

# **REVIEW OF THE ALTERNATIVES TO HOMOLOGOUS BLOOD DONATION**

A report by the  
Blood and Blood Products Committee

June 2000

Australian Health Ministers' Advisory Council

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# **ALTERNATIVES TO HOMOLOGOUS BLOOD DONATION REPORT**

## **STATEMENT FROM THE AUSTRALIAN HEALTH MINISTERS' ADVISORY COUNCIL - BLOOD AND BLOOD PRODUCTS COMMITTEE**

The Australian Health Ministers' Advisory Council (AHMAC) appointed a Working Party to undertake a review of alternatives to homologous blood donations, under the auspices of the Australian Health Technology Advisory Committee (AHTAC). With the cessation of AHTAC in mid-1998, responsibility for completion of this review was transferred to the AHMAC Blood and Blood Products Committee (B&BPC). The B&BPC considered the final report of the Working Party and recommended the report to AHMAC for endorsement with qualification.

AHMAC accepts the Report and the recommendations 1 to 8, relating to the alternatives to homologous blood transfusion and recommendations 13, 15 and 16 relating to the framework for establishing appropriate standards and quality. AHMAC does not endorse recommendations 9 to 12 and 14 and offers the following comments against these recommendations.

### Recommendations 9, 10 & 11:

Transfusion protocols should be developed nationally rather than having responsibility for their development residing with each clinician that practices blood transfusion. The Donor Deferral Working Group, established on 20/12/99 by Commonwealth, State & Territory Health CEOs, has also identified the lack of national transfusion protocols as a priority issue and has drawn this to the attention of the National Health Medical Research Council (NHMRC).

If the NHMRC were to develop a national transfusion protocol AHMAC considers it more appropriate for the NHMRC, rather than AHMAC, to arrange dissemination of the protocol.

### Recommendation 12

AHMAC considers that it is not appropriate for the Australian Red Cross Blood Service (ARCBS) to develop standards in relation to cell salvage as this is a hospital procedure which is unrelated to the collection, testing, storage and distribution of fresh blood products.

### Recommendation 14

The ARCBS is currently not regulated for autologous blood collections. The Therapeutic Goods Administration responsibility extends only to the ARCBS establishments and homologous blood collection. However, when ARCBS performs autologous donations, these will be handled in the same facilities using the same procedures as covered by the GMP license.

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# Executive summary

## Background

For many years blood transfusion using donated (homologous) blood has been accepted medical therapy for blood loss and severe anaemia. However, growing recognition of the adverse effects of homologous transfusion and community concern about the safety of donated blood has changed this perception. This has led to the rise of alternatives to homologous blood donation, such as pre-operative donation of the patient's own (autologous) blood for use during surgery, more complex techniques such as acute normovolaemic haemodilution and cell salvage, and pharmacological agents to minimise blood loss.

Although the actual risk of infection from screened homologous blood is very low, there is considerable enthusiasm for autologous donation. The technique is widely used despite the lack of definitive controlled trials to establish its efficacy. Other concerns are that having the patient's own blood available increases the risk of transfusion, and that there are complications and costs associated with the use of autologous blood that may outweigh its benefits.

Recent reviews suggest that the first priority should be to minimise blood loss and avoid the use of all blood products, whether autologous or homologous. Transfusion protocols provide clear guidelines on situations in which to transfuse and are highly effective in minimising the use of homologous blood.

This report aims to re-evaluate the alternatives to homologous blood transfusion, test the evidence for and against their use, and ascertain the circumstances in which their use is justified in terms of patient welfare, cost-effectiveness and clinical benefit. It was developed by a Working Party operating under the auspices of the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council. The technical basis of the report is a systematic review of the performance of alternatives to homologous blood transfusion, which examined the evidence for benefits, harms and costs of the major methodologies, and also examined current use of autologous blood donation and other technologies in Australia.

## Current use of alternatives in Australia

A two-phase survey of practice in Australian hospitals with 50 or more beds undertaking surgery revealed that pre-operative autologous donation is the intervention most widely used to minimise the need for homologous blood transfusion, being practised in 70 per cent of hospitals. Cell salvage and haemodilution are used in about 25 per cent of hospitals, while use of drugs to minimise surgical blood loss is low. There is considerable variation in practice between hospitals and between surgical specialties.

The demand for pre-operative autologous donation has increased significantly over the past five years, mostly due to patient and clinician request. It is likely that this enthusiasm represents a widespread clinical and community perception that it is a safe alternative to homologous blood.

## Effectiveness and cost-effectiveness of alternatives

The results of the systematic review indicate a modest effect of all interventions in reducing the need for homologous blood transfusion, although the quality of the evidence makes it difficult to quantify and compare outcomes.

Specifically:

- Pre-operative autologous donation reduces the need for homologous blood, but the risk of receiving a transfusion is increased when autologous blood is available. Furthermore, the impact of pre-operative autologous donation is reduced in the setting of a strict transfusion protocol.
- Any benefit from reductions in homologous blood use have to be balanced against the risks associated with autologous blood use. Without formal modelling or a properly conducted clinical trial, it is not possible to conclude whether the benefits of pre-operative autologous donation will definitely outweigh the possible harms.
- The benefits of acute normovolaemic haemodilution appear to be lost in clinical settings where a transfusion protocol is applied.
- The benefits of cell salvage are more convincing, but again show a clear dependence on the concomitant use of a transfusion protocol.
- The pharmacological agents most effective in minimising use of homologous blood and reducing re-operation due to bleeding were found to be aprotinin, and to a lesser extent, tranexamic acid.

There are no Australian data on the costs of blood transfusion or its alternatives, although the sources of costs have been identified. An analysis of cost-benefit studies suggests that the techniques to minimise homologous blood transfusion do not meet conventional cost-effectiveness criteria. This issue needs further investigation in properly conducted trials.

## **Conclusions**

The use of interventions designed to minimise exposure to homologous blood has risen to a high level, but it appears that these changes in practice are not well supported by evidence on their comparative effectiveness or cost-effectiveness. In addition, their use varies widely across Australia.

The most effective strategy for avoiding homologous blood transfusion in any situation where blood loss is anticipated is the use of clear guidelines that define processes for minimising blood loss, and include a transfusion protocol to define the conditions under which a patient will be transfused and with what product. If properly implemented, guidelines would also help to standardise practice and better align clinical practice with scientific evidence.

It is important to set standards for such guidelines, and for other aspects of the process such as blood collection and testing for infectious agents. It will also be important to develop an active strategy for disseminating and implementing the conclusions and recommendations of this report, both to the medical profession and to the public.

# Recommendations

The rationale for these recommendations, as well as background information and the evidence on which they are based, are presented in the body of the report. The recommendations are repeated here for ease of reference.

## Alternatives to homologous blood transfusion

1. There is a need to establish clear guidelines to cover the following issues which will have an impact on the need for transfusion:
  - minimisation of blood loss as the first priority;
  - minimisation of the use of all blood products, homologous or autologous;
  - implementation of a transfusion protocol that sets the criteria for transfusion and covers all elective and emergency situations likely to involve transfusion. The protocol should apply to all blood products, whether homologous or autologous, and potential alternatives; and
  - in a situation where blood loss leads to volume depletion, the use of fluid replacement (with crystalloid or colloid) should be a standard part of the transfusion protocol.
2. Cell salvage should be evaluated for cost-effectiveness and if found to be cost-effective according to conventional criteria, access should be improved through inclusion as a specified procedure on the Medicare Benefits Schedule, linked to certain operations. Its use should not be precluded in emergency situations with major blood loss.
3. Aprotinin should be actively supported by increasing its availability and affordability and promoting its use in appropriate settings (such as cardiac surgery), through the relevant Colleges.
4. A comparative study of antifibrinolytic drugs (tranexamic acid/epsilon aminocaproic acid versus aprotinin) in appropriate clinical settings should be supported and the most cost-effective solution to minimising blood loss and re-operation for excess bleeding should be adopted and promoted.
5. Pre-operative autologous donation should *not* be promoted, for the following reasons:
  - While pre-operative autologous donation reduces the need for homologous blood, any benefit from avoiding the adverse effects of homologous blood has to be balanced against the risks associated with the use of autologous blood or any blood product;
  - The chance of receiving a transfusion is significantly increased in those with autologous blood available, magnifying these risks and increasing the costs; and
  - In the absence of formal modelling or a properly conducted clinical trial, it is difficult to determine whether the benefits of autologous donation will definitely outweigh the harms.
6. Autologous donation should be available to those who wish to use it as a matter of personal choice, but not if resources are diverted from other health interventions in order to make it available.
7. Acute normovolaemic haemodilution for the sole purpose of avoiding homologous red cell transfusion should not be encouraged, as it is rarely indicated.
8. Erythropoietin and desmopressin should not be encouraged as routine methods for minimising homologous blood transfusion.

## **Framework for establishing appropriate standards and quality**

### **Standards for transfusion protocols**

9. Responsibility for the development of transfusion protocols should reside with each clinician who practices blood transfusion. The responsibility for ensuring that this happens should reside with hospital management and be monitored critically by the Australian Council on Health Care Standards accreditation process.
10. The Australian Health Ministers' Advisory Council should formally request that transfusion protocols for both homologous and autologous blood be applied as a right to practice, through the Australian Council on Health Care Standards and State health departments' regulatory processes. The use of protocols should be included in the criteria for hospital accreditation, and promoted through professional organisations and Colleges, including the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Surgeons, the Royal Australian College of Physicians, the Royal College of Pathologists of Australasia, the Australasian Society of Blood Transfusion, the Australian Council on Health Care Standards and the National Association of Testing Authorities/Royal College of Pathologists of Australasia Quality Assurance Program.
11. The Australian Health Ministers' Advisory Council should commission the development and wide distribution of a transfusion protocol framework to promote these recommendations.

### **Standards for autologous blood collection and cell salvage**

12. The Australian Health Ministers' Advisory Council should request that standards for autologous blood collection and cell salvage be developed by the Australian Red Cross Blood Service in consultation with the Australasian Society of Blood Transfusion, relevant Colleges and professional bodies, users and consumer groups.
13. These standards should focus on the risks of autologous donation that are preventable by the use of clear and defined protocols (eg labelling, testing, patient selection criteria).

### **Models of delivery**

14. For reasons of safety, the Australian Red Cross Blood Service should either be funded to provide autologous services, or should engage in cost recovery fee for service, with the criteria linked to patients where a specifically identified operation is scheduled. The private sector should apply the same standards as the Australian Red Cross Blood Service and should be accredited through the Therapeutic Goods Administration, but should not be funded through the public purse.

### **Testing of alternatives for infectious agents**

15. The Australian Red Cross Blood Service will need to test autologous blood for infectious agents in the same way as it does for homologous blood, for reasons of cost and efficiency.

### **Communication strategy**

16. An active communication campaign will be required to disseminate the findings of this review to a wider audience, with medical and consumer education as an integral part of the strategy.

# Introduction

## Background

Blood transfusion is an established method for treating blood loss and severe anaemia. Homologous blood transfusion, involving the use of donated blood, has been used since the 1930s and was regarded for many years as beneficial and free of risk. However, this perception has changed markedly. There is now a high level of concern in the community, and in the medical profession, about the safety of transfused blood (McGrath 1995). The concern has arisen from the discovery of HIV, Hepatitis B and C and HTLV1 in donated blood, and the occurrence of AIDS and Hepatitis C in transfusion recipients.

As the complications of transfusion were recognised, alternatives were developed, including the use of the patient's own blood instead of homologous blood (pre-operative autologous donation; PAD), and other methods such as haemodilution, cell salvage and pharmacological therapy to minimise blood loss and avoid transfusion altogether. The concerns about the risks of homologous blood led to considerable enthusiasm for these alternatives and the use of several technologies continues to increase, despite the absence of definitive controlled studies to establish efficacy. These alternatives too have complications, and there are important issues of funding and access. At the same time, improved screening has reduced the risk of infection from homologous blood. The risk of serious disease caused by homologous blood, collected and screened by the Australian Red Cross Blood Service (ARCBS), is very low (Whyte & Savoia 1997).

Recent research into the efficacy and risks of various methods for minimising homologous transfusion (especially autologous transfusion) has highlighted the difficulty of quantifying benefits and risks, and the need to question accepted views. Two main issues emerge from this work:

- in studies where a strict transfusion protocol identifying identical transfusion triggers for homologous and autologous blood is in place, the benefits of autologous blood are significantly reduced; and
- there is increasing recognition of the complications and costs associated with autologous blood.

This research suggests that the first priority should be to minimise blood loss and the use of all blood products, whether homologous or autologous.

It is now timely to re-evaluate the alternatives to homologous blood transfusion and test the evidence for and against their use. There have been few medical issues in modern times that have had such moral, ethical, political and scientific implications for society and medicine.

## Approach to this report

In 1995, the McKay and Wells report *Commonwealth Review of Australian Blood and Blood Products System* (McKay & Wells 1995) recommended a review of ARCBS autologous blood collection services. The review was considered necessary to establish national guidelines and nationally consistent funding arrangements. In addition, there were other pressures on the Commonwealth for change, including requests for review of the Medicare benefits payable and increased demands on the ARCBS for pre-operative autologous donations. Medical defence considerations and media publicity about contaminated blood and blood products were further incentives for an objective assessment of the scientific evidence on the performance of blood donation technologies and alternatives.

Cost analysis is also important, as some of the therapies and technologies reviewed are expensive, and their use may divert resources from alternative interventions that might bring greater benefits to a larger number of patients.

In 1997 the Australian Health Technology Advisory Committee (AHTAC) appointed a Working Party to undertake the review. With the cessation of AHTAC in mid-1998, the Working Party came under the auspices of the Blood and Blood Products Committee of the Australian Health Ministers' Advisory Council (AHMAC). The membership of the Working Party is at Appendix 1.

The Working Party was given the following terms of reference:

1. Examine the clinical evidence in Australia and internationally on alternatives to homologous blood donation, including autologous pre-donations, cell salvage, haemodilution, pharmacological agents and other strategies for minimising the need for homologous transfusion, to ascertain the circumstances in which the use of these alternatives is justified in terms of patient welfare (including relative risks to patient safety), cost-effectiveness and clinical benefit.
2. If alternatives to homologous blood donations are justified on the above grounds, advise on:
  - a) appropriate clinical criteria for selecting patients for these alternative services;
  - b) a framework for establishing appropriate standards and quality assurance protocols;
  - c) the extent to which the alternatives to homologous donation need to be tested for infectious agents;
  - d) appropriate models for the delivery of autologous donation and cell salvage services; and
  - e) appropriate consumer information.

In recognition of the importance of an evidence-based approach to evaluating medical therapies, the Working Party commissioned a systematic review of the performance of alternatives to homologous blood transfusion. This was carried out by Professor David Henry and the Systematic Review Group at the Faculty of Medicine and Health Sciences, University of Newcastle. The review examined the evidence for benefits, harms and costs of the major methodologies for minimising homologous transfusion, including:

- pre-operative autologous donation, where the patient's blood is 'donated' pre-operatively and stored, to provide compatible blood at the time of surgery;
- acute normovolaemic haemodilution, where the patient's blood is collected just before surgery, replaced with an equal volume of liquid to maintain normal blood volume (normovolaemia), and the blood is re-infused into the patient after significant blood loss has stopped;
- cell salvage, where blood shed during surgery is collected for re-infusion in order to conserve autologous red cells; and
- the use of the pharmacological agents erythropoietin, aprotinin, tranexamic acid, epsilon aminocaproic acid and desmopressin, which are used to regulate the haemostatic system during surgery and inhibit bleeding.

The results of the review of benefits and complications are summarised in Chapter 2 and presented in more detail in Appendix 3, and the analysis of costs is summarised in Chapter 3 and given in full in Appendix 5. The review also examined current use of autologous blood donation and other technologies in Australia and attitudes towards

their use, through surveys and relevant qualitative research undertaken by the Australian arm of the International Study on Peri-operative Transfusion (ISPOT<sup>1</sup>). These results are summarised in Section 1.3 and presented in more detail in Appendix 4.

The results of the review were used as the technical basis of this report. The Working Party also used the results of the review and cost analysis to formulate conclusions and recommendations on the use of blood transfusion and its alternatives.

## **Consultation**

Input into the development of the review was sought in October 1997, through an advertisement in the press and a letter sent to 100 organisations. Each of the 29 submissions received (listed in Appendix 2) was considered by the Working Party during the development of the report.

## **Consumer issues**

Community concern about the safety of blood transfusion makes the consideration of consumer issues and processes for informed consent particularly important. Blood transfusion can be complicated by psychosocial, ethical, logistic and financial issues which at times are inseparable from medical considerations.

As with any therapy, there must be a clear identification and understanding of the clinical problem and the patient's needs. In most circumstances, blood component therapy is used as supportive therapy to correct temporary haematological deficiencies, until the basic disease process can be corrected.

As blood transfusion may be associated with immunological, technical, infective and other complications, informed consent is essential. It is appropriate that patients are well informed by clinicians and those involved in presurgical preparation about the procedures they are to undergo. Included in this information should be sufficient detail of the risks and benefits of homologous and autologous blood transfusions and any alternatives being used to minimise blood loss. Clinicians will then make the necessary decisions concerning transfusion, based on indications at the time of surgery.

Even if fully informed consent cannot be addressed pre-operatively, due to the urgency of the situation, continuing explanation in the postoperative period to the patient and/or relatives will usually allay any unnecessary anxiety. The continuing process of informed consent is also beneficial for the medical and paramedical staff, to help clarify whether their decisions are the most appropriate.

An information booklet for consumers is being derived from this report (attached at Appendix 6).

In addition, there needs to be an active communication campaign to disseminate the findings of this review. As public opinion influences the degree of uptake of techniques such as autologous donation, consumer education will be an integral part of the strategy.

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<sup>1</sup> A collaborative study of alternatives to peri-operative homologous blood transfusion (Forgie et al 1998).



# 1 Minimising homologous blood transfusion — alternative techniques and current practice

This chapter discusses general principles for avoiding or minimising homologous blood transfusion, describes the main alternatives to homologous blood transfusion and their advantages and disadvantages, and describes current practice in their use as reported through a survey of Australian practice.

## 1.1 General principles for avoiding or minimising homologous blood transfusion

The use of homologous blood for transfusion should be avoided or minimised, for the following reasons:

- immunological differences between the donor and recipient may result in varying degrees of immunisation and possibly immunosuppression;
- haemopoietic stem cells may 'graft' in patients at risk, resulting in fatal transfusion associated graft-versus-host disease; and
- infectious agents may be transmitted.

Techniques for minimising homologous transfusions are particularly important in patients who have religious objections to homologous blood transfusion, and in patients with rare blood groups or other contraindications to homologous transfusion.

Prevention of blood loss during elective surgery depends on close cooperation between surgeons and anaesthetists. While surgeons have a major role in minimising blood loss, anaesthetists can make a considerable contribution by using techniques that either reduce blood loss or reduce the amount of homologous blood used to maintain normal blood volume.

*Minimising surgical blood loss depends on:*

- good surgical techniques;
- appropriate anaesthetic techniques;
- identifying high-risk patients for blood loss; and
- pharmacological techniques (see page 4).

*Avoiding homologous blood components in any clinical setting relies on:*

- fluid replacement, with crystalloid or colloid to replace volume of lost blood, as the first response; and
- use of transfusion protocols, which are clear guidelines on situations in which to transfuse any blood, whether homologous or autologous.

## 1.2 Description of alternatives to homologous blood transfusion

### Pre-operative autologous donation

Pre-operative autologous donation (PAD) is an intervention by which a patient scheduled for major surgery (ie total hip replacement or coronary bypass surgery) donates his or her own blood for storage, which is used during or after surgery if this is clinically indicated.

#### Technique

In general, the technique is identical to voluntary homologous donation of a single unit of blood, except that the blood is usually not fractionated. The collected blood is grouped and screened for infectious agents and usually stored as whole blood for up to five weeks. Rarely, it is cryopreserved and stored in the frozen state.

In recent years, bone marrow stimulation of erythropoiesis using recombinant erythropoietin has been combined with PAD in an attempt to increase the volume of red cells collected and minimise the anaemia.

#### Potential advantages and disadvantages

The use of autologous blood has the following advantages:

- serological compatibility — alloimmunisation to cellular components of blood is avoided;
- there is no transmissible infection risk for viral diseases; and
- there are reduced demands on homologous blood supplies.

The use of autologous blood has the following disadvantages:

- pressure to use autologous blood may result in transfusion when it is not necessary;
- greater costs and logistic difficulties than with homologous blood;
- collection and storage lesions of the autologous blood;
- bacterial contamination and transmission of bacterial infection; and
- risk to donor due to less stringent donor health criteria.

### Acute normovolaemic haemodilution

Acute normovolaemic haemodilution (ANH) is a procedure where autologous blood is donated immediately before surgery, and replaced by an equal volume of fluid, usually a crystalloid solution. The autologous blood is then re-infused into the patient after significant blood loss has stopped. The main use for this procedure is during cardiac bypass.

#### Technique

The blood is collected after induction of anaesthesia, from an arterial line or from a large vein. Blood volume is replaced simultaneously with a crystalloid or colloid in order to preserve normovolaemia.

Moderate haemodilution involves the reduction of the patient's haemoglobin concentration from normal to 80–100 g/L, or the haematocrit to between 0.24 and 0.30. This reduction of haemoglobin concentration does not result in a fall in tissue oxygen delivery, provided the cardiac output can be increased and normal arterial oxygen tension maintained so that the haemoglobin is fully saturated with oxygen. The safety of ANH with haemoglobin levels of between 80 and 100 g/L is based on the maintenance of normovolaemia.

The same effect can be achieved by replacing shed blood with crystalloid or colloid solutions.

### **Potential advantages and disadvantages**

The reduction in systemic vascular resistance that occurs with the reduction in blood viscosity results in a rise in cardiac output. This causes a proportional increase in cerebral, renal, hepatic and intestinal blood flow. The fresh autologous blood collected is also of benefit as it is less likely to have storage lesion and can increase the level of platelets and coagulation factors if the patient is deficient in these as a result of a large blood transfusion. Plasma, platelet concentrates and platelet fibrin gel can be prepared in association with ANH.

Disadvantages include the additional time taken during surgery to collect the blood, the risk of tissue hypoxia and hypovolaemia, and risks due to incorrect storage of the blood during surgery.

### **Intra-operative red cell salvaging**

Cell salvage is a term that covers a range of techniques that scavenge, or drain, blood from operative fields, and re-infuse the blood back into the patient, to reduce homologous red cell needs. Autologous salvage techniques conserve red cells only, with volume and haemostatic component needs addressed as separate issues. The term cell salvage is used in this report to denote red cell salvage.

### **Technique**

Available methodologies range from simple low-cost disposable equipment for collecting blood from the operative site or postoperative drainage, to sophisticated and expensive cell processing technologies that allow rapid collection and washing of autologous red cells for re-infusion. Autologous blood collected by the low-cost method is re-infused unwashed, a factor which has caused considerable debate in view of its possible effects on the haemostatic system.

The procedure is indicated in operations where blood loss is anticipated to be more than two litres. It is therefore applicable to a few elective operations such as cardiac surgery, vascular surgery, neurovascular and major orthopaedic surgery. There are, however, a number of emergency situations in which it is appropriate, such as ruptured spleen or liver, ruptured ectopic pregnancy, ruptured aortic aneurysm and penetrating wounds to the chest and abdomen.

Intra-operative scavenging is not appropriate in situations where the body cavity is contaminated with gastrointestinal contents, malignant cells or infection.

## Potential advantages and disadvantages

The major advantage of cell salvage is that shed blood is re-utilised. It is expensive and generally only appropriate for large blood losses. Predicting cases for which the procedure should be set up preemptively can be difficult.

## Pharmacological agents for enhancing haemostasis

There is a range of pharmacological agents available for minimising the use of homologous blood during surgery. These are summarised in the following table.

**Table 1.1: Pharmacological agents for enhancing haemostasis**

Mode of action	Reported effects	Indications	Adverse effects
<i>Erythropoietin</i>			
Genetically engineered glycoprotein normally secreted by the kidney which stimulates red blood cell production. Increases the red cell mass and haematocrit.	Reduces the need for homologous transfusion during surgery. If used with PAD, increases the volume of harvested blood and reduces any resulting anaemia.	Usually used in conjunction with PAD, but can be used on its own.	Increased haematocrit, thrombosis.
<i>Aprotinin</i>			
Naturally occurring serine protease inhibitor of plasmin, trypsin, kallikrein, chymotrypsin, activated protein C and thrombin — inhibits fibrinolysis.	Minimises the derangement of the coagulation system that occurs during cardiopulmonary bypass.	Cardiac surgery.	Hypersensitivity, renal dysfunction, thrombosis.
<i>Epsilon aminocaproic acid and Tranexamic acid</i>			
Synthetic lysine analogues — inhibits plasminogen/plasmin.	Inhibits fibrinolysis and minimises blood loss.	Cardiac, prostate, orthopaedic surgery.	Gastrointestinal symptoms, rarely myonecrosis, thrombosis.
<i>Desmopressin 1-desamino-8-D-arginine vasopressin</i>			
Analogue of arginine vasopressin with enhanced antidiuretic and reduced vasopressor activity which releases von Willebrand's factor — shortens the bleeding time, but potentiates fibrinolysis.	Increases coagulation and shortens prolonged bleeding times.	Patients with mild haemostatic disorders, but can also be used in people with normal haemostasis.	Hypotension, oedema, thrombosis.

## 1.3 Current practice in Australia

As part of the review commissioned for this report, surveys of Australian hospital practices conducted by ISPO were examined. Details of the survey methodology and results are at Appendix 4.

Two surveys of practice in Australian hospitals with 50 beds or more undertaking surgery were carried out as follows.

- Phase 1, where a questionnaire was mailed to the Chief Executive Officer of each hospital, requesting information on which of the listed techniques or drugs were used regularly by a range of specialties.
- Phase 2, where a more detailed questionnaire was mailed to a person identified during Phase 1 as a user of the technologies, requesting further details on a range of issues, including attitudes towards the technologies.

The following points summarise the main findings of the surveys:

- PAD was the intervention used most widely to minimise the need for homologous blood transfusion (in 70 per cent of institutions);
- cell salvage and ANH were employed by 27 per cent and 24 per cent of institutions respectively;
- Anti-fibrinolytic drugs and erythropoietin were used by less than 10 per cent of hospitals;
- The pattern of use of the technologies varied between specialties, with cell salvage and ANH being used most by cardiothoracic units. PAD was most heavily used in orthopaedic surgical units, but also by over 30 per cent of general and urological surgical units.
- About half of the users of PAD donation indicated that autologous blood was collected using ARCBS facilities, 44 per cent at their own hospital, 15 per cent at another hospital, and 25 per cent at other facilities.
- The demand for PAD services has increased over the past five years in 66 per cent of the institutions, mostly due to patient demand.

## Discussion

The survey results are probably accurate and representative, as the responses were unambiguous, and the response rate was high at around 87 per cent. However, the surveys employed brief and simple instruments and results relied on self report. The subsequent phases of ISPOT involve extensive qualitative research, which will help to explain some of the trends seen here.

The Phase 1 survey documented a high level of use of several procedures designed to minimise the need for homologous blood transfusion during elective surgery. In the case of PAD, use was strikingly high. Use of ANH and cell salvaging was also high, particularly in cardiovascular surgical units. In contrast, use of a range of drugs designed to minimise operative blood loss was low.

The views of the public as well as health professionals are important in determining the demand for PAD. It is assumed that the level of enthusiasm for autologous blood represents a widespread perception that it is a safe alternative to the traditional means of dealing with blood loss during surgery. It is likely that publicity for PAD (for instance advertising by private hospitals), promotion by professional bodies as well as media reports of transfusion-related diseases, have contributed to this.

There is considerable variation between surgical subspecialties, with orthopaedics and cardiothoracic surgery having the highest levels of activity. Hospital size also seemed to be important, with bigger institutions having the highest use. In contrast, public hospitals had a lower rate of use. It is possible that the pressure on public hospital beds, with uncertain scheduling of elective surgery, acts as a disincentive to PAD programs. As most clinical transfusion medicine expertise is based in the public teaching hospitals, it is also possible that there is greater awareness of the recent re-examination of PAD and ANH.

Phase 2 results gave general endorsement for greater use of PAD, ANH and (to a slightly lesser extent) cell salvage, because of concerns about the safety of the blood supply and perceptions of the effectiveness of the technologies (in terms of outcome and cost). Barriers to greater use of these technologies included institutional practices (for PAD) as

well as lack of interest and awareness on the part of surgeons. Cost considerations were mentioned as a barrier to greater use of cell salvage.

The results of these surveys are similar to those obtained in a German survey conducted in 1993 (Kasper et al 1995).

#### Key findings

- There is a range of strategies for minimising homologous blood transfusion, including:
  - surgical and anaesthetic techniques to minimise blood loss;
  - replacement of blood loss with crystalloid or colloid solutions;
  - use of transfusion protocols with clear guidelines on situations in which to transfuse; and
  - a number of alternative interventions such as pre-operative autologous donation, acute normovolaemic haemodilution, cell salvage and pharmacological agents to minimise blood loss.
- There is wide variation in the use of these strategies within Australian hospitals and between surgical specialities.
- Pre-donated autologous blood is used in around 70 per cent of Australian hospitals to minimise the use of homologous blood. It is likely that the level of enthusiasm for the use of autologous blood represents a widespread clinical and community perception that it is a safe alternative to homologous blood.
- Acute normovolaemic haemodilution and cell salvage are used in about 25 per cent of Australian hospitals.
- By contrast, use of drugs to minimise surgical blood loss is low.

## 2 Evidence of the benefits of alternatives to homologous blood transfusion

This chapter summarises the findings of the review commissioned by the Working Party for this report, and carried out by the University of Newcastle Systematic Review Group. The methodology and tables of results are at Appendix 3.<sup>2</sup>

The quality of the evidence makes it difficult to quantify the outcomes of homologous transfusion and its alternatives. Many of the benefits and harms of blood transfusion occur over a long period, and have not been captured by good quality trials of the type that are now consistently used when investigating new medical therapies. Because the risks of transfusion with screened homologous blood are low, it is difficult to show benefit from alternative approaches, and the required sample sizes for appropriate trials are large. It is also possible that a strong belief in the superiority of autologous transfusion has resulted in alternative approaches being poorly investigated (Forgie et al 1998).

As most of the available studies relate to minimisation of homologous transfusion in relation to elective surgery, this report concentrates on the peri-operative setting. However, in other transfusion settings alternative methods for minimising homologous transfusion may also be appropriate.

### 2.1 Evidence on the techniques

The results of meta-analyses indicate a modest effect of all interventions in reducing the need for homologous blood transfusion.

#### Pre-operative autologous donation

Trials of PAD showed a relative reduction in the need for homologous blood of 66 per cent, and an absolute reduction of 46.5 per cent. However, it should be noted that:

- the studies were unblinded, which may have influenced transfusion practices and overestimated the benefit;
- the overall transfusion rates in these trials were high, and even higher in patients recruited to the PAD arms of the trials;
- in trials that used a strict transfusion protocol with the same transfusion trigger for homologous and autologous blood, the benefits in reduced transfusion of homologous blood were decreased by half; and
- there were only a small number of trials of PAD, compared with the other interventions.

An analysis of data from all transfusions (homologous, autologous, or both) showed that the risk of receiving any transfusion of blood was actually increased by participation in an autologous blood donation program.

Increased transfusion episodes increase the risks of over-transfusion, bacterial infection and handling errors. Any benefit from avoiding transfusion of homologous blood has to be balanced against the risks associated with the technique itself. In the absence of

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<sup>2</sup> The full review, which includes the systematic review, the cost analysis, the ISPO survey and a full list of references, is available on request from the Special Access Programs Section, Department of Health and Aged Care.

formal modelling, or a properly conducted large clinical trial, it is not possible to conclude whether the benefits of PAD will definitely outweigh the possible harms.

Despite the modest potential benefits of this approach, there remains great enthusiasm for PAD, driven in part by fear of the 'next epidemic' resulting from infection of the homologous blood supply. A recent study by Lee et al (1998), revealed a strong preference for autologous blood, and a high willingness to pay, despite a thorough education of subjects regarding the low risks associated with screened homologous blood.

## **Acute normovolaemic haemodilution**

There have been strong expressions of support in the literature for the effectiveness of ANH in minimising homologous red cell transfusion. However, the trials of ANH have been small, and it appears that its benefits are modest. Overall, ANH reduced the rate of homologous blood transfusion by a relative 34 per cent, and an absolute 29.1 per cent.

Of particular note is the fact that any benefits of ANH appear to be lost in clinical settings where transfusion protocols are applied and enforced. In fact, the use of a transfusion protocol may be more effective in reducing the need for homologous blood transfusion than ANH itself.

## **Cell salvage**

Trials of cell salvage in reducing the need for homologous blood showed a relative reduction in the rate of homologous blood transfusion of 41 per cent, and an absolute reduction of 25.4 per cent. Technologies in which the salvaged blood is washed before re-infusion gave a lower relative risk of requiring homologous blood than the unwashed techniques, but this difference was not significant. As with ANH, the benefits of cell salvage seemed less when used in the context of a transfusion protocol to determine the use of homologous blood. Studies in which the volumes of blood lost, salvaged and transfused are small cannot be extrapolated to massive bleeding situations where special considerations apply.

## **Pharmacological agents**

### **Erythropoietin**

The analysed studies found that the benefits of erythropoietin on its own were modest, and the number of units of homologous blood 'saved' by its use were inconsistent across studies. It seems clear that erythropoietin augmented the effects of PAD in reducing the need for homologous transfusion although, as with PAD used on its own, the overall rates of transfusion were very high. Overall, erythropoietin reduced the rate of transfusion of homologous blood by a (relative) 46 per cent and an absolute 14.5 per cent.

The relative benefits of erythropoietin used alone appeared to be less when the drug was employed within a transfusion protocol than when no protocol was used. However, the numbers in this group were very small, and the trend not seen when erythropoietin was combined with PAD. In this case, the relative benefit of erythropoietin appeared to be greater when a transfusion protocol was used.

### **Aprotinin**

Aprotinin was impressive in reducing both the need for homologous blood and need for re-operation related to bleeding. Overall, aprotinin reduced the rate of transfusion of homologous blood by a relative 30 per cent and an absolute 21 per cent.

The drug has been intensively investigated in a large series of small trials, which raises concerns about the accuracy of estimates obtained from a meta-analysis. The relative effect of aprotinin appeared to be unaffected by whether it was used alone or in combination with another blood-sparing technique. There seemed little difference between the effect of aprotinin in trials that employed transfusion protocols and those that did not, although the number in the latter group were small.

In individuals with high transfusion requirements, aprotinin did not reduce the proportion of individuals requiring transfusion. When the transfusion rate in the control groups approached 100 per cent it was similar to the treatment group. However, the greater the volume of homologous blood in the control group, the greater the saving in blood with treatment.

### **Tranexamic acid**

Similar trends to those with aprotinin were seen with tranexamic acid, but the number of trials was smaller. Overall, there was a 34 per cent relative risk reduction in the incidence of transfusion with homologous blood in patients treated with tranexamic acid compared with the control group. This represents an absolute risk reduction of 18.6 per cent.

A number of trials directly compared tranexamic acid and aprotinin, the results of which favoured the use of aprotinin, but as the total number of subjects in the trials was small the differences did not reach statistical significance. There may be no significant difference between aprotinin and tranexamic acid in their blood-sparing effects, particularly when used in cardiac surgery. More data on tranexamic acid would be valuable as it costs considerably less than aprotinin. At present, perhaps because of the greater uncertainty about its effects, tranexamic acid is rarely used in Australia.

### **Epsilon aminocaproic acid**

Epsilon aminocaproic acid has a very similar mode of action to tranexamic acid, but is less potent. There were very few trials of epsilon aminocaproic acid, and pooling their results found no statistically significant trends.

### **Desmopressin**

In contrast with the other drugs reviewed, there was no evidence of efficacy with desmopressin in reducing blood loss or in lowering homologous transfusion. However, it should be emphasised that the studies of desmopressin were in relation to unselected patients and the question of its use in high-risk patients for bleeding has not been addressed. It may be in this subgroup that this drug is indicated.

## **2.2 Evidence on complications**

Data on outcomes associated with the use of homologous blood transfusion and its alternatives were also examined in the review, including mortality, non-fatal myocardial infarction, stroke, deep vein thrombosis, pulmonary embolus, wound infections/ complications, any infection, fever, re-operation for bleeding, and length of hospital stay.

Firm conclusions are difficult to reach because events such as infections, and measures such as length of hospital stay, have not been reported consistently across these studies.

The main findings include the following:

- There was a modest reduction in postoperative infections with the use of alternatives to homologous blood transfusion. However, the reductions in risk were not statistically significant, and further data will have to be included or definitive trials performed to confirm this potential benefit.
- The use of aprotinin in cardiac surgery reduced the risk of re-operation due to bleeding by a significant average of 58 per cent. This was not apparent in individual trials due to small numbers, but in aggregate the evidence is impressive. There was a similar trend with tranexamic acid but the numbers were small.
- The difference in length of hospital stay between intervention and control groups in these studies suggests a benefit of less than half a day in hospital. This is against rather long lengths of stay for the surgical procedures concerned, suggesting that there is not a great potential for benefit in this regard, particularly within the Australian health care system where lengths of hospital stay tend to be shorter.
- The other adverse effects reviewed did not show clear or particularly worrying trends. There was no clear evidence of an increased risk of haemorrhage with cell salvage.
- There was a trend towards increased deep vein thrombosis and stroke events in the studies of erythropoietin, but the numbers of affected subjects were too small to draw any definite statistical conclusions. However, erythropoietin increases haematocrit and whole blood viscosity, and has been associated with hypertension when used in other settings. This is a matter that needs further investigation, and in view of the relatively modest beneficial effect of erythropoietin, combined with its extremely high costs, there is presently no convincing evidence to support its use in anything other than carefully controlled clinical trials.

#### Key findings

A systematic review of the literature on alternatives to homologous blood transfusion indicate a modest effect of all interventions in reducing the need for homologous blood. The quality of the evidence makes it difficult to quantify the outcomes of any intervention.

Specifically:

- Pre-operative autologous donation reduces the need for homologous blood, but the risk of receiving a transfusion is increased when autologous blood is available.
- The impact of pre-operative autologous donation is reduced in the setting of a strict transfusion protocol.
- Any benefit from reductions in homologous blood use have to be balanced against the risks associated with autologous blood use. Without formal modelling or a properly conducted clinical trial, it is not possible to conclude whether the benefits of pre-operative autologous donation will definitely outweigh the possible harms.
- The benefits of ANH appear to be lost in clinical settings where a transfusion protocol is applied.
- The benefits of cell salvage are more convincing, but again show a clear dependence on the concomitant use of a transfusion protocol.
- The pharmacological agents most effective in minimising use of homologous blood and reducing re-operation due to bleeding were found to be aprotinin, and to a lesser extent, tranexamic acid.

## **3 Costs of alternatives to homologous blood transfusion**

Cost-benefit analysis is important in determining the funding of any medical intervention. This chapter examines the analysis of the literature on costs and cost-effectiveness of alternatives to homologous blood transfusion (the full cost-effectiveness analysis is given in Appendix 5) and discusses the relevance of results to the Australian setting.

### **3.1 Review of economic analyses of alternatives to homologous blood**

This review was based on a previous systematic review (Fergusson et al 1998) with updating from the literature searches described in Appendix 3.

Based on seven economic evaluations, the technologies used to minimise peri-operative transfusion do not meet conventionally accepted criteria for being considered 'cost-effective'. With the exception of one study (Healy et al 1994), the cost-effectiveness ratios for PAD range from \$40,000 to \$329 million per quality-adjusted life year or life year saved. The Healy study assumed a difference in the rate of postoperative infection for autologous and homologous transfusion, which has a large impact on the results (changing the cost-effectiveness ratio from unacceptably high to PAD becoming dominant). Although a trend towards lower postoperative infection with PAD was identified in the transfusion trials reviewed it was not significant, and the average length of stay was not significantly different between the control and test groups. This suggests that the issue needs to be further investigated by properly conducted large clinical trials, before being factored into the cost benefit.

### **3.2 Relevance of cost-effectiveness studies for Australian transfusion practices**

The main factor that will influence the interpretation of data from these studies is uncertainty regarding the clinical benefits of avoidance of homologous transfusion. However, it is important to consider the relevance of the costing methods used in these studies and how they compare with similar exercises conducted in Australia. A thorough search failed to identify any studies of the costs of blood transfusion in Australia, and it is not clear how relevant the results of the economic studies, most of which are from the United States, will be to the Australian health care system.

Although the actual costs associated with blood transfusion in Australia are not known, the sources of costs can be identified. Homologous transfusion is perceived as free, but there are substantial costs for the Commonwealth and State health systems, as well as the costs to individual patients and donors.

The current sources of costs are as follows:

- ARCBS expenses, in relation to the collection, preservation and preparation of blood components. In 1997–98, the Commonwealth and State and Territory governments provided over \$134 million to the ARCBS.
- Costs associated with grouping, antibody screening and cross-matching of red cells (these costs would be shared between the Health Insurance Commission, resulting from charging private patients, public and private hospitals, and the State public hospital system for the provision of these services to public patients).
- Costs incurred from the administration of blood and blood products by the clinician (these costs would be split between the Health Insurance Commission, patients and the public hospital system).

As part of the review, a Canadian study was examined as it was thought more likely to reflect the Australian setting (Tretiak et al 1996). The Canadian system for blood collection is not for profit, relying on unpaid, volunteer donors. Further, no charge is made to health care facilities or patients for blood products. Therefore it has similarities with the Australian system. The costs identified in this study are discussed in detail in Appendix 5.

While the economic analyses identified were based on decision-analysis models, making it difficult to substitute the Canadian costs, it appears that substituting the Canadian costs into a United States model (Goodnough et al 1994), to better reflect the Australian setting, is likely to result in a worsening of the cost-effectiveness ratios discussed in Section 3.1 and given in full in Appendix 5.

#### Key findings

- |  |
|--|
| <ul style="list-style-type: none"><li>• There are no Australian data on the costs of blood transfusion or its alternatives, although the sources of costs have been identified.</li><li>• An analysis of cost-benefit studies suggests that the techniques to minimise homologous blood transfusion do not meet conventional cost-effectiveness criteria.</li><li>• This issue needs further investigation in properly conducted trials.</li></ul> |
|--|

## 4 Conclusions

Based on the results of the ISPOT survey and the review of the literature, it can be concluded that the use of interventions designed to minimise exposure to homologous blood has risen to a high level, but that these changes in practice are not well supported by evidence on their comparative effectiveness or cost-effectiveness. The findings of the review are supported by very recent papers on transfusion medicine (Goodnough et al 1999a, 1999b) and on the use of transfusion in critically ill patients (Hebert et al 1999).

The variations in practice recorded here argue for development of guidelines for appropriate use, and increased efforts to align practice with the best available evidence. The most effective strategy for avoiding homologous blood transfusion in any situation where blood loss is anticipated is the use of a clear protocol that defines processes for minimising blood loss, and includes a transfusion protocol to define the conditions under which a patient will be transfused and with what product. It is important to set standards for such protocols, and for other aspects of the process such as blood collection and testing for infectious agents.

### **Pre-operative autologous donation**

The studies of autologous blood donation demonstrated that, although this technique did reduce the need for homologous donation, it also resulted in unnecessary transfusion of autologous blood such that the chance of receiving a donation was significantly increased in those with autologous blood available. The principal question raised by this is the degree to which risk is reduced when there is a smaller requirement for homologous blood, due to the use of a well-defined transfusion protocol.

There is a perception in the medical profession and the community that autologous donation protects against transfusion transmitted disease. However, this belief does not take into account the risks of autologous donation, which are enhanced by the practice of returning the blood even when the transfusion trigger haemoglobin level for homologous blood has not been reached. It also ignores the cost of blood wastage when the risk of needing a transfusion is low.

The evidence that use of homologous blood increases postoperative infection rates (compared with autologous donation) is equivocal. Thus the overall clinical benefits from autologous blood appear small.

Autologous donation can only be considered worthy of supporting where a patient is undergoing elective surgery for a procedure with a greater than 50 per cent probability of requiring transfusion, and is expected to live long enough to be at risk of the consequences of transfusion-transmitted disease (eg 10 years or more).

It may be necessary to allow access to autologous blood to those who have a fear of homologous blood and wish to exercise the right to choose. However, this should not divert scarce resources from more essential and cost-effective health care interventions.

### **Acute normovolaemic haemodilution**

This technique is rarely if ever indicated except in the unique situation associated with the use of cardiac bypass. The equivalent effect is achieved as effectively and more economically by replacing blood loss with the appropriate crystalloid or colloid solution as the blood loss occurs.

A modification of this technique may be indicated in order to obtain haemostatically active products, platelets and or fresh plasma before major surgery with a substantial

risk of massive blood loss. This is a separate issue to those considered under the terms of reference of this Working Party.

### Cell salvage

This is an effective alternative to homologous transfusion in the setting of substantial intra-operative blood loss and with a transfusion protocol in place. Again, this situation is limited to a small number of surgical procedures. Recent research indicates that washing the salvaged blood makes little difference to the risk of homologous transfusion. These conclusions do not relate to massive blood loss situations, where autologous salvage and washing of blood are increasingly used in management.

### Pharmacological agents

Pharmacological agents used to minimise blood loss were the most effective alternatives to homologous blood transfusion.

*Aprotinin* is very effective, particularly in the setting of cardiac bypass surgery where most of the evidence has been gathered, although there is also evidence of benefit in orthopaedic surgery. However, it is expensive. Although a cost-benefit analysis is needed to confirm cost-effectiveness, on current evidence aprotinin seems likely to reduce costs by substantially reducing the incidence of return to theatre for excessive bleeding.

On the limited evidence available, *tranexamic acid* appears to be effective, and is substantially less expensive than aprotinin, but is not available in Australia in the appropriate form. A comparative trial of tranexamic acid/epsilon aminocaproic acid versus aprotinin needs to be carried out to establish the most cost-effective approach to avoiding excessive blood loss using these agents.

*Erythropoietin* and *desmopressin* were not found to be effective agents.

## Recommendations

### Alternatives to homologous blood transfusion

1. There is a need to establish clear guidelines to cover the following issues which will have an impact on the need for transfusion:
  - minimisation of blood loss as the first priority;
  - minimisation of the use of all blood products, homologous or autologous;
  - implementation of a transfusion protocol that sets the criteria for transfusion and covers all elective and emergency situations likely to involve transfusion. The protocol should apply to all blood products, whether homologous or autologous, and potential alternatives; and
  - in a situation where blood loss leads to volume depletion, the use of fluid replacement (with crystalloid or colloid) should be a standard part of the transfusion protocol.
2. Cell salvage should be evaluated for cost-effectiveness and if found to be cost-effective according to conventional criteria, access should be improved through inclusion as a specified procedure on the Medicare Benefits Schedule, linked to certain operations. Its use should not be precluded in emergency situations with major blood loss.

3. Aprotinin should be actively supported by increasing its availability and affordability and promoting its use in appropriate settings (such as cardiac surgery), through the relevant Colleges.
4. A comparative study of antifibrinolytic drugs (tranexamic acid/epsilon aminocaproic acid versus aprotinin) in appropriate clinical settings should be supported and the most cost-effective solution to minimising blood loss and re-operation for excess bleeding should be adopted and promoted.
5. Pre-operative autologous donation should *not* be promoted, for the following reasons:
  - while pre-operative autologous donation reduces the need for homologous blood, any benefit from avoiding the adverse effects of homologous blood has to be balanced against the risks associated with the use of autologous blood or any blood product;
  - the chance of receiving a transfusion is significantly increased in those with autologous blood available, magnifying these risks and increasing the costs; and
  - in the absence of formal modelling or a properly conducted clinical trial, it is difficult to determine whether the benefits of autologous donation will definitely outweigh the harms.
6. Autologous donation should be available to those who wish to use it as a matter of personal choice, but not if resources are diverted from other health interventions in order to make it available.
7. Acute normovolaemic haemodilution for the sole purpose of avoiding homologous red cell transfusion should not be encouraged, as it is rarely indicated.
8. Erythropoietin and desmopressin should not be encouraged as routine methods for minimising homologous blood transfusion.

### **Framework for establishing appropriate standards and quality**

#### *Standards for transfusion protocols*

9. Responsibility for the development of transfusion protocols should reside with each clinician who practices blood transfusion. The responsibility for ensuring that this happens should reside with hospital management and be monitored critically by the Australian Council on Health Care Standards accreditation process.
10. The Australian Health Ministers' Advisory Council should formally request that transfusion protocols for both homologous and autologous blood be applied as a right to practice, through the Australian Council on Health Care Standards and State health departments' regulatory processes. The use of protocols should be included in the criteria for hospital accreditation, and promoted through professional organisations and Colleges, including the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Surgeons, the Royal Australian College of Physicians, the Royal College of Pathologists of Australasia, the Australasian Society of Blood Transfusion, the Australian Council on Health Care Standards and the National Association of Testing Authorities/Royal College of Pathologists of Australasia Quality Assurance Program.
11. The Australian Health Ministers' Advisory Council should commission the development and wide distribution of a transfusion protocol framework to promote these recommendations.

***Standards for autologous blood collection and cell salvage***

12. The Australian Health Ministers' Advisory Council should request that standards for autologous blood collection and cell salvage be developed by the Australian Red Cross Blood Service in consultation with the Australasian Society of Blood Transfusion, relevant Colleges and professional bodies, users and consumer groups.
13. These standards should focus on the risks of autologous donation that are preventable by the use of clear and defined protocols (eg labelling, testing, patient selection criteria).

***Models of delivery***

14. For reasons of safety, the Australian Red Cross Blood Service should either be funded to provide autologous services, or should engage in cost recovery fee for service, with the criteria linked to patients where a specifically identified operation is scheduled. The private sector should apply the same standards as the Australian Red Cross Blood Service and should be accredited through the Therapeutic Goods Administration, but should not be funded through the public purse.

***Testing of alternatives for infectious agents***

15. The Australian Red Cross Blood Service will need to test autologous blood for infectious agents in the same way as it does for homologous blood, for reasons of cost and efficiency.

***Communication strategy***

16. An active communication campaign will be required to disseminate the findings of this review to a wider audience, with medical and consumer education as an integral part of the strategy.



# Appendices

## Appendix 1

### Working Party to Review the Alternatives to Homologous Blood Donation — terms of reference and membership

#### Terms of reference

- 1 Examine the clinical evidence in Australia and internationally on alternatives to homologous blood donation, including autologous pre-donations, cell salvage, haemodilution, pharmacological agents and other strategies for minimising the need for homologous transfusion, to ascertain the circumstances in which the use of these alternatives is justified in terms of patient welfare (including relative risks to patient safety), cost-effectiveness and clinical benefit.
- 2 If alternatives to homologous blood donations are justified on the above grounds, advise on:
  - a) appropriate clinical criteria for selecting patients for these alternative services;
  - b) a framework for establishing appropriate standards and quality assurance protocols;
  - c) the extent to which the alternatives to homologous donation need to be tested for infectious agents;
  - d) appropriate models for the delivery of autologous donation and cell salvage services; and
  - e) appropriate consumer information.

#### Membership

Professor Katherine McGrath	Chair, expertise in pathology
Dr Jim Butler	Expertise in health economics
Dr Michael Davies	Expertise in anaesthesia
Dr Colin Feek	New Zealand Ministry of Health
Dr Robert Hetzel	Expertise in blood transfusion services
Mr Clifford Hughes	Expertise in cardiac surgery
Dr James Isbister	Nominee of AHMAC, expertise in transfusion medicine
Ms Kathy Meleady	NSW Department of Health; AHMAC member
Dr Richard Pembrey	Nominee AHMAC, expertise in blood transfusion services
Mr Allan Rennie	Representative from the Commonwealth Department of Health and Aged Care
Mrs Jennifer Ross	Consumer representative
A/g Professor Evan Willis	Consumer representative

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Ms Marilyn Folger

Secretary to the Working Party

**Consultant to the review**

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University of Newcastle

**Scientific writer and editor**

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## Appendix 2

### Consultation submissions

1. Mr Darren Banks, Baxter Healthcare Pty Ltd
2. Dr Wendy Erber, The Western Australian Centre for Pathology and Medical Research
3. Dr V Martyn, Willetton, WA
4. Dr Richard Davis, Daw Park, SA
5. Mrs Jennifer Ross, Haemophilia Foundation Australia
6. Mr Alun Davies, Hemosol Inc
7. Mr Paul Turner, Medtronic Australasia Pty Ltd
8. Dr Leo Popp, Hughesdale, Vic
9. Mr M Ray, Prince Charles Hospital, Qld
10. Dr Jeff Adams, Janssen Cilag Pty Ltd
11. Commonwealth Department of Veterans' Affairs, Canberra
12. Mr Gareth H Williams, Mandurah, WA
13. Mr James McMillan, Perfusion Services Pty Ltd, Melbourne
14. Dr Ross I Baker, Royal Perth Hospital
15. Dr DWG Kennett, Australian Red Cross Blood Transfusion Service, WA
16. Ms Tina Marsden, Bayer Australia Limited, Sydney
17. Mr Hubert Chan, Stryker Osteonics, Sydney
18. Ms Sue Young, Domedica, Sydney
19. Mr Shannon L Farmer, Fremantle Kaleeya Hospital
20. Ms Nancy Stringer, Hoechst Marion Roussel, Sydney
21. Mr WM Lloyd, Watchtower Bible and Tract Society of Australia, Ingelburn, NSW
22. Mr Colin MacLeod, Royal College of Pathologists of Australasia, Sydney
23. Dr Gordon Whyte, Australian Red Cross Blood Service, Melbourne
24. Dr Tim Bohane, The Australian College of Paediatrics, Melbourne
25. Mr Geoff Lavender, Department of Human Services, Victoria
26. Mr Ross Pitt, Queensland Health Technology Assessment Team, Brisbane
27. Dr Anne Fletcher and Dr Mark Dean, Australasian Society of Blood Transfusion, Sydney
28. Dr Margaret Buring, Australian Red Cross Blood Service, Brisbane
29. Dr Joanne Pink, Australian Red Cross Blood Service, Brisbane

## Appendix 3

### Systematic review of the literature

The AHMAC Working Party tendered out the task of systematically reviewing and analysing the literature on alternatives to homologous transfusion. The consultancy was conducted by the University of Newcastle Systematic Review Group, under the direction of Professor David Henry, Faculty of Medicine and Health Sciences.<sup>3</sup>

The consultancy provided information addressing Terms of Reference 1 and 2(a), summarised as follows:

- the performance of current and alternative techniques and procedures for blood donation supply, and their impact on health outcomes;
- the potential benefits and adverse effects from the use of these methods; and
- the cost-effectiveness and cost-benefit of these techniques and procedures.

The tasks were reformulated by the consultant as follows:

- to review the evidence of homologous blood transfusion alternatives in relation to beneficial and adverse effects, and the extent to which these vary across defined subgroups;
- to review and advise on the potential cost-effectiveness of the various technologies; and
- to describe the current use of autologous blood donation and other technologies in Australia, and attitudes towards their use.

### Methods

It was agreed by the Working Party that the following approaches would be adopted:

- The review of the evidence on benefits and harm should concentrate on randomised controlled trials of the various alternative technologies, and this systematic review should extend the literature searches developed ISPOT.
- It was agreed that the advice on the potential cost-effectiveness of the alternatives should be based on a systematic review of the published literature (results represented in Appendix 5), and should not involve the actual conduct of cost-effectiveness analysis, as this was beyond the scope of the consultancy.
- It was agreed that the evidence on the current use of autologous blood donation and other technologies should be based on the results of an ongoing survey being carried out by the Australian ISPOT study group at the Faculty of Medicine and Health Sciences, University of Newcastle (results presented in Appendix 4).

Information from the ISPOT study for all therapeutic interventions was utilised where available, and updates in Medline and Embase were performed. Unrestricted searches using Mesh headings and text-word terms for each technology were updated in Medline from 1995 to April 1998 for eight blood-saving methodologies: PAD, ANH, cell salvage,

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<sup>3</sup> The full review, which includes the systematic review, the cost analysis, the ISPOT survey and a full list of references, is available on request from the Special Access Programs Section, Department of Health and Aged Care.

erythropoietin, desmopressin, aprotinin, tranexamic acid and epsilon aminocaproic acid. Restricted searches aimed at identifying randomised controlled trials were updated in Medline from 1996 to May 1998, and in Embase from 1996 to December 1997. In Medline, three search filters were used, the ISPO filter restricting the search for blood transfusion trials, the Haynes filter restricting the search to clinical trials, and the modified Cochrane filter for randomised controlled trials. These filters were coupled with Mesh headings and relevant text words for each technology. The printouts of titles and abstracts were scrutinised to identify trials in which adult patients, scheduled for elective or semi-urgent surgery, were randomised to one of the alternatives to homologous blood, or to a control group who did not receive the intervention.

## **Trials identified**

*Pre-operative autologous donation.* The search update uncovered 684 references in the unrestricted Medline search, 438 in the restricted Medline search and 171 references in Embase. Of these, 156 articles were initially selected for further review; 61 of these articles were obtained and reviewed (many of the articles were relevant to the other technologies).

*ANH.* The search from 1966 to April 1998 uncovered 732 articles in the unrestricted search and 367 in the restricted Medline search, of which 205 articles were initially selected for further review. Of these, 32 randomised controlled trials were retrieved.

*Cell salvage.* The search update uncovered 821 references in the unrestricted Medline search and 455 in the restricted Medline search. Due to a large overlap between the cell salvage and PAD searches only 124 abstracts needed to be reviewed. Of these, 12 were selected for further review. A number of articles were also uncovered in the Embase autotransfusion search for PAD.

*Erythropoietin.* The search uncovered 1,556 references in the unrestricted Medline search, 269 in the restricted Medline search, and 241 references in Embase. Of these, 175 articles were initially selected for further review; 22 of these articles were retrieved.

*Aprotinin.* The search uncovered 319 references in the unrestricted Medline search, 127 in the restricted Medline search, and 78 articles were selected for further review; 53 were retrieved.

*Tranexamic Acid.* The search uncovered 73 references in the unrestricted Medline search, 49 in the restricted Medline search, and 30 articles were selected for further review; 22 were retrieved.

*Epsilon aminocaproic acid.* The search uncovered 88 references in the unrestricted Medline search, 36 in the restricted Medline search, and 30 articles were selected for further review; 10 were retrieved.

*Desmopressin.* The search uncovered 286 references in the unrestricted Medline search, 61 in the restricted Medline search, and 18 articles were selected for further review; six were retrieved and reviewed. An Embase search for clinical trials of aprotinin, tranexamic acid, epsilon aminocaproic acid and desmopressin uncovered 260 references; 57 articles were selected for further review; 47 were retrieved.

Following screening of these studies, the following numbers were identified in each category which fulfilled the criteria for inclusion in the meta-analysis:

- PAD 9
- ANH 28
- cell salvage 32
- erythropoietin 29
- aprotinin 68
- tranexamic acid 23
- epsilon aminocaproic acid 5
- desmopressin 15

### Criteria for inclusion

Trials selected for review were distributed amongst the group for reading and classification. A cover sheet with randomisation criteria, methodological descriptions, type of blood-sparing technique, transfusion protocol, treatment outcomes, and comments were completed for each article. For standardisation, articles were examined for inclusion/exclusion criteria by two independent raters with disagreements resolved by consensus.

Articles were included if they met the following criteria:

- The study was randomised with a concurrent control group.
- A blood-sparing technique of interest was examined.
- There was a relevant control of usual care or placebo. Studies with a combination of active comparisons were included if both intervention and control were exposed to the other technologies.
- The surgery being performed was elective. Allowance was made for semi-urgent operations.
- The study participants were adults (over 18 years) and not parturients. Trials were included if some participants under 18 years were enrolled, but the type of surgery was predominantly carried out in adult patients. Trials of blood-sparing techniques in paediatric surgery were excluded.

Non-English articles were included if the work involved in translating them was straightforward, for instance if they were in French or German (but not in Russian or Japanese).

Articles which met the inclusion/exclusion criteria were also quality assessed by two independent raters.

### Data extraction

Articles which met the inclusion/exclusion criteria were processed for data extraction. Articles identified as duplicate publications were combined to obtain one set of data. The study with the greatest number of patients was then represented in the analysis. Studies which did not report information on the proportion of patients transfused with homologous blood, or the amounts of homologous blood used, were excluded. Data were extracted by one person and then checked against the data extracted in the previous meta-analysis. Data from papers identified in the updates of the literature searches were checked by a statistician in the study team.

Data on the following outcomes were recorded: numbers of patients exposed to homologous blood; amount of homologous blood transfused; numbers receiving any transfusion (for PAD and erythropoietin plus PAD only); and postoperative complications (thromboses, infections, haemorrhage or increased length of hospital stay).

Information regarding demographics (age, sex), type of surgery, and the presence/absence of a transfusion protocol was also obtained. Data were extracted for homologous blood if it was expressed as whole blood or packed red cells. Information on fresh frozen plasma or platelets was disregarded.

## Data analysis

All analyses were performed using Review Manager 3.1.1 software which includes Meta-View 3.1. Data on the numbers of patients exposed to homologous blood and the numbers of patients in each treatment group were entered into Review Manager. The relative risks for homologous blood transfusion in the intervention group as compared with the control group, and corresponding 95 per cent confidence intervals, were calculated for each trial. Relative risks were pooled across trials using both the fixed and random effects models. Tests for heterogeneity were also performed. Trials were stratified according to presence or absence of a *transfusion protocol*, and by *type of surgery* (cardiac, orthopaedic, cancer, other) and results were pooled within strata.

The means (and standard deviations) of units or millilitres of homologous blood transfused in each treatment group were recorded and entered into Review Manager where possible. If amounts of blood transfused to be pooled consisted of units and/or millilitres, the standardised mean differences were calculated and pooled. Data in millilitres were converted to units by dividing by 300. The weighted mean differences in units of homologous blood were calculated and pooled using fixed and random effect models with 95 per cent confidence intervals.

For postoperative complications, the number of patients experiencing the event, and the total number of patients in each treatment group, were entered into Review Manager. The relative risk of the adverse event in the intervention group was compared with the control group and corresponding 95 per cent confidence intervals were calculated for each trial. Relative risks were pooled across trials using both the fixed and random effects models. Hospital stay (in days) was also entered if articles provided a mean and standard deviation. The weighted mean differences were calculated and pooled using fixed and random effect models with 95 per cent confidence intervals.

## Presentation of results

There are two main methods of analysing randomised trial data on the impact of techniques designed to diminish the need for homologous transfusions. The first is a comparison of the rate of homologous transfusion in patients receiving the intervention compared with that in a control group. The results are presented in the form of relative risks of homologous transfusion in the intervention compared with the control group. The absolute reductions in risk have also been derived from these data, and expressed as numbers needed to treat (NNT). NNT is the number of patients who would have to be treated with the intervention, so that one patient would avoid transfusion with homologous blood. Another form of presentation used in these results is the weighted mean difference, which is an expression of the average reduction in the numbers of units of homologous blood administered to the intervention group, compared with the control group.

The general form of expression of the results is important, and we have followed certain conventions. If the rate of homologous blood transfusion is reduced in the intervention compared with the control group, the relative risk is  $<2$ , and if the reduction in relative risk is statistically significant, the upper confidence limit will also be  $<1$ . In the case of risk differences the rate of homologous blood transfusion in the control group is subtracted from that in the intervention group; if the intervention is effective, the difference in rates will carry a minus sign, as will the lower and upper 95 per cent confidence limits if the difference is statistically significant. The number needing to be treated with an effective intervention is always  $>1$ , and carries a positive sign. The smaller the number, the more efficient is the intervention. In the case of weighted mean differences the average number of units in the control group is subtracted from that in the intervention group; if the intervention is successful, the difference will carry a minus sign, and if it is statistically significant so will the upper and lower 95 per cent confidence limits.

Cochrane Review Manager software was used to conduct these analyses and this provides a range of statistical manipulations. The random effects approach was chosen as the principal means of presenting the data. This approach is generally regarded as conservative in that it incorporates a term for 'between study' heterogeneity, and in the presence of such heterogeneity produces a wider confidence interval. Other forms of presentation are possible, including a fixed effects model, and the use of odds ratios.

This literature, in the main, is non-randomised, and is regarded as being of inferior quality because of the large potential for confounding; in non-randomised studies subjects who receive homologous transfusion can generally be assumed to differ from those who do not in respect of a range of clinical factors that are likely to influence the outcomes.

## Results of literature review

### Benefits of techniques for the minimisation of homologous blood transfusion

The results of the literature analysis of trials relating to the efficacy of the various methodologies for minimising homologous blood transfusion are summarised in the following tables.

#### Pre-operative autologous donation

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
8	1,089 subjects, 549 randomised to PAD	66%	46.5%	2.2 patients would have to undergo PAD for one to avoid homologous transfusion. 95% CI NNT was 1.6 to 3.3.	Halving of homologous transfusion rate. Trials employing transfusion protocols were predominantly in cancer surgery, and not possible to determine which variable accounts for differences in transfusion rates.	Rate of transfusion with homologous blood was reduced by around 85% in relative terms. Risk of receiving any transfusion is increased by a relative 25% by participation in an autologous blood donation program.	Relative risk for homologous blood less for orthopaedic procedures (relative reduction 84%) than for cancer surgery (relative reduction 54%). The 95% CI for these estimates do not overlap.  Trials did not give adequate information on the number of units collected or transfused.

*Note:* CI = confidence interval; NNT = numbers needed to treat.

#### Acute normovolaemic haemodilution

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
24	1,132 subjects, 595 randomised to ANH	34%	29.1%	3.4 patients undergo ANH for one to avoid homologous transfusion. 95% CI NT was 2.3 to 6.8.	18% relative reduction in rate of transfusion with homologous blood (not significant)	Rate of transfusion with homologous blood was reduced by around 48% in relative terms.	

*Note:* CI = confidence interval; NNT = numbers needed to treat.

### Intra-operative autologous salvage (cell salvage)

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
30 (17 control groups with no intervention)	2,120 subjects, 1,079 randomised to cell salvage	41%	25.4%	3.9 patients would have to undergo cell salvage for one to avoid homologous transfusion. 95% CI NNT was 2.8 to 6.4.	Most trials used protocol and there was a trend to a lower relative risk of homologous transfusion.	Numbers too small.	The average reduction in homologous blood transfusion when cell salvage compared with no intervention was 0.8 Units versus 0.4 when compared with another active intervention.

*Note:* CI = confidence interval; NNT = numbers needed to treat.

### Erythropoietin (EPO)

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
28 6 EPO alone, 19 Trials EPO combined with PAD compared with PAD alone	2295 subjects, 1429 randomised to EPO	Overall 46% EPO Alone 37% No significant difference	14.5%	6.9 patients would have to undergo cell salvage for one to avoid homologous transfusion. 95% CI NNT was 5.0 to 11.1.	The relative benefits of EPO were less when used in conjunction with a protocol, but numbers were too small.	Numbers too small.	Most trials were cardiac or orthopaedic surgery. No benefit noted in cancer surgery. It was difficult to estimate the number of homologous units saved, but on average it was about 0.25 of a unit.

*Note:* CI = confidence interval; EPO = erythropoietin; NNT = numbers needed to treat.

## Aprotinin

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
57 38 trials with no active control. Most trials in cardiac surgery	6,761 subjects, 3,894 randomised to aprotinin	30%	21%	4.7 patients would receive aprotinin for one to avoid homologous transfusion. 95% CI NNT was 4.0-6.1.	No effect, but numbers small.		The relative benefits of aprotinin were unaffected when used in conjunction with a another blood-sparing technique and were not effected by the type of surgery. There was a small dose effect. Trend to lower re-operation rates and lower mortality, but numbers too small.

*Note:* CI = confidence interval; NNT = numbers needed to treat.

## Tranexamic Acid

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion	Absolute reduction in homologous transfusion	NNT	Transfusion protocol	No transfusion protocol	Comments
18 11 trials with no active control. Most trials in cardiac surgery	1,342 subjects, 758 randomised to tranexamic acid	34%	18.6%	5.4 patients would receive tranexamic acid so one would avoid homologous transfusion. 95% CI NNT was 4.0-9.6.	Numbers too small.	Numbers too small.	6 trials reported volume of blood transfused was reduced by 1.35 units (0.75,1.95). Trend to lower re-operation rates and lower mortality, but numbers too small. 7 compared tranexamic acid with aprotinin and + trend towards aprotinin but not significant.

*Note:* CI = confidence interval; NNT = numbers needed to treat.

### Epsilon aminocaproic acid

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion
4	208 subjects, 106 randomised to epsilon aminocaproic acid	48%
11 trials with no active control.		Not statistically significant.
Most trials in cardiac surgery		

### Desmopressin

Number of randomised trials	Total number of subjects	Relative reduction in homologous transfusion
13	884 subjects, 453 randomised to desmopressin.	99%
8 trials with no active control		(ie no effect).

## Complications of use of homologous blood and the alternatives

This section focuses on the other outcomes associated with the use of homologous blood transfusion and its alternatives. These outcomes were not the primary outcomes of the trials and were reported inconsistently. Partially extractable adverse events were mortality, non-fatal myocardial infarction, stroke, deep vein thrombosis, pulmonary embolus, wound infections/complications, any infection, fever, re-operation for bleeding, and length of hospital stay. Data were extracted from trials that provided sufficient information, and were pooled within specific interventions. Where relevant, an attempt was made to pool the data across different interventions. This was done in situations where a general hypothesis could be tested eg reduction in homologous blood transfusion would lead to a lower rate of postoperative infections.

### Bleeding complications

The only variable that could be extracted consistently from the trials was bleeding complications necessitating re-operation. Overall these event rates were low. The main hypothesis to be tested in this subsection is that the re-infusion of salvaged blood might impair coagulation, and increase the rate of bleeding complications. There was a trend towards increased bleeding in subjects randomised to cell salvage, but the numbers were small and statistical significance was not reached. Of more significance was the observation that use of aprotinin in cardiac surgery reduced the risk of re-operation due to bleeding by a significant average of 58 per cent. This was not apparent in individual trials due to small numbers, but in aggregate the evidence is impressive. There was a similar trend with tranexamic acid but the numbers were small.

### Vascular events

The *overall mortality* rates are too low to draw more than tentative conclusions about the impact of these interventions. For convenience, overall mortality was included with vascular events although it is appreciated that death may have been from non-vascular causes. The majority of deaths occurred in the trials of erythropoietin. In trials that reported this event, there were 22 deaths out of 690 subjects randomised to receive erythropoietin, compared with 8 deaths out of 419 subjects in the control group. This constituted an approximate 50 per cent relative increase in overall mortality. However, the result was not statistically significant across the trials of erythropoietin. There was a small increase in the number of deaths with cell salvage, although the overall mortality appeared lower than in the erythropoietin trials. This may be due to differences in the nature of the surgical procedures being performed. In the case of PAD only one trial reported mortality, and the numbers of deaths in the small ANH trials were too low to discern any trends.

For *non-fatal myocardial infarction*, small numbers of events were observed for all of the interventions, and in particular there was no trend to a higher rate of this outcome in erythropoietin-treated patients.

For *stroke*, numbers of events reported were small, and although there was a higher rate of stroke in subjects randomised to erythropoietin than in their controls, this trend was not statistically significant.

There was no evidence of an increase in the rate of *deep venous thrombosis* with PAD, ANH or cell salvage. With erythropoietin there was evidence of an increase in the overall frequency deep venous thrombosis, with 31 cases being observed in 401 individuals randomised to erythropoietin, compared with 10 cases of deep venous thrombosis out of

212 individuals in the control groups. However, the overall relative risk (1.63) was not statistically significantly elevated. For *pulmonary embolism* the rates were generally too low, and too infrequently reported, to draw conclusions. In relation to thrombosis overall, the event rates were generally low, and no obvious trends were observed. In particular, and in contrast to the reported situation with stroke and deep venous thrombosis, there was no apparent increase in 'any thrombosis' in erythropoietin-treated patients compared with their controls.

### **Infections**

Included in this category were the variables 'any infection', wound infection/complication, and pyrexia noted in the postoperative period. For these outcomes it was considered relevant to pool data across the different interventions. As all of the interventions, especially when used in conjunction with a transfusion protocol, were shown to be effective in reducing the need for homologous transfusion, it can be hypothesised that there might be a general effect of these interventions in reducing immuno-suppression due to homologous transfusion. In the case of PAD, cell salvage and erythropoietin, there were trends to lower rates of infection in the intervention compared with the control groups. Rates of infection were not reported in the trials of ANH in a consistent manner, and there were insufficient cases to discern any trend. Across all interventions there was an approximate 22 per cent relative reduction in the risk of any infection. This reduction did not quite reach conventional levels of statistical significance (upper 95 per cent confidence limit 1.04). The data on wound infections were much more sparse, and these were really only reported in the case of cell salvage. Although there was a trend to a lower rate of wound infections, the trend was not statistically significant. Pyrexia was also inconsistently reported and no clear trend was seen.

### **Length of hospital stay**

Because all of the interventions were effective in reducing the rates of homologous transfusion, it was considered legitimate to pool data across them.

Length of hospital stay was reported in only a minority of the trials reviewed. The average length of stay reported in these studies (mainly for cardiac and major orthopaedic procedures) appears long compared with Australian hospitals. However, a long length of stay offers an opportunity for the interventions to demonstrate efficacy, but no convincing trend was observed. On average, length of stay was shortened by around 0.42 days, but this reduction did not approach statistical significance. The maximum that could be expected, based on these results, was 1.2 days, but the data are also consistent with a modest increase in length of stay.

### **Conclusions**

The results of meta-analyses indicate a modest effect of all interventions in reducing the need for homologous blood transfusion. It is important to note that the values given in the tables are not obtained from comparative 'head-to-head' trials. Consequently, the apparent differences in the various measures of benefit may be due to confounding factors and should not be taken to indicate a superiority of one technique over another.

Considering the different techniques the following conclusions can be drawn. There were only a small number of trials of PAD, compared with the other interventions. This may reflect a firm belief in the efficacy of this approach; investigators may consider that trials are not necessary. Although the trials of PAD showed a reduction in the need for homologous blood, they were unblinded studies, and transfusion practices may have

been influenced by knowledge of the trial status of individual patients (ie poor concealment of randomisation). Furthermore, the overall transfusion rates in these trials were high, and were actually increased by recruitment into the PAD arms of the trials. This raises questions about the true benefit of PAD as there was considerable potential for the trials to have introduced bias resulting in overestimation of the benefit. If over-transfusion is a possible consequence this could increase adverse effects. Concerns about the use of PAD include: volume overload; clerical handling errors; and bacterial contamination of the stored blood. Thus, any benefit from avoidance of short-term immunosuppression through reduced transfusion of homologous blood, and reduction in the risk of transmission of viral diseases (which are already extremely low), have to be set against the risks associated with the technique itself. In the absence of formal modelling, or a properly conducted large clinical endpoint trial, it is not possible to conclude whether the benefits of PAD will definitely outweigh the possible harms. Despite the small potential benefits of this approach there remains enormous enthusiasm for PAD, driven in part by fear of the 'next epidemic' resulting from infection of the homologous blood supply. A recent study of risk perception and willingness to pay by Lee et al (1998), revealed strong preference for autologous blood, and a high willingness to pay, despite a thorough education of subjects regarding the low risks associated with screened homologous blood.

There have been strong expressions of support in the literature for the use of ANH as an effective method for minimising homologous red cell transfusion. Goodnough et al (1998) elegantly pointed to the limitations of PAD, and the fact that this technique represents what they call 'minimal chronic haemodilution'. While their criticisms of PAD seem well made, their own modelling data suggest that the theoretical benefits of ANH are also likely to be quite small. This proved to be the case in the systematic review of the randomised trials covered in this report. These trials were small, and the effect sizes were modest. Of particular note was the fact that any benefits of ANH appeared to be lost in clinical settings where transfusion protocols were applied and enforced. The degree to which a transfusion protocol influences the results of the ANH studies is seen in the pooled data, suggesting that the effect was at least as great as any benefit of ANH in reducing the need for homologous blood.

The benefits of *cell salvage* in reducing the need for homologous blood were more convincing, but again showed a clear dependence on the concomitant use of a transfusion protocol. Using technologies in which the salvaged blood is washed before re-infusion there was a lower relative risk of requiring homologous blood than the unwashed techniques. As with ANH the benefits of cell salvage seemed less when used in the context of a set of rules determining the use of homologous blood.

The benefits of *erythropoietin* use on its own are modest, and the number of units of homologous blood 'saved' by its use were inconsistent across studies. It seemed clear that erythropoietin augmented the effects of PAD in reducing the need for homologous transfusion although, as with PAD used on its own, the overall rates of transfusion were very high. It should be noted that erythropoietin used in conjunction with PAD did not produce a higher rate of transfusion (of any type) compared with PAD alone. This is not surprising as this analysis tested the impact of erythropoietin, not PAD, and the results are not in conflict with the earlier observation that PAD can increase the rate of any transfusion.

The benefits of *aprotinin* were quite impressive in reducing the need for homologous blood and necessity for re-operation related to bleeding. The drug has been intensively investigated in a large series of small trials, which raises concerns about the accuracy of estimates obtained from a meta-analysis. Similar trends were seen with *tranexamic acid*, but the numbers were smaller. More data on tranexamic acid would have been

valuable when one considers the cost differential between aprotinin (\$365–\$731) and tranexamic acid (<\$60 per patient). With individuals with high transfusion requirements aprotinin does not reduce the proportion of individuals requiring transfusion. When the transfusion rate in the control groups approaches 100 per cent it was similar to the treatment group. However, the greater the volume of homologous blood in the control group, the greater the saving in blood with treatment.

The lack of efficacy of *desmopressin* in reducing blood loss and homologous transfusion is notable. However, it should be emphasised that these studies were in relation to unselected patients and the question of its use in high-risk patients for bleeding (eg von Willebrand's disease, renal impairment, platelet function defects) has not been addressed. It may be in this subgroup where that drug is indicated. There is some data not relevant to this analysis indicating this may be the case.

Some of the more interesting data extracted from the literature review concerned the *adverse reactions to homologous blood and its alternatives*. It is a weakness of this literature that events such as infections, and measures such as length of hospital stay, have not been reported consistently across these studies. In many ways these are the most important short-term outcomes. An economic analysis reviewed later in this report reveals how sensitive estimates of cost-effectiveness are to assumed lengths of hospital stay. It is regrettable therefore that more information could not be obtained from this aspect of the review.

In regard to infections, there was a trend to reduced rates when data were pooled across all of the interventions studied here. This is a rational approach in that the common effect of these interventions is to reduce the amount of homologous blood transfused before, during or after surgery. Consequently, the immunomodulatory effect of homologous blood might be expected to be reduced, with a consequent fall in the rate of postoperative infections. Indeed, this is what was seen and the pooled relative risk reduction just failed to reach statistical significance. However the magnitude of the effects seen in these trials was quite modest. Previous commentary articles have claimed that postoperative infection rates with homologous blood transfusion appeared to be seven to ten-fold higher than with autologous blood or no transfusion (Blumberg 1997). The same author claimed that homologous blood transfusion was associated in a dose-dependent manner with longer hospital stays and higher costs. It should be noted that these confident assertions appear to have been based on the results of observational studies, which may be seriously confounded by disease severity and comorbidity, which themselves were the indications for homologous blood transfusion. While the randomised data reviewed here raise the possibility of a modest reduction in postoperative infections, the reductions in risk were not statistically significant, and further data will have to be included, or definitive trials performed, to confirm this potential benefit of alternatives to homologous blood. Furthermore, the point estimate of the weighted mean difference in length of hospital stay between intervention and control groups in these studies suggested a benefit of less than half a day in hospital. This is against rather long lengths of stay for the surgical procedures concerned. This suggests that there is not a great potential for benefit in this regard, particularly in the Australian health care system where lengths of hospital stay tend to be shorter. The confident claims about the risk of homologous blood, and the benefits of avoiding it, need to be subjected to more rigorous tests than those applied in the past.

The other adverse effects reviewed did not show clear or particularly worrying trends. There was no clear evidence of an increased risk of haemorrhage with cell salvage. Although the datasets reviewed did not distinguish between washed and unwashed cell processing, further analyses of these data may be worthwhile. Further review suggests

that washing of salvaged blood results in a lower relative risk of requiring homologous blood, although the difference is not significant.

It should be emphasised that the trials of cell salvage were small, and the occurrence of haemorrhage was inconsistently reported and the volumes processed difficult to extract.

Of concern is the potential for erythropoietin to induce thrombosis. A trend was seen in the case of deep vein thrombosis and stroke in these studies, but the numbers of affected subjects were too small to draw any definite statistical conclusions. However, erythropoietin increases haematocrit and whole blood viscosity, and has been associated with hypertension when used in other settings. This is a matter that needs further investigation, and in view of the relatively modest beneficial effect of erythropoietin, combined with its extremely high costs, there is presently no convincing evidence to support its use in anything other than carefully controlled clinical endpoint trials.

# Results of the ISPOT survey — use of alternatives to homologous blood transfusion in Australia

As part of the consultancy undertaken at the University of Newcastle and reported by Professor David Henry, surveys of Australian hospital practices conducted by the Australian arm of ISPOT were examined. ISPOT is a collaborative study of alternatives to peri-operative homologous blood transfusion (Forgie et al 1998). ISPOT involves researchers in ten countries (Australia, Canada, Denmark, France, Israel, Japan, The Netherlands, Scotland, Spain and the United States), surveys of practices in each of the participating countries, and qualitative research to investigate factors that influence use of these technologies in each country.

Two surveys of practice in Australian hospitals with 50 beds or more undertaking surgery was carried out. In Phase 1, a questionnaire was mailed to the Chief Executive Officer of each hospital, requesting information on which of the listed techniques (PAD, ANH, cell salvage), or drugs (aprotinin, desmopressin, epsilon aminocaproic acid, tranexamic acid, erythropoietin), were used regularly by the following specialties: general surgery, cardiothoracic surgery, vascular surgery, orthopaedic surgery, neurosurgery, colorectal surgery, gynaecology, ear nose and throat surgery, urology and 'others'. The survey instrument also requested details of the number of beds in the hospital, and contact details for the most appropriate person in each nominated specialty from whom to obtain further information. The instrument was accompanied by brief details on the ISPOT objectives and study methods.

In Phase 2, a more detailed questionnaire was mailed to the named contact person in those institutions identifying themselves as 'users' of the technologies. The second survey requested further details on a range of issues, including the proportions of patients who received any of the interventions, and whether survey respondents thought that the technologies were used too infrequently, too frequently, or at an appropriate rate. Where there was conflict between Phase 1 and Phase 2 regarding whether an institution was a 'user' of the relevant technology, the results from the more detailed second survey were accepted, and the results from the first survey were corrected. In addition, a phone interview was undertaken to ascertain whether each of the surgical procedures were performed in the hospital.

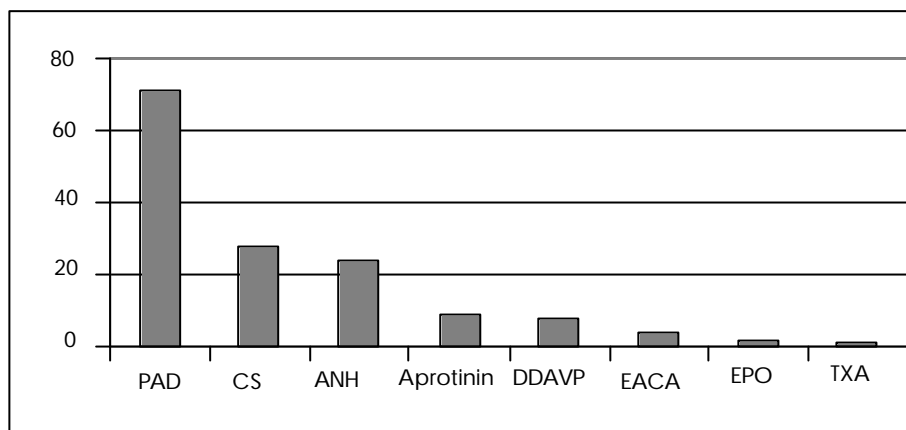
The corrected results from the Phase 1 survey were analysed with statistical analysis software. Simple descriptive statistics (mean and proportions) were calculated, and associations between study factors and use/non-use of the technologies were expressed as odds ratios with 95 per cent confidence intervals. Three institutional variables were examined — whether the hospital was public or private; teaching or non-teaching; and the number of beds (stratified around the median of 118 beds). Inspection of these variables showed a high degree of correlation between public hospital and teaching hospital status. The latter was omitted from multiple logistic regression analysis carried out to identify factors independently associated with use of the various technologies.

## Phase 1

A total of 400 Phase 1 questionnaires were mailed to hospital Chief Executive Officers. In all, 349 were returned with useable data, a response rate of 87.3 per cent. Of respondents, 218 (62 per cent) hospitals were public and 59 (17 per cent) were teaching hospitals. The proportions of institutions that described themselves as users of the

relevant technologies are summarised in Figure A4.1. PAD was the intervention used most widely to minimise the need for peri-operative homologous blood transfusion (70 per cent of institutions). Cell salvage and ANH were employed by similar proportions of institutions, 27 per cent and 24 per cent respectively. In comparison, anti-fibrinolytic drugs and erythropoietin were used by less than 10 per cent of hospitals.

Figure A4.1: Proportions of users of the various technologies



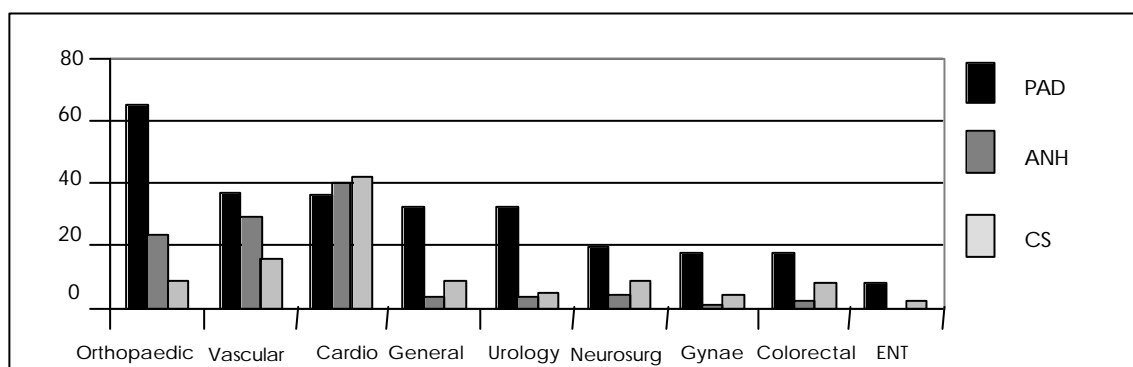
Note: ANH = acute normovolaemic haemodilution; CS = cell salvage; DDAVP = desmopressin; EACA = epsilon aminocaproic acid; EPO = erythropoietin; PAD = pre-operative autologous donation; TXA = tranexamic acid

All of these interventions were used more commonly in larger institutions (odds ratios > 2.9 for bed number >118 beds). However, public hospitals had reduced odds for use of all three interventions. This trend was more marked after adjustment for numbers of beds, and was statistically significant in the cases of autologous blood donation and cell salvage.

The pattern of use of the technologies varied between specialties, as seen in Figure A4.2. In the case of cell salvage and ANH, use was highest in cardiothoracic units. PAD was most heavily used in orthopaedic surgical units, but was popular in other specialties, being used by over 30 per cent of general and urological surgical units.

Multivariate analysis by specialty revealed similar trends to those seen with the analysis of institutions. Although there were variations between surgical specialities, the overall trend was for lower use of the technologies in public hospital units, and higher use in units sited in hospitals with more than 118 beds.

Figure A4.2: Proportions of users of the various technologies by surgical specialty



Note: ANH = acute normovolaemic haemodilution; CS = cell salvage; ENT = ear, nose and throat, PAD = pre-operative autologous donation

## Phase 2

A total of 605 forms were returned from the 1,119 surveys sent, a response rate of 54 per cent. Of these, seven forms were from the same hospital for the technology-speciality; a further 151 forms indicated that the technology was not used in the speciality. After these exclusions, a total of 447 survey forms are included in the analysis. The analyses presented here are restricted to three technologies: PAD; ANH; and cell salvage. The pharmacological agents were excluded from further analysis because of the low rate of use.

PAD was most used (at a median of 50 per cent or more cases) in orthopaedic, vascular (except abdominal aneurysm) and urological procedures (except transurethral resection). ANH was used in a median of 50 per cent or more cases in one orthopaedic (spinal fusion) and two neurosurgical procedures. Intra-operative cell salvage was used at a median of 50 per cent or more in cardiothoracic procedures, two vascular procedures, and two urological procedures. Postoperative cell salvage was also used in 50 per cent of two cardiothoracic procedures.

Of the 286 users of PAD, 53 per cent indicated that PAD blood was collected using ARCBS facilities, 44 per cent at their own hospital, 15 per cent at another hospital, and 25 per cent at other facilities. While 66 per cent of respondents indicated that the demand for PAD services had increased over the past five years, 6 per cent indicated that demand had decreased. The most common reasons stated for increased demand was patient demand.

Few responses (generally less than 5 per cent) indicated that the level of use of any of the three technologies was too high. In analysing the reasons given for greater use of the technology and the perceived barriers to its greater use, concerns about the blood supply, and perceptions that side effects were minor were common reasons given for the need for greater use of the three technologies. Of respondents, 64 per cent indicated that PAD had been proven effective, and 58 per cent indicated that patient demand was a reason for greater use of this technology. Greater use of ANH and cell salvage was indicated by 71 per cent and 50 per cent respondents respectively because of the cost-effectiveness of the technologies. Of respondents, 90 per cent indicated that cell salvage should be used more frequently because it reduces the need for homologous transfusion. Lack of communication (48 per cent), lack of surgeon interest (56 per cent), and scheduling of operations (59 per cent) were the most frequently nominated barriers to greater use of PAD. Lack of surgeon interest (79 per cent) and awareness of ANH benefits (71 per cent) were the most frequently indicated barriers to the use of this technology. Cost considerations (55 per cent) and lack of surgeon interest (40 per cent) were the barriers nominated most frequently for cell salvage.

## Discussion

The Phase 1 survey documented a high level of use of several procedures designed to minimise the need for homologous blood transfusion during elective surgery. In the case of PAD, use was strikingly high, with around three quarters of all Australian hospitals, reporting some activity. Use of ANH and cell salvage was also high, particularly in cardiovascular surgical units. In contrast use of a range of drugs designed to minimise operative blood loss was low.

The survey results are probably accurate and representative, as the responses were unambiguous, and around 87 per cent of hospitals in Australia, with 50 beds or more that perform surgery contributed data to this study. However, some limitations of the

work must be acknowledged, including reliance on self report, and the lack of detail in these results on the extent of use of these procedures in the study hospitals.

The three major technologies used here represent ways of substituting autologous for homologous blood. PAD differs from ANH and cell salvage in that it requires the close collaboration of patients who must donate blood at planned intervals prior to surgery. Consequently, the views of the public as well as health professionals are important in determining the demand for autologous donation. It is presumed that the level of enthusiasm for autologous blood represents a widespread perception that it is a safe alternative to the traditional means of dealing with blood loss during surgery. Although the authors are unaware of any surveys of the Australian community, it is likely that publicity for autologous donation (for instance advertising by private hospitals), as well as media reports of transfusion-related diseases, has led to a widespread perception that homologous transfusion presents a significant hazard to the recipient, and that this is entirely negated by the use of autologous blood.

Institutional and surgical sub-specialty factors appeared important in determining the use of these interventions. There was considerable variation in Phase 1 results, with orthopaedics and cardiothoracic surgery having the highest levels of activity. Hospital size also seemed to be important, with institutions with over 118 beds having the highest use. In contrast, public hospitals had a lower odds of use, and this trend remained after simultaneous adjustment for number of beds. It is possible that the pressure on public hospital beds, with uncertain scheduling of elective surgery, acts as a disincentive to PAD programs. As most clinical transfusion medicine expertise is based in the public teaching hospitals it is possible that there is also greater awareness of the recent re-examination of PAD and ANH.

Phase 2 results provided more detailed information on the variation in use of technologies within specialties. These respondents gave generally high endorsement for greater use of PAD, ANH and, to a slightly lesser extent, cell salvage, because of their concerns about the safety of the blood supply and perceptions of the effectiveness of the technologies (in terms of outcome and cost). Barriers to greater use of these technologies included institutional practices (for PAD) as well as lack of interest and awareness on the part of surgeons. Cost considerations were mentioned as a barrier for greater use of cell salvage.

There are a number of factors to consider when evaluating the high level of use of these technologies and the perception that they should be used more frequently. These are the magnitude of the risks associated with transfusion of screened homologous blood, the available evidence regarding the efficacy and costs of the various interventions reviewed here (in reducing the requirement for homologous blood), and perceptions of the overall value of these technologies.

As part of ISPOT, systematic reviews of published trials of the technologies have been performed. Some of these reviews have been published recently. The results show that PAD and ANH do reduce the need for homologous blood (Bryson et al 1998). However, in subjects randomised to PAD overall transfusion rates (autologous + homologous blood) were increased. The principal question raised by these reviews is what reduction in risk results from the smaller requirement for homologous blood.

A recent survey has shown that the risks of blood screened by the ARCBS being infective for HIV, Hepatitis B and Hepatitis C are 0.79, 2.71 and 4.27 (respectively) per million donations (Whyte & Savoia 1997). As noted, the evidence that this increases postoperative infection rates (compared with autologous donation) is equivocal. It is possible that the overall clinical benefits from autologous blood are small. The costs of providing autologous donation programs are high, and the cost-effectiveness of this

approach is questionable. Widespread use of autologous blood could reduce the demand for homologous blood, taking pressure off the supplies maintained by the Australian Red Cross. However this has to be set against the work involved in maintaining an autologous donation program, and the relatively high wastage of unused blood. In addition, a survey in Canada revealed a fairly high error rate in handling of autologous blood donations, and a separate study has documented a worryingly high rate of bacterial infection of stored autologous blood (Goldman et al 1997). These are important reminders that this approach is itself associated with an element of risk.

The results of our surveys are similar to those obtained in a German survey conducted in 1993 (Kasper et al 1995). Overall, 60 per cent of German hospitals with more than 25 beds used donated autologous blood, and 33 per cent employed this technique frequently or most of the time. ANH was used by 52 per cent of the responding hospitals, and 80 per cent reported use of some form of red cell salvage during operations.

The results of this study are confined to data obtained from surveys that employed a brief and simple instruments. The subsequent phases of the ISPOT study involve extensive qualitative research, which will help to explain some of the trends seen here. However it can be concluded that the level of use of interventions designed to minimise exposure to homologous blood has risen to high. As with other health technologies, these changes in practice are not well supported by evidence regarding their comparative effectiveness and cost-effectiveness. The variations in practice recorded here argue for development of guidelines for appropriate use, and efforts to align practice with the best available evidence.

Even though the survey demonstrates high usage of the techniques for minimising homologous blood transfusion, it does not provide significant information on the proportion of patients to whom these techniques are applied nor the volumes of blood transfused.

As reimbursement is not an incentive for the use of the three technologies, especially with cell salvage and ANH, this cannot be regarded as a factor encouraging use in the private sector. However, there is some reimbursement for PAD and if there were to be reimbursement for ANH and cell salvage this may significantly effect the usage. The extent to which this may be the case is difficult to estimate.

## Appendix 5

# Review of economic analyses of alternatives to homologous blood transfusion

Again undertaken as part of the University of Newcastle consultancy, the review of economic evaluations of technologies to minimise peri-operative transfusions was based on a previous systematic review (Fergusson et al, in press) with updating from the literature searches described in the Methods section of Appendix 3. An unpublished Canadian review (Fergusson et al 1993) was made available by the consultants and data are reproduced here with permission.

Studies were excluded if they had any of the following characteristics: editorials, reviews, non-English articles, abstracts or letters

The inclusion criteria were:

- comparison of the costs of at least two peri-operative transfusion strategies;
- inclusion of the use of homologous blood alone in one of the study arms; and
- indication that the economic evaluation of the technology was the main objective of the paper.

This literature review identified 18 papers, reporting 20 economic evaluations. One paper was an unpublished review of the cost-effectiveness of erythropoietin obtained from the ISPOC coordinating centre in Ottawa (Coyle et al, unpublished). Many of these evaluations were cost comparisons only; others confined their outputs to a calculation of the cost per unit of homologous blood avoided. Only papers that reported meaningful effectiveness outcomes (quality adjusted life years saved, life years saved) were included. However, because of potential relevance for costing exercises in Australia there is a detailed discussion of the Canadian costing study.

Five cost-effectiveness analyses of PAD were identified. All were published in the United States between 1993 and 1995. Only one cost-effectiveness analysis of cell salvage was identified. This was by Huber et al (1997), and published in the United States. This study evaluates the cost-effectiveness of routine use of the Haemonetics Cell Saver during elective infra renal aortic reconstructions. A cost-effectiveness analysis of erythropoietin was also identified. Coyle et al (unpublished) undertook an economic analysis of erythropoietin alone, and erythropoietin used to augment PAD in orthopaedic surgery.

The studies differ in the assumptions that they make. The cost per unit of autologous blood varies from \$76 to \$478, and from \$52 to \$277 per unit of homologous blood. All studies use a discount rate of 5 per cent. The assumed risks of infection are fairly consistent across the studies, as are the quality of life adjustments used.

The assumption that has the largest single impact on the cost-effectiveness ratio is the rate of postoperative infection, and costs associated with this. Only one study (Healy et al 1994) assumes a difference in the rate of postoperative infection for autologous and homologous transfusion. Healy et al (1994) assume that patients receiving at least two units of homologous blood spend an additional 1.4 days in hospital, due to postoperative infection. This assumption results in PAD being dominant over homologous transfusion. When this assumption is removed from the model (ie it is assumed that there is no difference in postoperative infection between those who receive homologous blood and those who receive autologous blood) the cost-effectiveness ratio becomes \$181,400 per life

year saved. Thus the estimated cost-effectiveness ratio is extremely sensitive to this assumption. Healy et al (1994) cite observational studies as a basis for their conclusion that homologous blood leads to a higher rate of infections, and longer length of hospital stay. The problem with these data is that they are highly likely to be confounded. Patients receiving blood transfusions during or after surgery are likely to be sicker than those who do not require blood, and it is likely that comorbidity, rather than the direct effects of transfusion, account for much of the difference noted in the observational studies. The data presented earlier in this review are relevant to this discussion. The meta-analysis of the randomised trials of alternatives to homologous blood indicated that these interventions had little impact on hospital stay. This was despite a fairly clear-cut reduction in the need for homologous blood. However, the number of studies reporting this secondary outcome was small, and because the studies were unblinded (other than with erythropoietin), a great deal of weight cannot be given to the findings. On the other hand, the upper confidence limit for the estimated change in length of stay was only 1.2 days, which makes it unlikely that there is any substantial benefit of these technologies in this respect. However, there is one caveat, and that came from the observation that overall infection rates were lower in subjects randomised to these technologies than the controls (see Results section). Clearly more information is needed regarding the short-term effects of homologous transfusion.

Based on these seven economic evaluations, the technologies used to minimise peri-operative transfusion do not meet conventionally accepted criteria for being considered 'cost-effective'. With the exception of Healy et al (1994), the cost-effectiveness ratios range from \$40,000 to \$329 million per quality-adjusted life year or life year saved. The conflicting evidence regarding the relationship between homologous blood and postoperative infection, and the large impact this assumption has on the results of the Healy study (changing the cost-effectiveness ratio from unacceptably high to PAD becoming dominant), suggests that this issue needs to be further investigated by properly conducted large clinical endpoint trials.

## **Relevance of these studies for Australian transfusion practices**

The main factor that will influence the interpretation of these data is the uncertainty regarding the clinical benefits of avoidance of homologous transfusion. However it is important to consider the relevance of the costing methods used in these studies and how they compare with similar exercises conducted in Australia. This has obvious relevance when attempts are made to make a fuller assessment of the likely cost-effectiveness of these technologies in the Australian health care system. With the exception of the Coyle et al paper, all economic analyses identified by the searches described earlier were American studies. Due to differences in the American and Australian health care systems, it is unlikely that American costs reflect costs in the Australian setting. A search of Medline (1966 to June 1998) and Current Contents (1993 to September 1998) using the key words cost, blood, transfusion and Australia failed to identify any studies of the costs of blood transfusion in Australia.

A Canadian study likely to better reflect the Australian setting, was identified (Tretiak et al 1996). The Canadian blood system is not for profit, relying on unpaid, volunteer donors. Further, no charge is made to health care facilities or patients for blood products. Therefore, it has similarities to the Australian system. Tretiak et al (1996) measured the costs associated with four stages of transfusion: the collection; the production; the distribution; and delivery phases. These included costs of personnel, purchases, external services, overheads, donors' time, patients' time, wastage and infection. Cost data were collected from six transfusion centres, eight hospitals, and through patient

questionnaires. The costs of infection (HIV and Hepatitis C) were based on published American data. The total costs were \$210 per unit of homologous blood and \$338 per unit of autologous blood, in 1993 Canadian dollars. The main factors accounting for this difference were the collection of autologous blood in hospitals, which is more expensive than collection at the Canadian Red Cross. Society and the difference in wastage (2 per cent of costs for homologous blood and 18 per cent for autologous). The breakdown of costs appears in the following table.

Cost category	Mean cost (%)	
	Homologous transfusion	Autologous transfusion
Purchases	33(16)	42(12)
External services	1(1)	1(0)
Personnel	127(60)	174(52)
Overhead	14(7)	30(9)
Donors' Time	30(14)	30(9)
Wastage	5(2)	61(18)
Risk of infection	1(1)	0
Patients' time	0	0
<b>Total</b>	<b>\$211(100)</b>	<b>\$338(100)</b>

The economic analyses identified were based on decision-analysis models, making it difficult to substitute the Canadian costs into the analyses. Of the analyses looking at the cost-effectiveness of autologous transfusion, all but the Goodnough et al (1994) paper used hospital acquisition costs for the cost of autologous and homologous blood. These values ranged from \$52–\$67 per unit of homologous blood and from \$76–\$90 per unit of autologous blood. Handling costs (which were assumed to be equal for the two types of blood collection) and infection costs were excluded. Goodnough et al (1994) undertook a survey, which calculated the cost per unit of homologous blood to be \$150 and \$198 per unit of autologous blood. These studies result in a much smaller difference in costs between autologous and homologous blood, compared with Tretiak et al (1996). Consequently, substituting the Canadian costs into the economic analyses, to better reflect the Australian setting, is likely to result in a worsening of the cost-effectiveness ratios reviewed earlier in this section.

## Consumer statement

### Should I have my own blood collected and stored?

The Australian Health Ministers' Advisory Council (AHMAC) has looked into the alternatives to using donated blood to treat blood loss that occurs in medical situations such as surgery. The Committee investigated whether it was preferable to collect and store a person's own blood (pre-donation), for use if needed during surgery.

After receiving expert advice which was considered carefully, AHMAC decided that pre-donation should not be encouraged for most people in the community, because there is now a very low risk of infection occurring through blood collected and screened by the Red Cross. In addition, as medical techniques improve blood transfusion is necessary on fewer and fewer occasions.

This brochure aims to answer some of your questions and concerns. You may like to take it with you when discussing future medical treatment with your doctor.

### What is a blood transfusion?

Transfusing blood from one person to another has been part of medicine for much of the twentieth century. Nowadays, the blood is divided into parts and people either receive red blood cells, plasma, or products made from plasma. Australians know of many instances where blood transfusion has saved lives and speeded recovery in emergencies such as accidents or following surgery.

Most people receive the blood of others, collected from voluntary donors by the Australian Red Cross Blood Service in each State. In more recent times, the choice to pre-donate your own blood for possible return following elective (planned) surgery has become available.

### How safe are blood transfusions?

It is important to look at the real risks of having a blood transfusion today.

#### *Problems in the past*

The arrival of the human immunodeficiency virus (HIV) in the early 1980s alerted governments and medical bodies to the fact that blood can pass on infections to people. Blood-borne viruses, like HIV and hepatitis B and C, did infect people at that time.

#### *What has changed?*

The introduction of thorough screening of all blood donors and the testing of all blood donations for HIV, hepatitis B, hepatitis C, syphilis and HTLV-1 has now reduced the risk of infection to close to zero.

Doctors have also revised their treatment to avoid the use of a blood transfusion where possible.

### ***What are the risks today?***

The risk of being infected with HIV or hepatitis through a blood transfusion is extremely low today, far lower than the many other risks we take in our daily lives. These risks are estimated to be:

- a 0.79 in a million chance of getting HIV through a blood transfusion;
- a 4.27 in a million chance of getting hepatitis C; and
- a 0.271 in a million chance of getting hepatitis B.

As blood transfusion is only given today in circumstances that are extremely serious and likely to involve loss of life, the very slim risk of blood borne infection makes this decision more straightforward.

### **What are the alternatives to transfusion?**

Since the early eighties, following public concern about the risks of receiving blood and blood products, doctors and scientists have been active in seeking alternatives to blood transfusion. At this time there are three main techniques:

- improving surgical methods to prevent as much bleeding as possible, and avoid transfusion altogether;
- using new procedures to minimise blood loss so that as little blood as possible needs to be transfused; and
- using alternatives to blood replacement, such as diluting the blood or using new drugs developed for this purpose.

However, there will still be situations where, due to the amount of blood lost or expected to be lost, a transfusion is the best treatment. Where there is expected blood loss in elective surgery, a decision can be made either to collect and store your own blood or to receive blood from the Blood Transfusion Service.

### **What are the advantages and/or disadvantages in pre-donating your own blood?**

Pre-donation can only be used for elective (pre-planned) surgery.

#### ***Advantages***

- Individuals are not exposed to the blood of another person or persons.

#### ***Disadvantages***

- Biological infections in your own blood can develop during storage.
- Time is needed for the collection before surgery.
- The technique is costly and uses the time and resources of hospital and Blood Transfusion Services.
- The blood is wasted if not transfused back to donor.
- There is an increased probability of you receiving a transfusion if your blood is available.

### **What did the Committee recommend about pre-donation?**

The Committee found that pre-donation of one's own blood has a limited use. Their recommendations state that:

- the first goal is to prevent bleeding;
- the second goal is to manage any bleeding without giving a blood transfusion;
- a blood alternative should be used wherever possible;
- if transfusion is necessary, red cells from donated blood or pre-donated blood (where requested) should be used; and
- all hospitals should have clear guidelines about the situations in which to transfuse donated or pre-donated blood.

### **The future**

While not in favour of the pre-donation of blood for most people in the community, AHMAC has recommended that further new developments in alternatives to blood donation should be encouraged and closely watched.

AHMAC sees a need for clear information for those making decisions about blood transfusion and encourages people to discuss the matter, and any concerns, with their doctor.

A more detailed summary of the work of the Committee and AHMAC's technical report on the alternatives to blood transfusion can be obtained from:

The Director  
Special Access Programs Section  
MDP 2  
Department of Health and Aged Care  
GPO Box 9848  
Canberra ACT 2601

## Glossary

**Acute normovolaemic haemodilution (ANH):** The process by which a patient is deliberately bled for the purpose of collecting autologous red cells for subsequent transfusion, for the preparation of autologous blood products (eg platelets, plasma, autologous 'glue') or to obtain specific benefits from the effect of reducing the viscosity of blood.

**Allogeneic blood transfusion:** See *Homologous blood transfusion*.

**Autologous blood transfusion:** The use of a patient's own blood for transfusion.

**Blood component therapy:** The term used for the preparation and use of human blood products.

**Cell salvage:** The collection of shed blood to be used for re-infusion, for the conservation of autologous red cells.

**Fibrin glue:** A preparation of fibrinogen for use as a haemostatic agent. Thrombin is added to make the fibrinogen clot.

**Erythropoietin:** A hormone produced by the kidney which regulates red cell production by the bone marrow. A genetically engineered product is available for therapeutic use. Its main role has been for use in the anaemia of renal disease.

**Homologous blood transfusion:** The transfusion of blood between members of the same species. The term allogeneic blood transfusion has exactly the same meaning and is increasingly the preferred term. However, due to longstanding usage the word homologous is used in this report to avoid confusion.

**Hazard of transfusion:** The hazard of a transfusion refers to the specific adverse effects and its level of harm.

**Haemodilution:** The process by which the circulating blood dilutes as blood is shed. Red cells are not replaced in the short term. The patient's circulating blood volume is maintained by either transcapillary refill from the patient's own tissue fluid reserves or by the therapeutic intravenous infusion of clear fluids.

**Platelet fibrin gel (Glue):** A preparation of concentrated platelet rich plasma for use as a haemostatic agent. Thrombin is added to make the fibrinogen clot.

**Platelet rich plasma:** Plasma which has been prepared from a patient or normal donor in which the platelets have been retained in the plasma during preparation

**Pre-operative autologous donation (PAD):** The pre-operative collection of autologous blood for transfusion.

**Risk of transfusion:** The risk of transfusion is the likelihood of a particular hazard occurring to a specific patient.

**Storage lesion:** Biological infections in autologous blood that can develop during storage.

**Transfusion protocol:** A clear set of guidelines to define the conditions under which a patient will be transfused and with what product.

**Transfusion trigger:** The haemoglobin concentration at which transfusion is instigated.

## Acronyms and abbreviations

AHMAC	Australian Health Ministers' Advisory Council
AHTAC	Australian Health Technology Advisory Committee
AIDS	acquired immune deficiency syndrome
ANH	acute normovolaemic haemodilution
ARCBS	Australian Red Cross Blood Service
CI	confidence interval
CS	cell salvage
DDAVP	desmopressin
EACA	epsilon aminocaproic acid
EPO	erythropoietin
HIV	human immunodeficiency virus
HTLV	human T-lymphotropic virus
ISPOT	International Study on Peri-operative Transfusion
NNT	numbers needed to treat
PAD	pre-operative autologous donation
TXA	tranexamic acid

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