct costs:** yes **Indirect costs:** no **Currency:** UK£ **Link between effectiveness and costs:** based on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Knight, 1998[139] **Setting:** community hospital, USA **Perspective:** not stated **Funding:** Group Health Foundation	Blood product usage	Cost study **Population:** patients undergoing total knee arthroplasty, $n = 149$, average age 72 years, 83 females, osteoarthritis for 127; decision to transfuse with autologous or allogeneic blood was based on clinical condition of patient; no PAD + hemovac drain (unilateral primary TKA, weight >130 lb, haematocrit on admission 40 or greater) = 19, no PAD + solcotrans drain (unilateral primary TKA, weight >130 lb, haematocrit on admission could be <40) = 28, 1 unit PAD + solcotran (28) or hemovac (19) drain (unilateral primary TKA) = 47, 2 units PAD + wound closed with solcotran (4) or hemovac (16) (unilateral primary TKA) = 20, 2 units PAD + solcotran (29 knees in 15 patients) or hemovac (13 knees in 7 patients) drain for bilateral TKA = 21, PAD optional + wound closed with solcotran (8) or hemovac (7) for revision TKA = 14	**Dates:** **Effectiveness:** 1993–5 **Resource use:** 1993–5 **Price year:** 1995 **Sources:** **Effectiveness:** prospective nonrandomised study in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** based on same patient sample
Name: Murkin, 2000[140] **Setting:** hospital, USA and Canada **Perspective:** not stated **Funding:** Bayer Corp.	3 different aprotinin regimens compared with placebo in patients undergoing elective primary unilateral total hip replacement	Cost study **Population:** patients undergoing elective primary unilateral total hip replacement; **Low-dose aprotinin group** (loading dose 500,000 KIU aprotinin but no subsequent continuous infusion) $n = 76$ (69 in efficacy analysis, mean age 63.7 years, 49% males) **Medium-dose aprotinin group** (1,000,000 KIU loading dose then continuous infusion 250,000 KIU per hour) $n = 75$ (68 in efficacy analysis, mean age 65.6 years, 40% males) **High-dose aprotinin group** (loading dose aprotinin 2,000,000 KIU then continuous infusion 500,000 KIU per hour) $n = 77$ (75 in efficacy analysis, mean age 63.4 years, 61% males) **Placebo** $n = 73$ (68 in efficacy analysis, mean age 63.2 years, 47% males) All patients received warfarin; allogeneic transfusion threshold was haematocrit <18%	**Dates:** **Effectiveness:** not stated **Resource use:** not stated **Price year:** not stated **Sources:** **Effectiveness:** multi-centre randomised placebo-controlled double-blind trial **Direct costs:** no **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs not based on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Sakert, 1996[141] **Setting:** hospital, USA **Perspective:** not stated **Funding:** Ignacio Christlieb MD	Intraoperative Haemonetics Cell Saver usage on postoperative allogeneic blood product requirements in CABG patients	Cost–consequences analysis **Population:** patients undergoing isolated non-emergency first-time CABG, cell saver group $n = 435$, mean age 63.1 years, 27% female, non-cell saver group $n = 81$, mean age 63.4 years, 23% female; after CPB all blood remaining in venous reservoir was transfused to patients in non-cell saver group, patient's chest closed and the residual CPB volume was aspirated and processed by the Haemonetics Cell Saver with all other post-CPB blood loss; transfusion protocol was haematocrit 18% on CPB and 21% or more post-CPB was accepted unless there was clinical evidence of hypoxia; patients with history of renal disease, preoperative Hb ≤ 10 g/dl, bleeding diathesis, preoperative serum creatinine >1.8 mg/dl, postoperative gastrointestinal haemorrhage were excluded	**Dates:** **Effectiveness:** 1993 **Resource use:** 1993 **Price year:** not stated **Sources:** **Effectiveness:** retrospective analysis of medical records in single centre using computerised cardiothoracic database, blood administration records and records of blood products issued **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs not based on same patient sample
Name: Serrano, 2000[142] **Setting:** teaching hospital, Spain **Perspective:** not stated **Funding:** not stated	Cell saver Intraoperative autotransfusion in aortic surgery	Cost study **Population:** consecutive elective primary aortic surgery TAA $n = 15$, 100% cell salvage AAA $n = 192$, 81% cell salvage, mean age 60.3 vs 59.8 years in cell salvage vs no cell salvage, 97.6 vs 96% male in cell salvage vs no cell salvage AOD $n = 227$, 56% cell salvage, mean age 67.6 vs 65.8 years cell salvage vs no cell salvage, 98.1 vs 100% male cell salvage vs no cell salvage Use of cell salvage machine was dependent upon availability, so when 2 aortic interventions performed at same time preference for cell salvage machine was given to patients with aneurysms rather than occlusive disease, bilateral over unilateral when 2 aortic interventions performed at same time	**Dates:** **Effectiveness:** 1993–7 **Resource use:** 1993–7 **Price year:** not stated **Sources:** **Effectiveness:** retrospective analysis of clinical records, cell salvage device register, blood bank inventory in single centre **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs based on same patient sample

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Sun, 1997[143] **Setting:** hospital, USA **Perspective:** hospital **Funding:** no funding or support by pharmaceutical manufacturer including the maker of aprotinin or by any outside funding	Aprotinin use	Cost study **Population:** patients undergoing CABG, valve repairs or both, inclusion criteria for aprotinin group were repeat sternotomy or patients who could not receive blood products (i.e. Jehovah's Witnesses); matched with no aprotinin group where inclusion criterion was cardiothoracic surgery; aprotinin group could have received high-dose ($n = 11$) (2 million KIU prime, 2 million KIU loading dose, 0.5 million KIU per hour constant infusion for duration surgery) or half-dose ($n = 4$); aprotinin group $n = 15$ mean age 62.3 years, male:female 12:13 vs control $n = 15$, mean age 62 years, male:female 12:3; cell saver records were not available for all patients so only matched values for 7 patients in each group were compared	**Dates:** **Effectiveness:** 1992–4 **Resource use:** 1992–4 **Price year:** not stated **Sources:** **Effectiveness:** prospective chart review of patients treated with aprotinin compared with retrospective review of historical matched controls who were treated before aprotinin became available **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** costs based on same patient sample
Name: Pereira, 1999[144] **Setting:** hospital clinic blood bank, Spain **Perspective:** not stated **Funding:** Ministerio de Sanidad Consumo, Government of Spain	Virus-inactivated plasma in comparison with standard plasma	Cost–utility analysis, Markov model used (Monte Carlo simulation) **Population:** 924 patients who received fresh frozen plasma, age range 1–102 years, 55.5% male	**Dates:** **Effectiveness:** 1996–7 **Resource use:** 1996–7 **Price year:** 1997 **Sources:** **Effectiveness:** literature review (13 primary studies) plus authors' estimates, sex adjusted life expectancy data from 1994 population survey **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** Markov model used

continued

Study characteristics	Comparators	Economic study type and population	Data
Name: Jackson, 2003[145] **Setting:** hospital, USA **Perspective:** societal perspective **Funding:** not stated	NAT	Cost–utility analysis with Markov decision model **Population:** one unit of allogeneic blood component tested for antibodies to HIV, HBV, HCV, HbsAg and HIVp24 antigen vs same plus nucleic acid amplication testing (NAT), mean recipient aged 60 years, analysed 8 strategies of possible combinations of whether to use minipool NAT (MPNAT), single-donation NAT (SDNAT), whether to include testing for HBV, whether to discontinue some of existing battery of infectious disease testing (p24 antigen and anti-HBc)	**Dates:** **Effectiveness:** 1996 **Resource use:** 1996 **Price year:** not stated **Sources:** **Effectiveness:** 2001 repeat donor incidence from American Red Cross for likelihood of viral infection (HBV incidence adjusted upwards by factor 2.38 to account for transient expression of HbsAg in acute infections), window periods for NAT based on REDS study (risks adjusted up to include 20% of donations that come from first-time donors, assumed two-fold greater incidence rate for HBV, HCV, HIV among first-time versus repeat donors); NAT risk modelled on window periods and incidence rate (assumed 100% infectivity of all units from infected donors) **Direct costs:** yes **Indirect costs:** no **Currency:** US$ **Link between effectiveness and costs:** Markov decision model

Appendix 13

Table of included economic evaluations

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Birkmeyer, 1994[58] **Setting:** hospital, USA **Perspective:** societal Funding: training grant from National Library of Medicine and the National Institutes of Health **Study aims:** to calculate the cost-effectiveness of PAD in elective CABG and compare the expected benefit of reducing allogeneic transfusions during CABG with the potential risks of donating autologous blood before operation **Economic study type:** CUA **Type of modelling:** Markov model **Population:** 30 consecutive patients undergoing primary elective CABG, average age 63 years, 73% male	**Dates:** **Effectiveness:** 1983–92 **Resource use:** 1983–92 **Price year:** not stated **Sources:** **Effectiveness:** study including 18 tertiary care hospitals representing each region of the USA Literature review of published studies, quality of life adjustments made by consensus of local clinicians and medical decision analysts after consideration of published values; baseline mortality rates from US Vital Statistics, adapted four-state Markov model of prognosis with HIV from previously published study, 3 cohort studies used to obtain survival data for complications; assumed fatal transfusion rate of autologous blood same as that of allogeneic blood **Direct costs:** transfusion costs obtained from each of the 18 institutions participating in transfusion audit of study used for effectiveness data, hospital acquisition costs, assumed handling and processing expenses and costs of administering blood products were identical for allogeneic and autologous units; costs associated with post-transfusion hepatitis estimated after consultation with gastroenterologist, hospital accounting office, audit of selected patient bills and review of published studies **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costing retrospectively collected in part on same patient sample as for effectiveness data	**Effectiveness:** **Cost:** costs and benefits were discounted at 5% per year Sensitivity analyses performed to test robustness of assumptions and data used in the model	**Effectiveness:** increase in life expectancy (days per patient, undiscounted) = 0.06 (2 units), 0.08 (3 units), 0.10 (4 units), 0.11 (5 units) Increase in quality-adjusted life expectancy (days per patient, undiscounted) = 0.10 (2 units), 0.13 (3 units), 0.15 (4 units), 0.17 (5 units) **Resource use and costs:** some quantities reported separately from costs **Resource use:** number of patients receiving RBC transfusion = 368 (74%) Mean units RBC transfused (per recipient) = 4.0 For mortality, virus risk and quality adjustments **Cost:** net additional cost of PAD = $81 per patient (2 units donated), $134 (3 units), $195 (4 units), $263 per patient (5 units donated); 40–50% higher cost of PAD due to procuring autologous units and wasted units, cost savings produced by fewer allogeneic blood complications defrays additional blood product costs by only 2–3% **Synthesis of costs and benefits:** cost-effectiveness of PAD compared with no donation: $508,000 (2 units collected), $621,000 (3 units), $752,000 (4 units), $909,000 (5 units) per QALY saved Incremental cost-effectiveness: $921,000 for collecting third autologous unit from a patient who already has donated 2 units, $1,392,000 for collecting fourth unit from patient who has already donated 3 units, $2,256,000 for collecting fifth unit from patient who has already donated 4 units PAD costs: $158,000 per QALY in 50-year-old patients undergoing CABG at centres with high transfusion rates Cost-effectiveness of PAD was strongly dependent on estimates of post-transfusion hepatitis incidence For fatality rates exceeding 1 per 101,000 autologous donations, the risks of PAD outweighed the benefits associated with fewer allogeneic transfusions	PAD in CABG patients is not cost-effective, producing small health benefits at high societal costs

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Healy, 1994[59] **Setting:** hospital, USA **Perspective:** societal **Funding:** not stated **Study aims:** to study the cost-effectiveness of packed RBCs from PAD compared with allogeneic packed RBCs in primary hip arthroplasty **Economic study type:** CEA **Type of modelling:** decision analytic Population: profile was of a 65-year-old patient undergoing primary hip arthroplasty; 2 strategies were PAD up to 2 units or allogeneic blood only	**Dates:** **Effectiveness:** 1985–93? **Resource use:** 1992? **Price year:** 1992 **Sources:** **Effectiveness:** prospective data collection of 73 patients presenting with prescription to predonate 2 units autologous blood prior to hip arthroplasty, retrospective chart review of 56 patients who had undergone THA to determine blood transfusion requirements during hospitalisation (patients may have had intraoperative cell salvage), virus risk data obtained from literature, DEALE used to model effects of increased mortality rates due to disease states on patients' life expectancy **Direct costs:** of PAD, blood administration, medical care costs associated with complications of transfusion – yearly costs derived from local Medicare cost data and literature (future earnings were not modelled Indirect costs: not considered **Currency:** US$ **Link between effectiveness and costs:** costs related to same patients used to determine blood requirements in model	**Effectiveness:** mortality discounted at 5% **Cost:** discounted at 5%, cost considered equivalent between the 2 strategies were not included, short-term costs were not modelled for any complication Sensitivity analyses were performed	**Effectiveness:** PAD = 16.8995 non-discounted years (= 0.18 day loss), allo only = 16.8987 non-discounted years (= 0.47 day loss), PAD = incremental life-years gained 0.0008 (when postoperative infection is removed from model = 0.0005) Average discounted life expectancy: PAD = 11.7926 years, allo only = 11.7921 years **Resource use and costs** Some quantities reported separately from costs **Resource use:** patients receiving 2 units or more of allogeneic blood would spend an additional 1.4 days (range 0–2) in hospital due to postoperative infection **Cost:** discounted cost per case of PAD = $568, allo only = $1293 (when postoperative bacterial infection removed from model PAD per case = $201, allo only = $99), non-discounted cost per case of PAD = $569, allo only = $1296 **Synthesis of costs and benefits:** marginal cost per life-year; PAD = $181,400 Dominant factor is postoperative bacterial infection on length of stay and resultant increase in costs (autologous transfusion becomes more costly than allogeneic transfusion at $201 per day and at 0.17 days saved, when likelihood of transfusing blood is less than 0.1, PAD begins to cost more than allogeneic	PAD results in net cost savings compared with allogeneic blood over wide range of complication rates, patients ages and transfusion requirements Did not specifically model hip replacement or consider mortality resulting from the procedure Data in text and Table 1 differ for per unit risk of hepatitis B

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Etchason, 1995[36] **Setting:** medical, USA **Perspective:** societal **Funding:** Robert Wood Johnson Clinical Scholars Program and Transfusion Medicine Academic Award from NHLBI **Study aims:** to calculate the cost-effectiveness of substituting autologous (PAD) for allogeneic blood **Economic study type:** CUA **Type of modelling:** decision analytic model **Population:** patients at risk of transfusion undergoing total hip replacement, CABG, abdominal hysterectomy and transurethral prostatectomy, mean age 62, 67, 49 and 68 years, respectively	**Dates:** **Effectiveness:** 1989–93 **Resource use:** 1992 **Price year:** 1992 **Sources:** **Effectiveness:** retrospective review of transfusion records of all patients undergoing the four included surgical procedures at the study hospital to obtain data on transfusion, published life tables, published estimates for data relating to transfusion complications **Direct costs:** mainly derived from observation of transfusion practice, hospital survey data for actual costs to the university hospital's blood centre of infectious disease and compatibility testing, processing and inventory management, complications were in part based on data from literature, cost of discarded blood units reflected in average cost per unit allogeneic and autologous blood transfused **Indirect costs:** not included **Currency:** US$ **Link between effectiveness and costs:** modelling performed	**Effectiveness:** each primary study provided the value for a single variable, published estimates sometimes adjusted by authors, biased in favour of autologous donation, benefits discounted at 5% per annum, effect of transfusion-related complications on discounted life expectancies was calculated with the use of 0.75 Mixed Declining Exponential Approximation of Life Expectancy, values assigned to health states represent author's consensus after reviewing existing studies **Cost:** discounted at 5% per annum Sensitivity analysis analysed variables in model over a range of values, also potential effect of lowering the cost of autologous blood and cost-effectiveness of PAD for hypothetical patients of various ages with different percentages of discarded units of blood	**Effectiveness:** QALYs saved by the avoidance of transfusion-associated infectious disease **Quality adjustments:** Persistent hepatitis = 0.99 Active hepatitis = 0.90 Cirrhosis or cancer = 0.90 Fulminant hepatitis = 0 HIV infection = 0.75 AIDS = 0.50 Adult T-cell lymphoma or HTLV associated myelopathy = 0.90 Incremental QALYs saved per autologous blood unit transfused, relative to an allogeneic blood unit = 0.00029 (total hip replacement), 0.00022 (CABG) Probability of infection per allogeneic unit: (1) hepatitis C = 0.0003; (2) hepatitis B = 0.000005; (3) HIV = 0.0000067; and (4) HTVL-I and HTLV-II = 0.000017. Probability of disease per unit of infected blood: (1) hepatitis C virus: (a) persistent hepatitis = 0.28; (b) active hepatitis = 0.13; (c) cirrhosis = 0.10; (d) fulminant hepatitis = 0.01; (2) hepatitis B virus: (a) carrier status = 0.04; (b) persistent hepatitis = 0.02; (c) cirrhosis or cancer = 0.01; (3) HIV: (a) AIDS = 1.00; and (4) HTVL-I and HTLV-II: (a) ATL or HAM = 0.04 **Resource use and costs** Costs and quantities were not reported separately **Resource use:** ratio of autologous units transfused/units donated = 0.84 for total hip replacement, *n* = 80, 0.72 for CABG, *n* = 24 **Cost:** total cost per allogeneic blood unit transfused = $168.19, incremental cost of transfused autologous unit, relative to allogeneic = $68 (total hip replacement), $107 (CABG) **Synthesis of costs and benefits:** incremental cost per QALY saved = $235,000 (total hip replacement), $494,000 (CABG) Discarded units primarily responsible for higher cost of autologous blood	Increased safety of using PAD is limited and may not justify the increased cost

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Blumberg, 1996[37] **Setting:** hospital, USA **Perspective:** hospital **Funding:** Ortho Biotech Inc, R.W. Johnson Pharmaceutical Research Institute **Study aims:** to assess the cost-effectiveness of using allogeneic transfusion only, autologous transfusion only (PAD), or both allogeneic and autologous transfusion in patients undergoing hip replacement surgery. **Economic study type:** CEA? **Type of modelling:** not performed **Population:** Cohort 1 = 33 patients received 2–3 units of PAD blood (mean age 58 years, 62% male), 49 patients received 2–3 units of allogeneic blood (mean age 59 years, 62% male); free of chronic infection, autoimmune or malignant disease, osteoarthritis sole cause of joint disease, primary hip replacements only Cohort 2 = 140 patients donated own blood and then received autologous blood only or autologous blood plus allogeneic blood; primary and repeat joint replacement included	**Dates:** **Effectiveness:** 1986–8 and 1992 **Resource use:** 1986–8 and 1992 **Price year:** 1992 **Sources:** **Effectiveness:** one case–control cohort and one controlled cohort **Direct costs:** hospital charges, patient charges and transfusions based on actual hospital data for same patients; incremental cost of collection of unit autologous blood included incremental nursing time, clerical time, medical coverage, institutional overhead, did not include wastage or policy of not testing for infectious disease **Indirect costs** not included **Currency:** US$ **Link between effectiveness and costs:** costs for same patient sample collected retrospectively	**Effectiveness:** no power calculations reported Not stated if analysis based on ITT or completers, groups comparable at baseline except for haematocrit (38 vs 41% autologous vs allogeneic); two-way ANOVA and multiple linear regressions performed on relationship between allogeneic transfusion and various variables **Cost:** charge data from 1986–8 patients were normalised to 1992 by using the daily room rate for each period to correct for inflation, costs were reflated from 1989 to 1992 using a correction factor based on increases in institution charges. Compounded overall inflation factor also calculated based on data from Bureau of Labor Statistics in Washington for the medical care component of the Consumer Price Index to convert charge data to 1992 dollars. Produced similar results to room-rate adjustment which was then applied Student's *t*-test was used to compare groups for average cost. CIs reported No sensitivity analysis was performed	**Effectiveness:** rate of infection or suspected infection was 3% (n = 1) for the autologous group and 32% (n = 16) for the allogeneic group (p = 0.0029) (cohort 1); 6 wound infections, 4 non-wound cutaneous infections, 4 urinary tract infections, 3 unexplained persistent fevers treated with extended courses of antibiotics **Resource use and costs** Some quantities were reported separately from prices **Resource use – cohort 1 PAD vs allogeneic:** mean units autologous blood only received vs mean units allogeneic blood only received: 2.3 vs 2.3 units Duration of surgery (autologous only vs allogeneic only) 148 vs 143 minutes Mean length of stay (autologous only vs allogeneic only): 12.1 vs 13.5 days (p = 0.043); dose-dependent relationship between length of stay and allogeneic blood Allogeneic only received mean 1.3 additional days of antibiotic therapy than autologous recipients **Resource use – cohort 2 PAD plus allogeneic vs PAD:** PAD plus allo (n = 30) = 15.2 vs 9.4 days length of stay for PAD or no transfusions (n = 110) (p = 0.0001) **Costs: cohort 2:** mean total hospital charges for allogeneic and autologous blood = $26,490 versus $19,295 for autologous only or no transfusion (p = 0.0001). Average incremental hospital cost per unit of allogeneic transfusion was $1480 for 1992 cohort 2. Additional cost of allogeneic transfusion was $1043 for 1986–88 cohort 1. **Synthesis of costs and benefits:** costs and benefits not combined since autologous transfusion was the dominant strategy	Allogeneic transfusions were associated with incremental cost of $1000–1500 per unit transfused when compared with costs for similar patients receiving no transfusion or 1–5 units of autologous blood Cohort sample avoided bias relating to any difference in number of units transfused and any differences between patients who donate and those who do not or cannot Effectiveness data used in the economic evaluation (rate of infection) was not immediately apparent – refers to previously published study

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Kilgore, 1998[63] **Setting:** hospital, USA **Perspective:** healthcare provider and payer **Funding:** not stated **Study aims:** to assess the cost-effectiveness of transfusing unwashed filtered shed mediastinal chest tube drainage after CABG, septal defect closure, valve repair and cardiac transplantation compared with allogeneic blood transfusion **Economic study type:** CEA, query CCA? **Type of modelling:** two decision trees **Population:** mean age 62 years, 81 kg, 67% male undergoing CABG, valve replacement or repair, cardiac transplantation, 843 patients examined, data missing relating to 221 patients	**Dates:** **Effectiveness:** 1996–7 **Resource use:** 1991–6 **Price year:** 1997 **Sources:** **Effectiveness:** retrospective cohort study in single centre and review of the literature **Direct costs:** hospital data and published studies, cost of unit packed RBCs, laboratory handling, administration, handling and washing unused units, cost of treating complications, cost of cell salvage equipment and disposables; marginal costs for allogeneic units were estimated; costs related to initial typing and screening, fixed costs, blood bank administration excluded (authors state making cell salvage available will have negligible impact on transfusion service), hospital stay due to infection related to transfusion-induced immunosuppression were not included **Indirect costs:** not included **Currency:** US$ **Link between effectiveness and costs:** costs partially performed retrospectively on same patient sample as effectiveness data	**Effectiveness:** duration of follow-up until discharge, no losses to follow-up reported, power calculations not done; bootstrapping used to estimate means and 95% CIs, analysis showed older patients received more cell salvage **Cost:** not discounted owing to short timeframe One-way sensitivity analysis on probability of receiving allogeneic blood in absence of available cell salvage, cost of unit of banked blood, potential effect of capturing social costs	**Effectiveness:** reduction in need for allogeneic blood transfusion by using cell salvage estimated to be 54% **Resource use and costs** Cost items reported separately, resource use data not systematically reported **Resource use:** expected value of allogeneic units with and without cell salvage was 1.7 and 3.1 units, respectively **Clinical outcomes:** the estimated risk per unit (range) was: HIV, 1/493,000 [1/(202,000 to 2,778,000)]; hepatitis B, 1/63,000 [1/(31,000 to 147,000)]; hepatitis C, 1/103,000 [1/(28,000 to 288,000)]. The estimated risk per unit for anaphylactic, haemolytic, febrile and other reactions were 0.00011, 0.00016, 0.00200, and 0.00162, respectively. **Cost:** cost of 1 unit of allogeneic blood was $107.7 ($105.77–113.27), savings due to the use of postoperative cell salvage were $55 per case **Synthesis of costs and benefits:** not combined as cell salvage was associated with risk reduction and cost saving	Use of cell salvage blood has the potential to reduce significantly the costs and risks associated with transfusing allogeneic blood after cardiac operations

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Coyle, 1999[64] **Setting:** hospital, Canada **Perspective:** Canadian healthcare system **Funding:** CCOHTA **Study aims:** to assess the cost-effectiveness of preoperative EPO when used alone or to augment PAD in orthopaedic patients **Economic study type:** CEA **Type of modelling:** decision tree analysis to determine lifetime costs and effects **Population:** profile was a 65-year-old female weighing 72.5 kg undergoing orthopaedic surgery, analysis conducted in 2 contexts: EPO alone vs no intervention in orthopaedic patients with preoperative Hb 100–130 g/l and EPO to augment PAD versus PAD alone in patients with same preoperative Hb but who were not expected to predonated their complete perioperative needs without EPO	**Dates:** **Effectiveness:** 1987–97 **Resource use:** 1988–98 **Price year:** 1996 **Sources:** effectiveness: data on quantity of transfusion received obtained from meta-analyses from systematic literature review, data on risks of transfusion-related illness and life expectancy obtained from additional reviews of literature, at least 27 studies included **Direct costs:** quantities and costs based on actual data, list price EPO obtained from pharmacy department of hospital, other cost estimates from published studies, included cost of EPO, allogeneic and autologous blood collection and delivery, costs associated with hepatitis B and C, HIV, haemolytic reactions and febrile reactions **Indirect costs:** not included, loss of production would produce small costs given age of population but acknowledged omission of costs related to informal caregivers **Currency:** Can$ **Link between effectiveness and costs:** modelling done	**Effectiveness:** pooled data from studies as no consistent difference between dosage regimens of EPO for effectiveness **Cost:** future costs and outcomes discounted at a 5% annual rate Statistical analysis of costs not reported Sensitivity analysis assessed cost-effectiveness of EPO under more favourable scenarios, threshold analysis conducted (Can$100,000)	**Effectiveness:** number of life-years gained EPO alone increased life expectancy compared with no intervention by 0.000024 life-years, EPO to augment PAD increased life expectancy by 0.0000006 life-years compared with PAD alone **Resource use and costs** Quantities and costs were not reported separately **Resource use:** EPO alone reduced exposure to allogeneic blood OR 0.38 (95% CI 0.24 to 0.63). For EPO to augment PAD reduced exposure to allogeneic blood, OR 0.42 (95% CI 0.28 to 0.62) EPO alone reduced mean number of units received by 57.5% (from 1.27 to 0.54 units per patient) EPO to augment PAD reduced mean number of units received by 25.7% (from 0.35 to 0.26 units per patient) **Clinical outcomes:** for HIV, hepatitis B and hepatitis C, the base case risks per unit of allogeneic blood transfused were 2/1,000,000, 16/1,000,000 and 10/1,000,000. The risks of haemolytic transfusion reactions associated with all transfusions were 52.3/1,000,000 for a non-fatal reaction and 1.67/1,000,000 for a fatal reaction. These risks were assumed to be the same for both allogeneic and autologous blood The risk of a febrile reaction was estimated to be 1/100 units. For patients who did not contract any transfusion-related infections, the discounted life expectancy was estimated to be 13.04 years. The estimate of the discounted life expectancies for Canadian patients with HIV was 8.47 years, for hepatitis B 12.97 years and for hepatitis C 12.96 years **Cost:** EPO alone cost Can$1857 per patient compared with Can$269 for no intervention and EPO to augment PAD cost Can$2904 per patient compared with Can$968 for PAD alone **Synthesis of costs and benefits:** incremental cost per life-year gained for EPO compared with no intervention was Can$66 million, for EPO to augment PAD the incremental cost per life-year gained was Can$329 million	Use of EPO to reduce peri-operative allogeneic transfusions in orthopaedic surgery was not cost-effective

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Sonnenberg, 1999[60] **Setting:** hospital, USA **Perspective:** third-party payer **Funding:** American Association of Blood Banks and career development award from National Library of Medicine **Study aims:** to determine the impact that a possible increased risk of bacterial infection would have on the cost-effectiveness of PAD **Economic study type:** CUA **Type of modelling:** Markov cohort simulation model **Population:** hypothetical cohort of patients undergoing elective total hip replacement, 65-year-old patient of composite sex and race used as base case	**Dates:** **Effectiveness:** 1993 **Resource use:** 1993–5 **Price year:** 1997 **Sources:** **Effectiveness:** age-specific mortality rates using DEALE, quality of life weights were determined from the literature, CEA and multi-centred cohort study used for data on prognosis of HIV, transfusion data obtained from Mayo clinic study of 332 patients undergoing hip replacements, authors used average of published rates and/or ranges of values for transfusion-associated viral infection, average of the RRs of 2 RCTs was used to estimate base case for bacterial infections with entire range of reported values examined in sensitivity analysis, probability of serious bacterial infection and associated mortality obtained from reviewing 2000 patient records from 4 New Jersey hospitals **Direct costs:** costs obtained from three published CEAs, estimates and primary data collection by authors of hospital databases (cost-to-charge ratios applied when relevant) and chart review, nurse identified all resource use attributable to infection (no published data on cost of bacterial infection) **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costs collected retrospectively and prospectively from published studies and actual data but not on same patient sample as effectiveness data	**Effectiveness:** life expectancies discounted at annual rate of 3% **Cost:** costs adjusted using medical care component of the Consumer Price Index Costs were discounted at annual rate of 3% Statistical analysis of costs was not reported Two-way sensitivity analyses were performed on combinations of cost and RR of infection, type of surgery and blood wastage and other variables	**Effectiveness:** QALYs PAD resulted in a gain of 0.0522 QALYs over allogeneic blood transfusion **Resource use and costs** Cost items reported separately but not quantities **Resource use:** probability of transfusion in elective hip replacement = 0.89 Probability of autologous patient receiving additional allogeneic blood = 0.36 Average transfusion requirement of allogeneic blood = 2.8 units Average number of units in patients receiving only autologous blood = 2.4 units Average number of units of allogeneic blood received by autologous patients receiving additional blood = 1.1 units Nurse identified all resource use attributable to infection including antibiotics – wholesale price paid by hospital, laboratory tests and radiological studies – charges multiplied by cost-to-charge ratio, consultation (initial and follow-up – Medicare reimbursement), additional bed days (regular and intensive care – hospital accounting department); not reported **Cost:** PAD was $129.03 more per patient than costs for allogeneic blood, difference in cost per unit of autologous blood was $59, would need to be less than $16 to dominate allogeneic transfusion **Synthesis of costs and benefits:** the cost-effectiveness of PAD is $2470 per QALY. Threshold analysis demonstrated that autologous transfusion has a cost-effectiveness of less than $50,000 per life-year if the RR of bacterial infection after allogeneic transfusion exceeds 1.1 and autologous transfusion dominates allogeneic transfusion if the RR exceeds 2.4; autologous transfusion has a cost-effectiveness of less than $50,000 per QALY if the mortality from infections exceeds 0.012; autologous transfusion is dominant if cost of infection exceeds $19,700 If assumed no increased risk of infection with allogeneic blood then autologous transfusion would cost $341 more per patient with a gain of only 0.000098 QALYs, resulting in a cost-effectiveness of $2,545,000 per QALY Repeated analysis using figures for units donated and average percentage of autologous units transfused per patient for THA and CABG from Etchason study (included in this table): cost-effectiveness per QALY was $1190 for total hip replacement, $1470 for CABG	Until more definitive data are available on the magnitude and costs of the risk of bacterial infection, the cost-effectiveness of PAD is still open to debate. Some assumptions biased analysis against autologous transfusion Data not input into Excel as updated data used instead

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Woronoff-Lemsi 1999[57] **Setting:** hospital, France **Perspective:** health service? Not explicitly stated **Funding:** not stated **Study aims:** to determine the cost-effectiveness of the use of rHuEPO for PAD in orthopaedic surgery, comparing two strategies of PAD with or without rHuEPO during total hip replacement to prevent hepatitis C infection. **Economic study type:** CEA **Type of modelling:** decision analytic model **Population:** hypothetical cohort of 100,000 patients entering a PAD programme, transfusion data based on RCT with 50 patients who received rHuEPO plus PAD vs 45 patients who received placebo plus PAD	**Dates:** **Effectiveness:** 1994–6 **Resource use:** 1996–7 **Price year:** 1997 **Sources:** **Effectiveness:** literature review, at least 2 primary studies, one RCT used to obtain transfusion data **Direct costs:** the estimation of quantities and costs was based on actual data, RBC unit price was based on the official French tariff for blood components, unit prices for rHuEPO obtained from wholesale price lists for the Besancon University Hospital Pharmacy in 1997, costs included the cost of allogeneic transfusion (white cell reduction and phenotyping costs), the cost of the PAD programme and the cost of rHuEPO; only differential costs corresponding to rHuEPO and RBCs were assessed **Indirect costs:** not considered **Currency:** US$, with FF6 = US$1 **Link between effectiveness and costs:** costs collected retrospectively and not on same patient sample as for effectiveness data	**Effectiveness:** no further study details reported **Cost:** costs were not discounted given the short timeframe of the study (less than 1 year) Statistical analysis of costs not performed Sensitivity analyses were performed on the probability of transfusing allogeneic RBCs, the residual risk of HCV infection, the number of RBCs, the administration schedules of rHuEPO and the cost of rHuEPO	**Effectiveness:** the number of hepatitis C infections prevented The number of HCV infections prevented per 100,000 people by the use of rHuEPO as adjunct to PAD was 0.30562. Risk = 8.26 per million **Resource use and costs** Quantities and costs were reported separately. **Resource use:** the probability of transfusing allogeneic RBCs varied between 0.03 and 0.9 It was assumed that each patient received 3 RBC units during an operation whether autologous or allogeneic rHuEPO = 500 IU/kg twice per week for 3 weeks **Cost:** the added cost of the rHuEPO adjunct to PAD amounted to $2712 per patient **Synthesis of costs and benefits:** rHuEPO as an adjunct to PAD produced an incremental cost of preventing one HCV infection of $880,000,000. These results did not change in the sensitivity analysis	The cost-effectiveness ratio was so large that variations only slightly modified the size of the result. From the societal perspective, it was not cost-effective to add rHuEPO to preoperative blood donation. Some cost estimates were based on tariffs and, hence, do not represent true opportunity costs. The evaluation of efficiency was based solely on HCV residual risk

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Coyle, 2000[65] **Setting:** hospital, Canada **Perspective:** Canadian health system **Funding:** CCOHTA **Study aims:** to assess the cost-effectiveness of epoetin-alpha to augment PAD versus PAD alone in patients undergoing elective cardiac surgery for reducing use of allogeneic transfusions **Economic study type:** CEA and CUA as part of sensitivity analysis **Type of modelling:** decision tree to model lifetime cost and effects **Population:** hypothetical cohort of elective cardiac patients, profile derived from systematic reviews and review of hospital patients; profile was a 56-year-old male weighing 72 kg	**Dates:** **Effectiveness:** 1992–8 **Resource use:** 1988–97 **Price year:** 1998 **Sources:** **Effectiveness:** literature review and author assumptions (risk of haemolytic transfusion reaction was the same for autologous and allogeneic blood), at least 14 primary studies including meta-analysis of 6 published randomised trials from a systematic review **Direct costs:** hospital pharmacy list price for epoetin-alpha (costs of administration, patient education and travel were not included), literature review for all other costs, extreme analysis conducted to assess effects of indirect costs of disease by assuming total costs of patient having one of the disease to be Can$1 million, no further details given **Indirect costs:** not included **Currency:** Can$; the conversion rate from other currencies was not stated **Link between effectiveness and costs:** decision tree analysis	**Effectiveness:** no other details reported **Cost:** discounted at 5% Statistical analysis of cost not performed Univariate and multivariate sensitivity analyses were conducted on number of parameters	**Effectiveness:** life-years gained and QALYs gained (sensitivity analysis only). Discount rates for future effects were 5%. Epoetin-alpha plus PAD, life expectancy 13.10693 years; PAD alone, 13.10689 years, leading to 0.000035 incremental life-years gained. **Resource use and costs** Cost items were reported separately from quantities. **Resource use:** probability of receiving allogeneic blood, epoetin-alpha plus PAD = 12.7%, PAD alone 31.6%, RR reduction = 60% (study range 4.75–100%) Probability of receiving predonated blood, epoetin-alpha plus PAD = 77.3%, PAD alone = 58.4% Mean number allogeneic blood units received epoetin-alpha plus PAD 0.74, PAD alone 1.74 = 58% reduction Epoetin-alpha 300 units/kg given subcutaneously twice weekly for 3 weeks for a total of 6 doses, supplemented with 300 mg oral ferrous sulfate 3 times a day for 3 weeks prior to surgery **Clinical outcomes:** discounted life expectancy for a 56-year-old man, 13.107 years; discounted life expectancy for a patient with hepatitis B was 12.997 years, with hepatitis C 12.816 years, and with HIV 8.476 years; probability of fatal haemolytic reaction per unit of blood was $1.67/10^6$ ($1 - 1.67/10^6$); probability of febrile reaction per unit was 1/100; probability of haemolytic reaction/unit of blood was $52.6/10^6$ ($52.6 - 166.7/10^6$); probability of hepatitis B/unit of allogeneic blood was $16/10^6$ ($5 - 300/10^6$); probability of hepatitis C/unit of allogeneic blood was $10/10^6$ ($9.7 - 660/10^6$); and probability of HIV/unit of allogeneic blood was $2/10^6$ ($1.33 - 6.7/10^6$) **Cost:** epoetin-alpha plus PAD cost Can$2579 per patient compared with Can$1019 per patient for PAD alone, resulting in an incremental cost per allogeneic unit avoided of Can$1559 **Synthesis of costs and benefits:** incremental cost per life-year gained for epoetin-alpha to augment PAD was Can$44.6 million Cost per QALY gained from epoetin-alpha (assuming extreme effects of hepatitis and HIV) was Can$4.02 million	Epoetin-alpha to reduce perioperative allogeneic transfusion in cardiac surgery is not cost-effective Epoetin-alpha may be cost-effective if it leads to a reduction in average length of stay by more than 3 days per patient No systematic utility analysis

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Jackson, 2000[62] **Setting:** hospital, USA **Perspective:** societal **Funding:** not reported **Study aims:** to evaluate the cost-effectiveness of postoperative RBC salvage in preventing viral complications of allogeneic transfusions **Economic study type:** CEA **Type of modelling:** Markov decision analysis model **Population:** hypothetical cohort of patients undergoing total joint arthroplasty, average age 65 years (range 20–80 years)	**Dates:** **Effectiveness:** 1987–98 **Resource use:** 1987–98 **Price year:** not stated **Sources:** **Effectiveness:** 3 published studies for transfusion data, viral infection risk and quality of life estimates from 2 other published studies, mortality rates from US vital statistics **Direct costs:** Canadian cost study for blood costs, cost of illness from same published study used for quality of life estimates **Indirect costs:** not considered **Currency:** US$, no currency conversions reported **Link between effectiveness and costs:** modelling performed	**Effectiveness:** no further details **Cost:** 3 and 5% per annum Statistical analysis of costs not reported Sensitivity analyses performed on several parameters	**Effectiveness:** Relative quality of life associated with different stages of HIV was 0.76 for phases 1 to 2 and 0.6 for phases 3 to 4 Postoperative cell salvage extended quality-adjusted life expectancy by approximately 5 minutes per device (net cost $53), use of postoperative RBC salvage in all 386,000 arthroplasties performed annually in the USA would result in a total of 3.5 additional years of patient longevity **Resource use and costs** Costs and quantities not reported separately **Resource use:** no data reported **Cost:** use of postoperative RBC salvage in all 386,000 arthroplasties performed annually in the USA would cost $20 million **Synthesis of costs and benefits:** ICER was $5.7 million per QALY (increased to $6.7 million per QALY at a 5% discount rate) RBC salvage would only be cost neutral and save healthcare resources if cost less than $73 per device, and only cost neutral when returned volume exceeded 200 ml	In most clinical situations postarthroplasty RBC salvage was not as cost-effective as other medical interventions N.B. modelled washed postoperative cell salvage but did not include cost of washing

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Marchetti, 2000[38] **Setting:** hospital, Italy, although not explicitly stated **Perspective:** health service? Not stated **Funding:** not reported **Study aims:** to establish the cost–utility of using epoetin to control blood transfusion needs in CABG, in a clinical scenario without a blood containment policy, compared against the combined use of PAD and epoetin, PAD alone and neither **Economic study type:** CUA **Type of modelling:** decision tree **Population:** hypothetical cohort of 67-year-old males undergoing CABG	**Dates:** **Effectiveness:** 1990–9 **Resource use:** 1993–9 **Price year:** 1998 **Sources:** Effectiveness: literature review with at least 20 references, including RCTs, meta-analyses, longitudinal, observational and cost-effectiveness models, point estimates taken from one paper for each of the effectiveness measures, other related papers used to obtain ranges for sensitivity analyses **Direct costs:** cost per unit allogeneic blood taken from costing paper and included cost of blood collection and processing, infectious disease testing, inventory management, compatibility testing and indirect costs which were not stated; cost of epoetin based on cost to Italian hospitals with baseline cost of epoetin including associated pharmacy expenses and administration; lifelong costs of HCV and HBC estimated from published Markov studies, cost of MI came from study looking at hospital cost, overall cost of HIV from a 1993 cost-effectiveness paper **Indirect costs:** not included **Currency:** US$; the conversion rate from other currencies was not stated **Link between effectiveness and costs:** model analysed outcomes alongside costs	**Effectiveness:** all outcomes discounted at 5% per annum **Cost:** costs standardised to current year (1998) by using a 5% per annum inflation rate Deterministic point estimate costs with sensitivity analysis performed on stated range for each cost Sensitivity analysis performed on all effectiveness variables except actual QALY values used for given health states	**Effectiveness:** QALYs gained (values obtained from published literature) Epoetin-alpha plus PAD: life expectancy (QALY) 7.310686, PAD alone 7.310633, epoetin alone 7.310626, none 7.310633, leading to incremental effectiveness (QALY) for each strategy relative to none: epoetin plus PAD 0.000146, epoetin alone 0.000086, PAD alone 0.000093 **Resource use and costs** Some quantities were reported separately from prices. **Resource use:** allogeneic blood transfusion rate: Control = 57% (35–92%) Epoetin plus PAD = 72% (50–80%) Epoetin = 33% (10–75%) PAD = 46% (30–60%) Autologous transfusion rate: 84% Average volume of patients receiving allogeneic blood = 3.6 units (0–4 units) Mean units of allogeneic blood per patient: EPO + PAD = 0.66 EPO alone = 1.30 PAD alone = 1.00 None = 2.01 Epoetin based on 10 x 6000 IU administrations over a 4-week period, plus 325 mg daily ferrous iron **Clinical outcomes:** perioperative mortality in CABG surgery: 2.7% (range: 2–4%) Discounted life expectancy for CABG survivor: 11.76 years (7.46 QALYs) Quality adjustments for short-term state of acute hepatitis: 2 weeks (range: 1–3) Quality adjustments for short-term state of myelopathy: 30 weeks (range: 10–40) Transfusion reactions, blood-borne virus transmission and clinical consequences with discounted life expectancy **Cost:** epoetin plus PAD cost $1359, epoetin alone $1189, PAD alone $687, none $521 **Synthesis of costs and benefits:** incremental cost per QALY, relative to a no-drug strategy: epoetin plus PAD $5,739,726, epoetin alone $7,767,441, PAD alone $1,784,946; epoetin alone cost per allogeneic transfusion avoided was $1095 If risk of bacterial infection following allogeneic transfusion was included then epoetin alone cost $6288 per QALY saved Epoetin plus PAD and PAD alone became cost-effective when postoperative complications were included in the model, other sensitive parameters included adverse effects of epoetin and PAD, age of patient. All drug strategies were cost-effective in best-case scenario	Epoetin with PAD was more cost-effective than PAD alone, but neither was more cost-effective than a do-nothing strategy Not clear how values for QALYs were derived, some effectiveness data selectively chosen by authors

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
Name: Sonnenberg, 2002[61] **Setting:** hospital, USA **Perspective:** third-party payer **Funding:** American Association of Blood Banks and career development award from National Library of Medicine **Study aims:** to update a previously published CUA (included in table) to take into account new data, update the economic basis to year 2000 dollars and to incorporate a newer model of HIV that reflects contemporary treatment and prognosis **Economic study type:** CUA **Type of modelling:** Markov cohort simulation model **Population:** hypothetical cohort of patients undergoing elective total hip replacement, 65-year-old patient of composite sex and race used as base case	**Dates:** **Effectiveness:** 1993 **Resource use:** 1993–5 **Price year:** 2000 **Sources:** **Effectiveness:** age-specific mortality rates using DEALE, quality of life weights were determined from the literature, more recent published data from the same multi-centred cohort study used in previous CUA and a more recent CEA of the same cohort study used to obtain annual probability of developing AIDS after HIV infection and annual excess mortality after developing AIDS, study by the College of American Pathologists used to obtain data on probability of minor and major transfusion reaction (changed values used in previous CUA for minor reactions and major reactions not included in previous CUA) transfusion data obtained from Mayo Clinic study of 332 patients undergoing hip replacements, probability of serious bacterial infection and associated mortality obtained from reviewing 2000 patient records from 4 New Jersey hospitals **Direct costs:** costs obtained from three published CEAs, cost of a major transfusion reaction obtained from study by Huber *et al.* but no further details, estimates and primary data collection by authors of hospital databases (cost-to-charge ratios applied when	**Effectiveness:** life expectancies discounted at annual rate of 3%, authors used average of published rates and/or ranges of values for transfusion-associated viral infection, average of the relative risks of 2 RCTs was used to estimate base case for bacterial infections with entire range of reported values examined in sensitivity analysis, **Cost:** costs adjusted using medical care component of the Consumer Price Index. Costs were discounted at annual rate of 3% Statistical analysis of costs not reported	**Effectiveness:** QALYs PAD resulted in a gain of 0.0523 QALYs over allogeneic blood transfusion, also incremental QALYs for HIV, hepatitis, transfusion reaction, bacterial infection **Resource use and costs** Cost items reported separately but not quantities **Resource use:** probability of transfusion in elective hip replacement = 0.89 Probability of autologous patient receiving additional allogeneic blood = 0.36 Average transfusion requirement of allogeneic blood = 2.8 units Average number of units in patients receiving only autologous blood = 2.4 units Average number of units of allogeneic blood received by autologous patients receiving additional blood = 1.1 units Nurse identified all resource use attributable to infection including antibiotics – wholesale price paid by hospital, laboratory tests and radiological studies – charges multiplied by cost-to-charge ratio, consultation (initial and follow-up – Medicare reimbursement), additional bed days (regular and intensive care – hospital accounting department); not reported **Clinical outcomes:** probability of postoperative bacterial infection without transfusion = 0.037 RR of postoperative bacterial infection with allogeneic transfusion = 1.85 Mortality from postoperative bacterial infection = 26% (calculated) For virus risk data and quality of life weights and mortality **Cost:** PAD was $144 more per patient than costs for allogeneic blood, difference in cost per unit of autologous blood was $66, would need to be less than $13 to dominate allogeneic transfusion **Synthesis of costs and benefits:** the cost-effectiveness of PAD is $2750 per QALY Threshold analysis demonstrated that autologous transfusion has a cost-effectiveness of less than $50,000 per life-year if the RR of bacterial infection after allogeneic transfusion exceeds 1.1 and autologous transfusion dominates allogeneic transfusion if the RR exceeds 2.39; autologous transfusion has a cost-effectiveness of less than $50,000 per QALY if the mortality from infections exceeds 0.012; autologous transfusion is dominant if cost of infection exceeds $19,600 If assumed no increased risk of infection with allogeneic blood, then autologous transfusion would cost $380 more per patient with a gain of only 0.00014 QALYs, resulting in a cost-effectiveness of $2,545,000 per QALY Repeated analysis using figures for units donated and average percentage of	Modifications to the previously published CUA did not materially change the results or the conclusions. If there is only a modest increase in the risk of bacterial infection following allogeneic transfusion, autologous transfusion would result in improved outcomes at a cost-effectiveness that compares favourably to well-accepted health interventions

continued

Study characteristics	Data	Analysis	Results	Conclusion and notes
	relevant) and chart review, nurse identified all resource use attributable to infection (no published data on cost of bacterial infection) **Indirect costs:** not considered **Currency:** US$ **Link between effectiveness and costs:** costs collected retrospectively and prospectively from published studies and actual data but not on same patient sample as effectiveness data	Sensitivity analyses were performed on difference in cost per unit of autologous blood Two-way sensitivity analyses were performed on combinations of cost and RR of infection, type of surgery and blood wastage and other variables	autologous units transfused per patient for THA and CABG from Etchason study (included in this table): cost-effectiveness per QALY was $2580 for total hip replacement, $532 for CABG	

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