Health Policy Advisory Committee on Technology

New and Emerging Health Technology Report

Cell salvage as a patient blood management strategy

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HealthPACT

emerging health technology

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HealthPACT Advice

Peri-operative cell salvage is a technique by which a patient's extravasated blood is peri-operatively reinfused in order to replace haemoglobin stores. The underlying premise is that by avoiding blood transfusion, one avoids the infectious and immunomodulatory risks associated with transfusions. Its use in patient blood management practices to reduce the need for transfusion of allogeneic blood has been described by the National Blood Authority (NBA).

This Report is primarily intended to assist policy makers. Notwithstanding the NBA guidance, the role and value of cell salvage needs to be contextualised against the use of other surgical or pharmacological interventions to reduce blood loss or need for transfusion. Thus, this report focuses on recent evidence for cell salvage vs allogeneic blood transfusion, the procedure groups in which the effectiveness of perioperative cell salvage is demonstrated, evidence for the timing of cell salvage, and aspects of cost associated with cell salvage.

The report notes that there is evidence for benefit of cell salvage in reducing the need for allogeneic transfusion in orthopaedic (total hip and total knee replacement), cardiothoracic procedures and for the elective repair of ruptured abdominal aortic aneurysms. The report, however, notes that the impact of cell salvage upon post-operative haemoglobin, complication rates, post-operative recovery and length of stay, even in these indications, is inconclusive. As with other procedures and technological interventions, the operating model must be defined in order to safely introduce the technology and to realise the financial benefits of cell salvage. Across Australia, there are diverse practices, ranging from dedicated technicians operating the cell salvage equipment to its running by diverse in-theatre staff. Such models impact upon the staffing costs and training required and thus upon cost effectiveness. Variability in costing is also introduced by whether one compares cell salvage to the cost of blood products vs the cost of managing transfusion related reactions and complications. Finally, we note that the existing publications do not permit comparison between cell salvage vs other surgical and pharmacological interventions to reduce blood loss.

In conclusion, HealthPACT notes that cell salvage represents one option in reducing a patient's requirement for allogeneic blood transfusions in specific orthopaedic and cardiothoracic procedures. However, this intervention alone has not been shown to impact other clinical measures in these patient groups. Furthermore, the cost effectiveness of cell salvage in the context of other measures to reduce blood loss or need for transfusion has not been proven. Should health services seek to introduce cell salvage, consideration of the operating model and optimisation of other patient blood management interventions is recommended.

Executive summary

What is cell salvage?

Cell salvage, a type of autologous blood transfusion, is a patient blood management (PBM) technique which aims to reduce the requirement for allogeneic blood, i.e. blood sourced from a donor, in clinical settings where blood loss may be high. The process involves collection of the patient's own blood during the perioperative period which is then reinfused into the patient as required.

By avoiding allogeneic transfusion, the risk of infection from blood borne pathogens in donor blood is theoretically eliminated and the incidence of other adverse reactions associated with allogeneic transfusion may be mitigated. Cell salvage has been used primarily in surgery – for example, in cardiopulmonary bypass with a 'heart-lung machine', orthopaedic surgery, or in obstetric procedures.

Based on a review of the available literature, this Report aims to address the following questions:

1. What are the most appropriate clinical contexts/ patient indications for the use of perioperative cell salvage, based on the available high-level evidence, published subsequent to the NBA's guidelines on PBM?
2. Is there evidence which identifies differences in outcomes (for patients and the health system) according to whether cell salvage is carried out post-operatively or intra-operatively?
3. What are the costs of perioperative cell salvage compared to allogeneic transfusion?, and
4. What are the costs of outsourcing of perioperative cell salvage compared to the strategy of maintaining a program in a hospital (e.g. hospital-owned equipment (i.e. not leased) and 'in-house' trained personnel)?

1. Appropriate clinical contexts for cell salvage

The highest levels of evidence found (systematic reviews of RCTs) were in patients undergoing orthopaedic surgery, cardiac surgery and vascular surgery. The National Blood Authority (NBA) guidelines on PBM reported that the highest level of evidence available on the use of cell salvage was in patients receiving a total hip arthroplasty (THA) or total knee arthroplasty (TKA). A meta-analysis of the results of randomised controlled trials (RCTs) found that cell salvage was associated with no difference in post-operative haemoglobin or blood requirements when compared to no cell salvage in THA patients. In fact, the only difference noted was that cell salvage resulted in a lower rate of superficial infections.[4] In contrast, a meta-analysis reporting on TKA, found that cell salvage was associated with fewer patients requiring allogeneic transfusion, lower allogeneic transfusion volume and a

shorter duration of hospital stay compared to no cell salvage.[5] It is unclear if the small difference in hospital stay was clinically meaningful. Another meta-analysis found that cell salvage was associated with a lower likelihood of allogeneic blood transfusion, but because this analysis included THA and TKA patients combined it was not possible to compare results with the other two meta-analyses that reported on THA and TKA separately.[6] In the combined analysis of THA and TKA, there were statistically significant differences in post-operative haemoglobin, length of hospital stay and febrile reactions between the cell salvage and no cell salvage groups. The differences in hospital stay and post-operative haemoglobin were small. The Cochrane review on cell salvage included more than thirty studies on hip and knee arthroplasty, using a variety intra-operative and post-operative devices and washed and unwashed cells.[7] For all orthopaedic studies combined, it found a statistically significantly lower incidence of allogeneic transfusion and smaller volume of allogeneic blood transfused in the cell salvage group, and the reduction in incidence of allogeneic transfusion was very similar in the washed and unwashed cells groups.

The same Cochrane review also considered cardiac surgery, primarily coronary artery bypass grafting, and similarly found a statistically significantly lower incidence of allogeneic transfusion and volume of blood transfused in the cell salvage group.[7] The reduced incidence of allogeneic transfusion was greater in the washed cells group than the unwashed cells group.

For the comparison of cell salvage versus no cell salvage in the elective repair of abdominal aortic aneurysm (AAA), a meta-analysis demonstrated that cell salvage was associated with a significantly lower incidence of allogeneic blood transfusion; no other significant findings were reported.[8] The Cochrane review, conversely, found no differences in incidence of allogeneic transfusion or volume of blood transfused between the cell salvage and control groups.[7] There was some evidence that cell salvage is also associated with shorter hospital stay and lower volume requirements for allogeneic blood in patients undergoing emergency repair of ruptured AAA (based on single, low level studies included in the systematic review but that were unable to be incorporated in a meta-analysis).

The evidence for cell salvage use in liver resection was limited to one RCT that found no difference in the incidence of allogeneic blood transfusion, morbidity, mortality, length of hospital stay, or liver function test results when cell salvage and non-cell salvage groups were compared.[9]

Evidence from two systematic reviews describing several cohort, case control studies and case series indicated that cell salvage is not associated with a higher risk of cancer recurrence (in cancer surgery patients), or prostate cancer recurrence (in prostate cancer surgery patients) than the alternative of no cell salvage.[10, 11] The systematic reviews reported that the risk of cancer cells entering into the blood stream from reinfusion of salvaged blood, and associated metastasis, is minimal based on the available evidence.

A review using quasi-systematic methodology reported on the use of cell salvage in caesarean section. Results from a *small* controlled trial indicated that cell salvage is associated with significantly fewer allogeneic transfusions, significantly higher post-operative haemoglobin and significantly shorter hospital stays. No discussion of the *clinical* importance of these statistical findings was provided.[12]

2. Intra-operative versus post-operative cell salvage

The systematic reviews and meta-analyses included in this Report did not report on any comparison regarding the timing of cell salvage in patients with the same indication; it is therefore unclear as to whether intra-operative or post-operative cell salvage provide optimal performance. The Cochrane review did report on washed and unwashed cells subgroups for some indications, and found similar results for incidence of allogeneic transfusion and volume of blood transfused for the two techniques when used in orthopaedic surgery, and a greater reduction in the risk of allogeneic transfusion in the washed cells group in cardiac patients, although both groups had a statistically significantly lower incidence than the control group.[7] It should be noted that a comparison of washed versus unwashed cell salvage was not in the scope of this Report.

3. 'True' costs of cell salvage compared to allogeneic transfusion

When looking at the question of the cost of intra-operative cell salvage compared to the 'true' cost of allogeneic blood transfusion, no straightforward answer was found. Economic analyses based in the Australian health system were not found. Despite knowing the manufacturing cost of a unit of blood in Australia ($346), the 'true' cost of allogeneic blood is unknown, and the factors that need to be included when calculating a 'true' cost of cell salvage and allogeneic transfusion are not universally accepted. Indeed, the local hospital, health service and health system conditions will all impact on the 'true' cost, thus making this calculation extremely complex. Moreover, inputs to the cost are difficult to obtain due to limitations in the data available. The literature that was found showed considerable variation in both the inputs used for the costing analysis and in the results. In most cases there was a lack of detail. These results were mirrored by a large economic modelling study conducted in the UK that found a similar variation in costings. In terms of the 'true' cost of allogeneic blood transfusion - the practice that cell salvage is intended to reduce - some studies only considered the cost of a unit of packed red blood cells, others considered the entire episode of care associated with transfusion and still others modelled the short and long term risks associated with allogeneic blood transfusion. However in all of these studies no consistent answer was found. A comprehensive economic analysis using Australian data is required to properly answer the question regarding the cost-effectiveness of cell salvage, relative to allogeneic blood transfusion, in our health system.

4. Costs of outsourcing of cell salvage vs managing a program internally within a hospital

No published literature was located that could inform a comparison of outsourcing the cell salvage procedure versus hosting the service within a hospital. It is probable that any literature on this topic would be unpublished ("grey literature" such as internal government reports) and therefore difficult to source within the constraints of a rapid review of the evidence.

In conclusion, the clinical place and the associated costs of intra-operative cell salvage in the Australasian context are difficult to ascertain and complicated by: inconsistency in research findings about the effectiveness and cost of cell salvage; limitations in the data available in Australia to inform the actual use and cost of allogeneic transfusion; limitations in the data available about the number of potential cases that could utilise cell salvage and therefore its potential to reduce the need for allogeneic transfusion; and, no universally accepted components for calculating the 'true' costs associated with cell salvage and allogeneic transfusion. What is clear is that the effectiveness and cost-effectiveness of cell salvage is specific to site, health service and health system, and these individualities need to be taken into account when cell salvage is considered.

Background

Register ID

WP176

Technology name

Cell salvage as a patient blood management strategy

Patient indication

Surgical procedures in which substantial blood loss may occur.

Description of the technology

The range of equipment used in intra-operative and post-operative cell salvage is diverse; many systems are manufactured specifically for use in certain surgical contexts (e.g. CardioPAT for use in cardiac surgery with cardiopulmonary bypass[a]).[13] Modern cell salvage emerged *circa* 1970 and various modifications have occurred over time.[1]

In general, shed blood (e.g. from the site of surgery or a major penetrating trauma) is aspirated by means of a vacuum into a reservoir. The aspiration process involves the use of a double sucker tube which provides for immediate mixing with heparin, an anticoagulant. The filtered, anti-coagulated blood is then centrifuged, and heavier, denser red blood cells (RBCs) are separated to the periphery of the apparatus, while the lighter, lower density plasma floats inwards to form a supernatant. The separated red cells are then mixed with normal saline ready for reinfusion. The various devices available for cell salvage have some differences in operation; discussing all the systems is not within the scope of this document.

Company or developer

Various companies provide cell salvage systems for the intra-operative and/ or post-operative transfusion of autologous blood. Notable examples include Cellplex Pty Ltd, Fresenius Kabi Australia, Haemonetics, and Medtronic Australia.

Reason for assessment

Cell salvage has been widely researched. Numerous systematic reviews and meta-analyses have been published on the various uses of cell salvage. The National Blood Authority (NBA) has produced five Patient Blood Management (PBM) Guidelines[2] in the following areas: Critical Bleeding/Massive Transfusion, Perioperative, Medical, Critical Care and Obstetrics and Maternity. These guidelines cover a range of strategies for blood management, with the aim of enhancing and conserving the patient's own blood. Cell salvage is *one* of these strategies. The PBM guidelines are accompanied by an Intra-operative Cell Salvage guidance

[a] The equipment used in cardiopulmonary bypass is frequently referred to as a 'heart-lung' machine.

document, which includes resources to help health professionals, hospitals and patients implement the guidelines.[b] Despite the available Guidelines and implementation guidance, policy makers have questions about the appropriate patient indications for cell salvage, the timing of cell salvage and the costs associated with it.

Jurisdictional representatives of HealthPACT requested that evidence, where available, be collated and synthesised to provide additional insight into the effective implementation of cell salvage within hospital settings. In consultation with HealthPACT, the following policy questions have been addressed:

1. What are the most appropriate clinical contexts/ patient indications for the use of perioperative cell salvage, based on the available high-level evidence, published subsequent to the NBA's guidelines on PBM?
2. Is there evidence which identifies differences in outcomes (for patients and the health system) according to whether cell salvage is carried out post-operatively or intra-operatively?
3. What are the costs of perioperative cell salvage compared to allogeneic transfusion?, and
4. What are the costs of outsourcing of perioperative cell salvage compared to the strategy of maintaining a program in a hospital (e.g. hospital-owned equipment, i.e. not leased, and 'in-house' trained personnel)?

Limitations of this review

Within the overarching aims of the present Report, it is stressed that the usual limitations of horizon scanning practice and rapid review methodology apply. This Report is not a systematic review of all available evidence and is based on a limited literature search consistent with the time frame and resourcing of the review. In particular, it is not an update of the PBM guidelines associated with perioperative cell salvage. Pertinent evidence may have been missed. Evidence that was collated has not been thoroughly critically appraised to determine whether the reported findings are valid and reliable. Meta-analyses have not been updated and the cost comparison is simply indicative. Consistent with the Disclaimer on the inside front cover of this Report, the conclusions that have been presented are not a definitive statement on the safety, effectiveness or cost-effectiveness of cell salvage. The aim of this Report is to provide a high level overview of the key or emerging issues concerning cell salvage, with the scope defined by the policy questions.

[b] http://www.blood.gov.au/patient-blood-management

Stage of development in Australia

- ☐ Yet to emerge
- ☒ Established
- ☐ Experimental
- ☐ Established *but* changed indication or modification of technique
- ☐ Investigational
- ☐ Should be taken out of use
- ☐ Nearly established

Licensing, reimbursement and other approval

Several blood cell salvage systems, usually referred to as 'autotransfusion units', are listed on the Australian Register of Therapeutic Goods (ARTG) of the Australian Therapeutic Goods Administration (TGA). Examples are provided in Table 1.

Table 1 Selected cell salvage systems commercially available in Australia[14]

Product name	Licensed provider	Manufacturer	ARTG number and registration date	Medical device classification
BRAT 2	Cellplex Pty Ltd	Sorin Group Italia SRL (Italy)	120872 July 2005	IIb
CATS Plus	Fresenius Kabi Australia Pty Ltd	Fresenius Kabi AG (Germany)	127137	IIa
Cell Saver® CardioPAT® OrthoPAT®	Haemonetics Australia Pty Ltd	Haemonetics Corp (USA)	133978 December 2006	IIb
autoLog®	Medtronic Australasia Pty Ltd	Medtronic Inc (USA)	121637 August 2005	IIa

ARTG, Australian Register of Therapeutic Goods; USA, United States of America

Autotransfusion units are classified as Class IIa or IIb Medical Devices. Class IIa indicates there is a 'low-medium' risk posed to the patient, user and environment through the use of these units, while Class IIb indicates 'medium-high' risk. The classification occurs in alignment with regulations of the TGA which consider the degree of invasiveness to the human body, duration and location(s) of use and whether the device requires a source of energy other than the body or gravity.[15]

Technology type

Device/ procedure

Technology use

Therapeutic/ preventative

Patient Indication and Setting

Clinical need and associated mortality and morbidity

The transfusion of blood products comprises an indispensable part of everyday medical care. The World Health Organization (WHO) has indicated that despite continued efforts to develop and implement synthetic substitutes for human blood products (e.g. synthetic haemoglobin-based oxygen carriers[16]), their regular use in clinical care remains some years in the future. At present, the success of standard medical practice relies heavily on access to safe blood or blood products in a timely manner for the treatment of anaemia secondary to substantial blood loss from surgery and trauma, malignant blood diseases, non-blood cancers, and non-malignant blood diseases such as aplastic anaemia, thalassaemia, sickle cell anaemia and haemophilia.[16, 17]

Australia commonly employs the transfusion of blood products to sustain advanced medical procedures including trauma management, cardiovascular surgery, neurosurgery, transplantation, and care of premature infants. Indications for different blood components vary: red blood cells (RBCs) are particularly important for the treatment of haemorrhagic trauma victims and surgical patients, and in Australia it is in elective surgical patient groups that cell salvage is of the most relevance. In cell salvage other blood components, such as platelets and plasma[c], are discarded in the processing and the RBCs are retained for reinfusion. Cell salvage can therefore reduce the need for transfusion of RBCs, but cannot be used to replace plasma and platelets.[17, 18]

The NBA is the primary repository for data on the volume and type of blood product issued each year in Australia. In 2013-14, approximately 700,000 units of RBC were issued in Australia for use in transfusions, with the number of units declining over recent years due to improvements in appropriate usage and reductions in waste.[19] In New Zealand, over 100,00 units of RBC were transfused in 2013, also a decline from previous years.[20]

In Australia and New Zealand pressure on the blood supply is particularly influenced by the ageing population, with the majority of transfusion procedures occurring in patients aged over 50 years. This is reflected in the transfusion data for red cells and for other blood products, with nearly half of all RBC transfusions in Australia occurring in people aged 65-84 years.[21]

The trend of increasing blood product consumption associated with increasing age in the developed world has prompted international research in the area of blood supply.

[c] Platelets have primary applications in the treatment of leukaemia and other cancers and to treat bleeding/ coagulation disorders; plasma is often used in patients who have sustained burns or shock; and cryoprecipitate is pivotal in the treatment of haemophilia and other blood disorders.

Investigators in Finland have used data on RBC usage from thirteen developed countries, including Australia, to model changes in blood supply and demand between 2010 and 2050. These simulations suggest that the number of units of RBCs consumed per 1,000 population could rise by as much as ten units over the next ten years. While such estimates indicate that the demand for blood in Australia is likely to increase further in the future, the magnitude of this increase should be interpreted with some caution as these figures are based on the age-distributed variation in RBC consumption in Finland between 2002 and 2006.[22]

In the Netherlands Borkent-Raven et al developed two models to forecast national demand for RBCs.[23] The first model, based on age and sex predicted a 23 per cent increase in the consumption of red cells from 2008 to 2015. The second model incorporated the age and sex variables as well as clinical RBC use, which resulted in the prediction of an eight per cent *decrease* over the same period.

When the changing clinical use of RBC is assessed, some authors have reported decreases in RBC use. Tinegate et al used surveys to follow the changing patterns of RBC use in 1999, 2004 and 2009 in Northern England.[24] Between 1999 and 2009, they found that the mean age of patients transfused with RBCs increased from 62.7 years to 63.2 years, but that there was a reduction in the overall RBC transfusion rate over this period, down from 45.5 units to 36 units per 100,000 population. From 1999 to 2008, the authors reported the surgical use of RBCs dropped significantly from 41 to 29 per cent among recipients aged 50 to 80 years. In contrast, medical use of RBCs did not change significantly between 1999 and 2008. It was found that the most common medical use of RBCs was haematology, accounting for 28 per cent of all RBCs transfused during 2009.

The NBA reported on an Australian RBC linkage program which audited red cell use within the South Australian public hospital system. During the period from 2008-2009 to 2010-2011, the program found that the surgical use of RBCs decreased and the issue of RBCs per 1000 population decreased slightly. The most common medical indication for RBC was haematology. Consistent with the findings of Tinegate et al, haematology was found to account for one quarter of total red cell use.[24]

Based on the findings of these studies, it is likely that although demand for red blood cells is decreasing, due to improved patient blood management strategies, the impact of population ageing will be a key driver in increasing demand for RBC in Australia and New Zealand.

Pre-operative autologous blood donation (PAD) prior to elective surgery has been suggested as one measure to reduce allogeneic transfusion-related risks; however the routine use of PAD is not recommended in the PBM guidelines.[2] In addition, PAD is not viewed as a cost-effective practice as patients may donate many units of blood (500 mL or one unit of blood twice a week, up until 72 hours before surgery), much of which will not be used.[25]

In Australia, the residual risk of transfusion transmitted infection (TTI) subsequent to donor screening, testing and processing of blood products is low. The 2013 Australian Haemovigilance Report provides estimates of the residual risk of contracting HIV (<1/1,000,000) hepatitis C (HCV, <1/1,000,000), hepatitis B (HBV, ~1/764,000), human T-lymphotrophic virus (HTLV, <1/1,000,000) and malaria (<1/1,000,000).[21] The National Haemovigilance Program reports on the actual incidence of four different TTI categories – bacterial, viral, parasitic and 'other' (e.g. variant Creutzfeldt-Jakob disease). However, no TTIs from viruses have been reported through routine screening in recent years. Most TTIs that occur are usually a result of bacterial contamination, for which the estimated residual risk is slightly higher than for viral infections. During 2008-2011 there were a total of 32 TTIs reported in Australia, all of which were considered to be due to bacterial infections, but not necessarily confirmed. There were no reports of any TTI resulting from viral or parasitic contamination. Overall, there was an increase in TTI reports from three in 2008-2009 to 18 in 2009-10 and a decrease to eleven in 2010-2011; there were two cases of TTI that were considered to be life threatening in severity.[21]

In New Zealand, estimates of residual TTI risk have not been updated since 2010. These estimates are based on data from 1.3 million donations over the preceding nine years, with residual risk estimates of 3.4/1,000,000 for HBV, and <1/1,000,000 for HCV, HIV and HTLV.[26]

During 2009, there were two occurrences of TTI reported in New Zealand and these were ascribed to bacterial contamination of pooled platelet concentrate and resuspended red cells. The clinical severity of these TTIs was unreported.[26] The most recent New Zealand Haemovigilance annual report, published in 2013,[20] did not provide data on the occurrence of TTI among recipients of blood products. Without additional data, a viable estimate of residual risk cannot be calculated for 2013.

In addition of the risk of TTI, allogeneic blood transfusion is associated with a number of non-infectious adverse events that may be reduced if patients can be alternatively managed by reinfusion of salvaged blood, i.e. avoiding allogeneic sources altogether. Recent Australian data on *all* adverse events following transfusion of allogeneic blood products during 2010-2011 and for the entire period of haemovigilance reporting in Australia are provided in Table 2. Also shown is the risk of each event occurring per unit transfused. Additional NBA data suggest that adverse events related to transfusion remain largely under-reported.[21]

Table 2 Transfusion related adverse events 2010-2011 and for all years in which haemovigilance reports have been published, Australia[21]

Event type	2010-2011	All reports		Risk per unit transfused
		Number	Per cent	
FNHTR, n	321	633	52.4	0.1-1% of transfusions with universal leucocyte depletion*
Severe allergic reaction, n	142	313	25.9	NR
IBCT, n	30	75	6.2	NR
Anaphylactoid/ anaphylactic reaction, n	33	53	4.4	1 in 20,000 to 1 in 50,000
TACO, n	24	42	3.5	Up to 1% of patients receiving transfusions
DHTR, n	10	22	1.8	1 in 2,500 to 1 in 11,000
TTI, n	11	32	2.7	Rare
AHTR, n	2	15	1.2	1 in 76,000
TRALI, n	8	19	1.6	1 in 1,200 to 1 in 190,000
PTP, n	1	3	0.2	Rare
Total, n	582	1207	100	NA

AHTR, acute haemolytic transfusion reaction; DHTR, delayed haemolytic transfusion reaction; FNHTR, febrile non-haemolytic transfusion reaction; IBCT, incorrect blood component transfused; NA, not applicable; NR, not reported; PTP, post-transfusion purpura; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; TTI, transfusion transmitted infection; UCT, unclassifiable complication of transfusion.

*Leucocyte depletion refers to the removal of white cells from the blood to negligible levels.

New Zealand data summarising non-infectious adverse events associated with allogeneic transfusion during 2013 are provided in Table 3.[20]

Table 3 Transfusion related adverse events (non-infectious) 2013 by event type and imputability score, New Zealand[20]

Event type	Imputability score*					
	1	2	3	4	5	Total
FNHTR, n	30	20	149	45	1	195
Allergic, n	-	1	52	61	4	117
UCT, n	5	12	22	7	-	29
TAD, n	1	1	23	3	-	26
IBCT, n	-	-	-	1	23	24
TACO, n	-	-	6	8	2	16
DSTR, n	-	-	2	4	6	12
Near miss, n	-	-	-	-	11	11
Hypotension, n	-	-	1	1	-	2
DHTR, n	-	-	-	-	2	2
AHTR, n	-	-	-	1	-	1
TRALI, n	-	-	-	1	-	1
Total, n (%)	*37 (7.3)*	*34 (6.7)*	*255 (50.3)*	*132 (26.0)*	*49 (9.7)*	*507 (100)*

AHTR, acute haemolytic transfusion reaction; DHTR, delayed haemolytic transfusion reaction; DSTR, delayed serologic transfusion reaction; FNHTR, febrile non-haemolytic transfusion reaction; IBCT, incorrect blood component transfused; TACO, transfusion-associated circulatory overload; TAD, transfusion-associated dyspnoea; TRALI, transfusion-related acute lung injury; UCT, unclassifiable complication of transfusion.

* 1 = Excluded, i.e. there is conclusive evidence beyond reasonable doubt for attributing the event to alternative causes; 2 = Unlikely, i.e. there is evidence clearly in favour of attributing the event to causes other than transfusion; 3 = Possible, i.e. when the evidence is indeterminate for attributing the event either to the transfusion or alternative causes; 4 = Likely, probable, i.e. when the evidence is clearly in favour of attributing the even to the transfusion; 5 = Certain, i.e. when there is conclusive evidence beyond reasonable doubt for attributing the event to the transfusion.

Specialty

Various specialties, usually surgical, potentially including but not limited to cardio-thoracic, vascular, orthopaedic, hepatobiliary, oncological, trauma and emergency, obstetric and paediatric surgery; also anaesthetists, perfusionists, nursing staff.

Technology setting

General and specialist hospitals.

Impact

Alternative and/or complementary technology

Cell salvage is intended to reduce the need for allogeneic blood transfusion, but cannot be considered purely as a substitution technology. Even as part of a well-managed PBM program, cell salvage remains as a complementary technology and appears unlikely to eliminate the requirement for allogeneic blood in the foreseeable future.

Current technology

Allogeneic transfusion is currently the mainstay for patients requiring blood products in Australia; however, some centres (see below; *Diffusion of technology in Australia*, page 9) have incorporated cell salvage into their PBM programs. According to expert clinical advice, use of pre-operative autologous donation as an alternative to allogeneic blood is an increasingly diminishing practice.[d] Holmberg and Whitaker explain that advancements in surgical techniques, as well as the waste associated with pre-operative autologous donation, have led to the practice falling out of favour.[25]

Diffusion of technology in Australia

Clinical expert advice was sought regarding the level of diffusion of cell salvage throughout the healthcare system in Australia but was not informative. Jurisdictional feedback indicated that cell salvage is widely diffused in Australia. A brief internet search revealed some examples of services in which cell salvage occurs: the Royal Adelaide Hospital, South Australia with the assistance of a trained anaesthetic nurse[27]; cell salvage equipment has been donated to the Gold Coast Hospital, Queensland[28]; the Royal Children's Hospital Melbourne, Victoria provides online instructional and policy material relating to institutional use of cell salvage[29]; and cell salvage guidance has been established for the Princess Margaret Hospital and King Edward Memorial Hospital, Perth, Western Australia.[30, 31] Difficulty in assessing the current usage of cell salvage, among other forms of patient blood management, is highlighted by the NBA who acknowledge

> *"a significant amount of data and information exists within the Blood Sector, however, the extent to which this data is currently available to the parties that need it, the quality of the data, and the capacity of the systems that hold it, varies widely.*

[d] Personal communication (27 January 2015) with specialist anaesthetist and senior clinical lecturer in acute care medicine. The clinician's advice was that pre-operative autologous donation occurs in very select cases, e.g. in certain patients with particular antibody profiles.

The majority of data/information is held either in supplier's systems or hospital systems".[32]

Cost infrastructure and economic consequences

A diverse literature was identified which included comparisons of costs and cost effectiveness analyses (economic evaluations). Given these findings, it was considered sensible to provide a separate discussion of all the literature identified that reported on costs. For this discussion, see Economic evaluation, page 26.

Training and accreditation

Training on the medical aspects of cell salvage is included in a ten week autotransfusion course offered by the Australasian Board of Cardiovascular Perfusion. The course is available to all staff currently employed in public and private healthcare. There is no course fee for members of the Australian and New Zealand College of Perfusionists, although a fee of $250 applies for non-members.[33] Training in the use of the particular model of cell salvage device is also required for proficiency in the technique.

Ethical, cultural, access or religious considerations

Religious considerations

In the literature examined, no specific issues were identified, other than consideration of patients of Jehovah's Witness faith. Cell salvage technology is seen as particularly attractive/ useful within the context of surgery for these patients, and for others that refuse blood for religious or other reasons. Usually, Jehovah's Witnesses do not accept transfusion of any blood products; but they may accept perioperative autologous blood if given that option.[34, 35] The availability of cell salvage can provide these patients and their treating clinicians with additional clinical options when blood transfusion is medically indicated.

There are another two ethical considerations that are notable with respect to the use of cell salvage: informed consent and access.

Informed consent

No literature on the issue of informed consent for reinfusion of autologous blood was identified; however, it is assumed that the consenting process would not be dissimilar to that applied to allogeneic blood transfusion. The ICS guidance has a patient information leaflet attached for use in hospitals.[3]

Informed consent provisions should allow patients to expect, and have full confidence, that transfusion of any blood product (allogeneic or autologous) is as safe as possible and available when required. Indeed, the governments of Australia and New Zealand have a moral and legal imperative to ensure the safe supply of blood products.

Access/ blood supply considerations

No obvious access issues associated with the use of cell salvage and reinfusion of autologous blood were identified. Allogeneic blood is currently donated, collected and processed in numerous city and regional Red Cross Blood banks and then distributed, via a cold chain, to public and private hospitals throughout Australia according to need. The use of cell salvage technology avoids this distribution process. The current availability of cell salvage is not known (due to deficiencies in national data collection, as described previously); however, cell salvage equipment is currently only likely to be available (with access to a trained workforce) in locations where elective surgery likely to result in substantial blood loss is undertaken. By comparison, allogeneic blood is more widely and readily available.

Cell salvage as part of a PBM strategy may also represent a means to partially mitigate demand for RBC by helping to decrease the volume of allogeneic blood transfused per patient.[36] The Australian and New Zealand governments have an obligation to supply sufficient blood products to meet demand; however, shortfalls in supply have been recognised in the past.[37] The WHO recommends a donation rate of 50 donated units per 1,000, with Australia currently collecting 48.5 donations per 1,000 population. As noted earlier, while cell salvage may be well positioned to reduce allogeneic RBC usage, at this stage it cannot be used to reduce requirements for plasma or other blood components.

Evidence and Policy

Safety and effectiveness

The safety and effectiveness of cell salvage in particular clinical contexts is discussed with reference to evidence published since the NBA's development of the PBM guidelines.

The available literature comprises nine systematic reviews/ meta-analyses on the use of cell salvage. It is not the intention of this report to update the systematic review that formed the background for the PBM guidelines; rather, this report focussed on the safety and effectiveness of perioperative cell salvage in the specific patient and clinical indications in which it has been studied. The report did not consider differences in washed or unwashed auto-transfusion as this was not within scope.

Scoping searches revealed that a large body of literature on the use of cell salvage has been published since the NBA guidelines were released, and therefore, only *systematic reviews and meta-analyses* which have subsequently emerged are included in this Report.[e] The characteristics of the studies reporting results on the use of cell salvage are shown in Appendix A, page 41.

Key research question: 1. What are the most appropriate clinical contexts/ patient indications for the use of cell salvage, based on the available high-level evidence, published subsequent to the NBA's guidelines on PBM?

Summary:

High level evidence was found for cell salvage in orthopaedic surgery, cardiac and vascular surgery, with limited other evidence identified for liver resection, cancer-related surgery and caesarean section.

Level 1 evidence reported by Carless and colleagues found cell salvage to be associated with a reduced incidence of allogeneic transfusion and a reduced volume of allogeneic blood transfused in patients undergoing THA or TKA.[7] Another systematic review reported by Li and colleagues[4] suggested that cell salvage is associated with a lower rate of superficial infections compared to no cell salvage in THA patients. In TKA patients, Markar and colleagues[5] reported level 1 evidence indicating that cell salvage is associated with fewer patients requiring allogeneic blood transfusion and lower allogeneic transfusion volume. Shorter duration of hospital stay was also reported in the cell salvage group, but the clinical significance of this result is uncertain. Zhao et al reported level 1 evidence on THA and TKA patients combined, and found that cell salvage was associated with a significantly shorter length of hospital stay, higher post-operative haemoglobin concentration, and reduced risk of febrile reactions in the cell salvage group compared to the no salvage group. The differences in length of hospital stay and post-operative haemoglobin were small.

[e] It was initially considered to limit the Report to level 1 evidence (i.e. systematic reviews or meta-analyses of randomised controlled trials); however, on the basis of capturing evidence on the use of cell salvage in more novel clinical settings in which trials may not (yet) be possible, it was decided to include systematic reviews or meta-analysis of any study design.

For the comparison of cell salvage versus no cell salvage in the elective repair of AAA, one review found evidence to suggest that cell salvage is associated with a significantly lower incidence of allogeneic blood transfusion; however another found no differences in incidence of transfusion or volume of blood transfused.[7, 8] Low level evidence suggests that cell salvage may be associated with shorter hospital stay and lower volume requirements for allogeneic blood in patients undergoing emergency repair of ruptured AAA.[38]

The evidence for cell salvage use in liver resection (Gurusamy et al[9]) reported no differences in a comparison of cell salvage to no cell salvage.

A mix of low to medium level evidence (Kumar et al[10]; Waters et al[11]) suggested that cell salvage is not associated with a higher risk of cancer recurrence, or prostate cancer recurrence compared to no cell salvage, in patients undergoing any cancer surgery and prostate cancer surgery, respectively. Rates of survival are equivalent. For any cancer considered (gynaecological, hepatobiliary, gastrointestinal and urological), the use of cell salvage was associated with reduction in the requirement for allogeneic blood compared to no cell salvage.

There is limited evidence (see Dhariwal et al[12]) to suggest that cell salvage is associated with significantly fewer allogeneic transfusions, significantly higher post-operative haemoglobin and significantly shorter hospital stay for women who have undergone caesarean section. The clinical significance of the findings is uncertain.

The identified evidence included comparisons between cell salvage and no cell salvage in the following clinical indications, listed according to level of evidence, from highest to lowest:

A. Orthopaedic surgery: THA and/ or TKA; four meta-analyses of RCTs, of which two meta-analysis reported only combined outcomes for THA and TKA patients,[6, 7] one reported outcomes for TKA patients[5] and one on outcomes for THA patients.[4]

B. Cardiac surgery: one systematic review on a range of cardiac procedures including coronary artery bypass grafting, valve replacement and repair, myocardial revascularisation and non-specified cardiac surgery.[7]

C. Elective and emergency repair of AAA: three systematic reviews, two on elective and emergency repair of ruptured AAA,[7, 8] for which some meta-analyses were presented; the remaining systematic review on emergency repair only did not present any meta-analysis. [38]

D. Liver resection: one Cochrane systematic review presented[9] outcomes for a number of studies that investigated several blood saving interventions; among these one RCT reported on cell salvage.

E. Cancer surgery: two systematic reviews, of which one included a meta-analysis of several cohort and case control studies[11] and one qualitatively summarised the results of cohort and case control studies and case series.[10]

F. Caesarean section: one quasi-systematic review, including outcomes from case series and a small controlled trial.[12]

These results of these studies are discussed below according to clinical indication. The primary source of data for the recommendations for intra-operative cell salvage in the Perioperative module of the NBA's Patient Blood Management Guidelines was the Cochrane systematic review conducted by Carless and colleagues (2006).[39] This review has since been updated (2010) and where it reported on separate clinical indications, the results are discussed below.[7] There is some overlap in the included studies in the reviews presented, however the meta analyses included different primary studies and so all relevant results have been presented.

It was found that there was considerable overlap of studies included in the NBA guidelines on TKA and THA and those included in the meta-analyses published subsequent to the guidelines.[6] The systematic review by Zhao and colleagues[6] conducted meta-analyses on the use of autologous blood transfusion (ABT) drainage compared to standard drainage (i.e. without reinfusion of blood) across six RCTs in which patients underwent TKA or THA. The authors reported on incidence of allogeneic transfusion, post-operative haemoglobin concentration, incidence of infection, incidence of febrile reactions and length of hospital stay. Overlap with the findings presented in the meta-analyses considered by the NBA was excluded for the outcomes of post-operative haemoglobin concentration, incidence of infection, incidence of febrile reactions and hospital stay. The results of the newer meta-analyses[6] concerning these outcomes on the use of cell salvage in TKA and THA patients has therefore been discussed immediately below. However, where evidence was identified that would not supplement the evidence base presented in the NBA guidelines it has not been reproduced in this Report.

A. Orthopaedic surgery: Knee and hip arthroplasty

Four identified meta-analyses[4-7] reported on the effects of cell salvage in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). Carless and colleagues included studies of TKA and THA which used a variety of intra-operative and post-operative cell salvage devices.[7] The study by Li and colleagues[4] compared outcomes between cell salvage by ABT drainage and no drainage or closed-suction drainage for patients undergoing primary THA. Similarly, Markar et al[5] compared cell salvage by post-operative ABT drainage and suction drainage in TKA patients. Zhao et al[6] compared cell salvage by ABT drainage to standard drainage without reinfusion of autologous blood in patients undergoing either TKA or THA. There was substantial overlap of the studies included in Zhao et al.'s meta-analysis with those included in the NBA guidance.

Results of these meta-analyses are discussed below according to patient-relevant outcomes: incidence and volume of allogeneic blood transfusion; post-operative haemoglobin level/ change in haemoglobin level; morbidity; mortality; and length of hospital stay.

Incidence and volume of allogeneic transfusion

The systematic review by Carless et al included 32 trials of TKA or THA, with either intra-operative cell salvage, post-operative cell salvage or both, that reported on the incidence of allogeneic transfusion.[7] The comparators for these studies were control (no patient blood conservation measures) and active control (blood conservation measures other than cell salvage); the cell salvage group also received control blood conservation measures. Meta-analysis of all 32 studies found a statistically significant reduction in the incidence of allogeneic transfusion in the group randomised to cell salvage (RR: 0.46, 95% CI 0.37, 0.57), and a statistically significant reduction in the volume of allogeneic blood transfused (MD= -0.81, 95% CI -1.22, -0.39). The difference in incidence was also found when the comparator was a control group (RR: 0.45, 95% CI 0.34, 0.60, k=21) or an active control group (RR: 0.46, 95%CI 0.33, 0.65, k=11). Likewise, with a control group the volume of allogeneic blood transfused was less in the cell salvage group (MD=-0.82, 95% CI -1.36, -0.27, k=7) and also with an active control group (MD= -1.10, 95% CI -1.91, -0.29, k=2). Within these orthopaedic trials, there was little difference in the incidence of allogeneic transfusion between washed (RR: 0.48, 95% CI 0.38, 0.64, k=10) and unwashed cell salvage (RR: 0.47, 95% CI 0.36, 0.63, k=22).

The systematic review by Li et al[4] reported on one RCT (out of 12 included RCTs) for which data on the incidence of allogeneic blood transfusion were available. Li et al independently calculated an odds ratio comparing the rate of allogeneic transfusion in the group of THA patients that received cell salvage (by "ABT drainage") and the group of THA patients that did not ("closed-suction" drainage and no drainage groups). No significant difference was observed for the comparison of ABT versus no drainage (OR: 4.33, 95% CI 0.46, 40.61), nor for the comparison of ABT versus closed-suction drainage (OR: 4.33, 95% CI 0.46, 40.61).

Given that only five allogeneic transfusions occurred (1/40 patients in the cell salvage group and 4/40 patients in both non-cell salvage groups, i.e. no drainage and closed-suction drainage), it is appears likely that this RCT was underpowered to detect any difference between the groups.

In a meta-analysis of all eight RCTs included by Markar and others[5] cell salvage using ABT drainage resulted in significantly fewer patients requiring allogeneic transfusion compared to suction drainage without cell salvage (OR_p: 0.36, 95% CI 0.15, 0.85; p=0.02). Cochran's Q test indicated significant statistical heterogeneity (Q=31.69). In addition, on average the number of allogeneic blood units transfused per patient was nearly one unit less for the ABT group than for the suction drainage only group (mean difference, MD_p=-0.84, 95% CI -1.13, -0.56; p<0.001). This meta-analysis showed no significant statistical heterogeneity (Q=1.93).

Post-operative haemoglobin level/ change in haemoglobin level

Of the twelve RCTs included in the systematic review by Li et al[4], three were included in a meta-analysis comparing post-operative haemoglobin concentration (g/dL) between THA patients undergoing cell salvage (by "ABT drainage") and those that did not. No significant difference was found for ABT versus no drainage (MD_p=-0.14, 95% CI -0.32, 0.03)(heterogeneity: I^2=0%), nor for ABT versus closed-suction drainage (MD_p=-0.04, 95% CI -0.22, 0.13)(heterogeneity: I^2=33%).

The pooled analyses presented by Markar et al[5] included three RCTs comparing cell salvage TKA patients with non-cell salvage patients and found that haemoglobin levels at post-operative day 57 were equivocal.

Of the six RCTs included in the systematic review by Zhao et al[6], four were pooled in a meta-analysis which compared haemoglobin levels across post-operative days 1-7 in THA and TKA patients randomised to either cell salvage or no cell salvage. The meta-analysis showed a small but statistically significant difference, favouring cell salvage. However, on any post-operative day (from 1-7), haemoglobin concentration was between 9.7 g/dL and 11.4 g/dL for the ABT group and between 9.6 g/dL and10.8 g/dL for the standard drainage group who did not receive cell salvage. Based on currently available guidance, none of these values correspond to a haemoglobin level that alone would indicate a trigger for the transfusion of allogeneic blood.[2, 40, 41]

Morbidity

Carless et al reported on a number of morbidity indicators in their review however did not report the different patient indications separately.[7]

Li and colleagues reported on post-operative haematoma, post-operative pain score, and the rate of post-operative complications in THA patients - including superficial infections, deep infections, surgical revision, persistent drainage, deep vein thrombosis (DVT), pulmonary embolism (PE), trochanteric fracture and wound healing.[4] With the exception of

superficial infections, no differences in outcomes were observed between patients who received cell salvage and those who did not. The rate of superficial infections in the ABT group was found to be four times higher than either non-cell salvage group, i.e. no drainage group and the closed-suction group ($p<0.01$).

The systematic review by Markar and others reported on post-operative wound infection and DVT among TKA patients randomised to either cell salvage or no cell salvage.[5] No significant differences between the groups were observed.

Zhao et al reported on the incidence of infection and febrile reactions in TKA and THA patients undergoing their procedure with the use of cell salvage or without any cell salvage.[6] No differences in infection rate were observed based on a meta-analysis of four RCTs (RR: 1.09, 95% CI 0.54, 2.21, p=0.80). The meta-analysis which compared the rate of febrile reactions, also including four RCTs, did find a difference, but with considerable uncertainty regarding the magnitude of the reduction in febrile reactions associated with cell salvage(RR: 0.66, 95% CI 0.44, 0.98, p=0.02).

Mortality

Two RCTs which reported on post-operative mortality in THA patients were included by Li et al, with five deaths in the closed suction group and none in the other groups.[4]

Length of hospital stay

In the comparison of cell salvage versus no cell salvage in THA patients, Li and colleagues found no substantive difference in the length of hospital stay for cell salvage when compared to no drainage (MD=-0.24, 95% CI -0.85, 0.38) or closed-suction drainage (MD= 0.47, 95% CI -0.61, 1.55).

Markar et al[5] found that the use of ABT drainage cell salvage resulted in shorter duration of hospital stay compared to no drainage, i.e. no cell salvage, but the reduction by a ¼ of a day was very small (MD_p=-0.25, 95% CI -0.48, -0.01; p=0.04; Cochran Q=3.9).

Three RCTs were included in the meta-analysis presented by Zhao and colleagues,[6] comparing the length of hospital stay in TKA or THA patients who had their surgery either with or without cell salvage. A small, statistically significant difference was also observed (MD= -0.79, 95% CI -1.54, -0.05).

B. Cardiac surgery

One systematic review considered cell salvage in patients undergoing a variety of cardiac procedures, mostly coronary artery bypass grafting, but also valve replacement and repair, myocardial revascularisation and unspecified cardiac surgery.[7] The studies in this meta-analysis were dated from 1979 through to 2008, and the authors reported statistical heterogeneity in the analyses. Overall, a benefit for cell salvage on the incidence of allogeneic blood transfusion was found (RR: 0.77, 95% CI 0.69, 0.86, k=31). There was also a decrease in volume of allogeneic blood transfused in the cell salvage group (MD: -0.67, 95% CI -0.89, -0.44, k=19). The authors also considered incidence of allogeneic transfusion in washed versus unwashed cell salvage in cardiac patients, and found the reduction in incidence was greater in patients receiving washed cells (RR: 0.66, 95% CI 0.55, 0.80, k=13) than unwashed cells (RR: 0.85, 95% CI 0.76, 0.95, k=18).

C. Abdominal aortic aneurysm repair

Three systematic reviews reported on the effects of cell salvage in patients requiring abdominal aortic aneurysm (AAA) repair.[7, 8, 38] Shantikumar et al reported on both elective and emergency repairs, while Tavare et al and Carless et al reported only on elective AAA repair.

The study by Shantikumar and colleagues[8] compared outcomes across 23 studies for patients who received either: (a) cell salvage with or without acute normovolaemic haemodilution (ANH) and/ or pre-deposited autologous blood; or (b) no cell salvage (the control group). Of the 23 studies included in the systematic review, 17 reported on the comparison between a cell salvage group without ANH or pre-deposited autologous blood and a control group; only these studies are considered in this Report.

The review by Carless et al included five RCTs of patients undergoing elective AAA repair, and in all studies intra-operative cell salvage was compared to a control group that did not receive cell salvage.[7]

Tavare et al[38] conducted a systematic review of cell salvage performed in elective AAA, but did not meta-analyse the results. Eight of the 10 studies included in the systematic review reported on the comparison of cell salvage versus no cell salvage and are relevant to this Report; two studies included by Tavare et al are not considered here as they included the use of ANH in addition to cell salvage. Of these eight studies, only one, a case series by Kalra and colleagues[42] was not captured in the Shantikumar review[8]. Kalra reported only on biochemical markers of post-operative renal and liver function, with no results indicating a clinical benefit from cell salvage. The results of Tavare et al[38] are therefore not further discussed.

Relevant outcomes reported in available studies comparing cell salvage with no cell salvage for the patient indication of AAA include: incidence of and volume of allogeneic blood transfusion; mortality; and length of hospital/ ICU stay.

Incidence and volume of allogeneic blood transfusion

Of the 17 relevant studies included in the review by Shantikumar et al[8], eight controlled trials (of which three were randomised) were included in a meta-analysis comparing the number of elective AAA repair patients who received allogeneic transfusions according to the use of cell salvage. The pooled relative risk (RR_p=0.61, 95% CI 0.44, 0.84) indicated that significantly fewer patients in the cell salvage group were transfused with allogeneic blood components (p=0.002). Five of the studies included in the review (all non-randomised) reported on the use of cell salvage versus no cell salvage in the emergency repair of ruptured AAAs,[43-47] but the study authors reported that these could not be included in a meta-analysis. Of these studies, three[43-45] reported that the volume of allogeneic blood products (RBCs and/ or fresh-frozen plasma) used was significantly lower in the cell salvage

group, and one[47] reported that the mean number of allogeneic transfusions was significantly lower in the cell salvage group.[f] The available data are shown in Table 4.

The Carless study found no statistically significant difference between the incidence of allogeneic transfusion in the cell salvage and control groups (RR: 0.63, 95% CI 0.34, 1.15, k=4) nor in the volume of blood transfused (MD: 0.02, 95% CI -0.34, 0.38, k=3).[7] All of the included studies used washed cells.

Table 4 Allogeneic blood requirements for cell salvage versus no cell salvage in emergency AAA repair[8]

	Mean units of allogeneic blood product, RBCs/ FFP		p (between group comparison), RBCs/ FFP
Study	Cell salvage group	No cell salvage group	
Markovic 2009	NR	NR	NR but reported to be "significant"
Posacioglu 2002	3.6/ 1.5	5.8/ 4.5	0.03/ 0.01
Serracino-Inglott 2005	4/ NR	7/ NR	<0.01/ NR
Tawfick 2008	6/ NR	12/ NR	NR/ NS

FFP, fresh frozen plasma; NR, not reported; NS, not significant; RBC, red blood cell

Length of hospital/ ICU stay

One study (case-control) included by Shantikumar et al[8] (see Posacioglu et al[44]) reported a shorter duration of hospital stay in the cell salvage group (no data provided). Similarly, a case-control study by Tawfick and others[47] reported a shorter duration of hospital *and* ICU stay in the cell salvage group (no data).

Mortality

A case-control study[44] included in the systematic review by Shantikumar et al[8] compared mortality outcomes in emergency AAA repair patients who either did or did not receive cell salvage. No difference in the number of deaths was observed (no data).

Another study included in the Shantikumar review[8] (Serracino-Inglott et al[45]) reported increased survival in the cell salvage group compared to the no salvage group (76% vs 56%) despite no difference in post-operative complications between the groups but the analysis excluded patients who died in theatre.

[f] For the purposes of this Report, it is assumed that the results presented in the systematic review by Shantikumar et al (2011) are accurate and complete. The full text of the individual studies were not retrieved in consideration of the *a priori* decision to limit the evidence to systematic reviews and meta-analyses of any study design as opposed to extracting results presented in individual low level studies.

D. Liver resection

A Cochrane review by Gurusamy et al[9] presented the results of cardiopulmonary interventions to reduce blood loss/ transfusion in the setting of liver resection. Of the ten RCTs included in this systematic review and meta-analysis, only one[48] was considered relevant to this Report. Despite conflicting reporting by Gurusamy et al[9] and the authors of the original study[48] regarding the nature of the study intervention, it has been assumed that the relevant comparison was cell salvage versus no cell salvage[g] Reported relevant outcomes were incidence of allogeneic blood transfusion; morbidity; mortality; length of hospital stay and liver function test results. There were no differences between the cell salvage group and no cell salvage group with respect to any of these outcomes.[9]

[g] The intervention for this study was described as "pre-operative autologous blood donation" in Gurasamy et al 2012. However, the original trial (Hashimoto et al 2007) reported that "intra-operative blood salvage" was the intervention and suggested that pre-deposited autologous blood donation had occurred among some patients (a confounding factor that was claimed to have been adjusted for in the analysis).

E. Cancer surgery

Two systematic reviews reported on the use of cell salvage in cancer surgery; one included a review of 23 studies (including prospective and retrospective cohort studies and case series) without meta-analysis[10] and the other[11] reviewed 11 studies (cohort studies and case control studies) of which 10 were able to be included in a meta-analysis of overall cancer recurrence. Of these 10 studies, five reported on the use of cell salvage in prostate cancer surgery, and were included in a meta-analysis of prostate cancer recurrence. The reported relevant outcomes were allogeneic blood requirements, morbidity (including rates of tumour recurrence, metastasis and post-operative complications), and survival.

Allogeneic blood requirements

No data were reported on allogeneic blood requirements among patients undergoing cancer surgery. Based on two cohort studies included in the review by Kumar and colleagues[10], it was reported that compared to no cell salvage, intra-operative cell salvage reduces the need for allogeneic blood in patients undergoing surgery for gynaecological cancer patients (no data were reported in the review). In the same review, there were five relevant studies (mix of cohort studies and case series) included on the use of intra-operative cell salvage in surgery for cancers of the hepatobiliary system. The review reported that for this clinical indication, cell salvage reduces allogeneic blood requirements, but it is unclear which of the five studies reported this finding. One prospective cohort study in gastrointestinal cancer patients also found intra-operative cell salvage was associated with lower requirements for allogeneic blood compared to no cell salvage.

Morbidity

Rates of metastasis and post-operative complications were not reported by Kumar et al.[10] However, evidence from 16 studies (case series and cohort studies) included on surgery in patients with hepatobiliary, gastrointestinal and urological cancer suggested equivalent tumour recurrence rates for cell salvage and non-cell salvage groups.

The review by Waters et al[11] indicated that the recurrence of cancer of any type following the use of cell salvage was similar to cancer recurrence where no cell salvage was used (the odds ratio slightly favoured the cell salvage group, i.e. slightly lower likelihood of recurrence; $p<0.04$), suggesting the risk of metastases from reinfusion of cancer cells in salvaged blood collected during oncology surgery is low. This finding was based on a meta-analysis of 10 studies of mixed levels of evidence and so there is a risk of bias. Results for the analysis of prostate cancer recurrence were based on a meta-analysis of five studies of mixed levels of evidence and were found to be equivocal (no significant difference).

Survival

In the review by Kumar et al[10], one included prospective cohort study reported equivalent cumulative survival for cell salvage and non-cell salvage groups undergoing surgery for

hepatocellular carcinoma; of the 14 studies of patients undergoing urological cancer surgery, none found any differences in short or long-term biochemical survival.

F. Caesarean section

One quasi-systematic review by Dhariwal et al[12] reported on six studies that investigated the use of cell salvage with or without comparison to a control group. Relevant outcomes included incidence of allogeneic blood transfusion; post-operative haemoglobin level; morbidity; and length of hospital stay.

Incidence of allogeneic blood transfusion

One of the studies included by Dhariwal et al[12], a small controlled trial,[49] was reported to have found that the number of allogeneic transfusions in the cell salvage group was far lower than in the non-cell salvage group among women undergoing caesarean section (no data were provided).

Post-operative haemoglobin level

The only controlled study[49] included by Dhariwal and colleagues[12] found that of the women undergoing caesarean section, those in the cell salvage group had significantly higher post-operative haemoglobin levels (no data reported).

Morbidity

An included retrospective cohort study[50] reported one case of heparin toxicity in the cell salvage group of women undergoing caesarean section.

Key research question: 2. Is there evidence which identifies differences in outcomes (for patients and the health system) according to whether cell salvage is carried out post-operatively or intra-operatively?

Summary: No literature was identified that reported a comparison between post-operative and intra-operative cell salvage in patients with the same indication. A systematic review by Carless looked at intra-operative and post-operative subgroups within their review and reported similar results. The timing of cell salvage is often dependent on the type of surgical procedure being performed.

No studies were identified that reported on a direct comparison of post-operative versus intra-operative cell salvage in patients with the same indication; therefore a comparison between these different techniques was not possible. The review by Carless et al did consider the effect of timing of cell salvage on the incidence of allogeneic blood transfusion, and conducted three separate meta-analyses of studies using intra-operative only, post-operative only and combined intra and post-operative cell salvage.[7] These meta-analyses included studies on orthopaedic, cardiac and vascular surgery; results are shown in Table 5. It should be noted that intra-operative and post-operative cell salvage were not compared to each other within trials; these are merely subgroup analyses within the meta-analysis.

Table 5 Comparison of effect of timing of cell salvage on incidence of allogeneic blood transfusion[7]

	Intra-operative		Post-operative		Intra and post-operative	
Outcome	**Number of studies**	**Result RR [95% CI]**	**Number of studies**	**Result RR [95% CI]**	**Number of studies**	**Result RR [95% CI]**
Incidence of allogeneic transfusion	11	0.59 [0.46, 0.76]	46	0.63 [0.54, 0.74]	9	0.70 [0.54, 0.92]

A possible explanation as to why no evidence was found comparing post-operative and intra-operative salvage is that cell salvage timing is largely dependent on practical considerations particular to the surgical procedure being performed. In the example of TKA, a tourniquet is frequently used during surgery for the control of intra-operative bleeding, and thus any salvage of lost blood necessarily occurs post-operatively in this clinical scenario. By contrast, during THA, blood from surgical drains may be more readily collected intra-operatively for immediate processing and reinfusion.[51] Most of the systematic reviews and meta-analyses included in this Report did not actually specify whether the primary studies included in their analyses made any distinction between post-operative and intra-operative timing of the salvage procedure.

Economic evaluation

<u>Key research question</u>: 3. What is the cost of intra-operative cell salvage compared to the 'true' cost of allogeneic blood?

Summary: There is no one answer to the question of whether intra-operative cell salvage is cost effective compared to the 'true' cost of allogeneic blood. The literature identified covered a wide variety of study designs and there was considerable variation in the items included in the costing analyses. No Australian studies were identified. The results of the studies were as varied as their methodologies, with some studies finding cell salvage to be cost saving whilst others found net costs, of varying degrees, associated with the practice. The only clinical area with any consistency in results was in knee and hip arthroplasty, where cell salvage was not cost effective.

The financial impact of a cell salvage service is likely to depend on the hospital, the availability of trained staff to undertake the procedure, as well as the throughput of patients likely to use the equipment.

Similarly, the cost effectiveness of an intervention is highly specific to the setting in which it occurs. The delivery of the service is likely to have different resource use between health systems and the extent of replacement of allogeneic blood transfusion is also likely to differ according to the PBM policies that are in place.

A full cost effectiveness analysis using key Australian data would be required to properly determine the economic advantages of cell salvage relative to allogeneic blood transfusion.

Unfortunately there is no simple answer to the research question that has been posed. Although the National Blood Authority provides a cost of manufacturing each unit of red blood cells for allogeneic transfusion, this cost does not account for other factors that could be considered part of the 'true' cost. For example, the resources associated with the identification and treatment of transfusion-related reaction could be considered part of the 'true' cost of allogeneic blood. The manufacturing cost of a unit of red blood cells is currently $346.86.[52] A study from WA reported that the total cost of a unit of transfused blood was $875 in 2010, with the cost of the blood accounting for $339 of this total; other studies have also reported transfusion costs being well above the cost of the blood.[53]

The NBA report that over $9 million worth of red blood cell product was discarded in 2011-12; however, due to data limitations it is not clear how much of this was preventable or whether this wastage has been included in the costs of allogeneic blood transfusion.[54]

Similarly, the costs associated with cell salvage and its potential for reducing the need for allogeneic blood are very difficult to ascertain. Until the release of the NBA PBM Guidelines, the clinical circumstances for transfusion in Australia were not well understood. The units of blood provided and eventually used are reported by the National Blood Authority but it is acknowledged that the linkage of systems involved in blood supply, including the supply chain and clinical systems, are not well connected. There is a lack of information about

'how, why and where' blood products are used.[32] Nationally available hospital or procedure data do not inform this question due to a lack of detail available in these datasets. The issue is currently being addressed by the NBA.

The NBA have made a commitment to intra-operative cell salvage in their Guidance and have provided material to institutions to help them make a business case for intra-operative cell salvage.[2] It is important to recognise that at present, blood is available free of charge to any individual who requires it, with the manufacturing cost being shared by the Federal and State governments. The other costs associated with allogeneic transfusion are borne by the hospital sector (public) and/or the patient (private).

Recognising that the factors that contribute to the 'true' cost of both cell salvage and allogeneic blood transfusion are not universally accepted, a range of studies assessing the costs of cell salvage for different clinical indications have been identified and summarised to show the variation in both the costing methods and the results obtained. No Australian studies that compared intra-operative cell salvage and allogeneic blood transfusion were identified.

Reported costs and cost-effectiveness of cell salvage

The studies varied considerably with regard to the cost inputs included, and although all used a unit cost for allogeneic blood, the price attached to this was largely unexplained. In some studies the cost was relatively modest, in others it was higher, and in one study the cost of one unit of blood was arbitrarily quadrupled to approximate the 'true' cost.[55] In some of the cost analyses, only the transfusion costs were considered, whereas costs associated with downstream clinical factors, such as length of hospital stay and complications, were measured in other analyses. In studies that conducted economic modelling, the risks associated with allogeneic blood transfusions were also considered (e.g. risk of blood-borne virus infection).

The results of these economic analyses were, not surprisingly, variable. The use of cell salvage was associated with considerable cost-savings in some studies and large net incremental costs in others. Approximately half of the studies reported an increased cost, while the other half reported decreased costs, associated with cell salvage. There was no relationship between the variables included in the costing analysis and whether cell salvage was found to be cost saving; studies that included broader costs associated with hospital stay and those that only included transfusion costs were not associated with any particular direction of result. Some consistency was found in the joint arthroplasty studies. In these studies, cell salvage was not found to be cost-saving, although one study that explored different scenarios for cell salvage use, identified cost savings with some scenarios. In all of these studies, caution is required when comparing the findings as the heterogeneity in cost inputs and lack of detail regarding costing assumptions means that in most cases the

analyses are not comparable. A succinct summary of the direction of findings in these studies is given in Table 6. Study profiles are provided in Appendix B, page 43.

One health technology assessment from 2006, conducted on behalf of the UK National Health System (NHS), considered various methods of reducing allogeneic blood transfusion, including cell salvage.[56] This assessment included two full economic evaluations related to cell salvage. The results from these two papers were at odds. A decision analytic economic model was therefore constructed, using inputs from the systematic review and various sources in the UK. It was concluded that for the one month time frame, cell salvage was associated with lower costs and a slightly higher gain in quality adjusted life years (QALYs) when compared to the other transfusion strategies, with the exception of preoperative autologous donation and acute normovolaemic haemodilution. The range of expected costs, QALYs and net benefits was quite broad, suggesting there was some uncertainty in the conclusions. This comprehensive study could provide a foundation for an equivalent study using updated effectiveness data and Australian cost inputs.

Table 6 Brief summary of results from studies investigating the cost effectiveness of cell salvage

Study ID	Design	Indication	Inputs to cost analysis	Cost of cell salvage relative to allogeneic blood transfusion
Albright et al[57]	Modelled cost analysis	Caesarean section	'total expenditure', includes short and long term complications	↑ cost
Almeida & Leitao[58]	Trial-based cost analysis (non randomised prospective study)	Cardiovascular surgery with cardiopulmonary bypass	Blood only	↑ cost
Bowley et al[59]	Trial-based cost analysis (RCT)	Emergency penetrating torso injury	Blood only	↓ cost
Boese et al[60]	Case note review	Knee arthroplasty; post-operative cell salvage	Blood costs only	↑ cost
Canan et al[61]	Case note review and modelled cost analysis	Posterior lumbar decompression and fusion surgery	Blood only	↑ cost
Haynes et al[62]	Trial-based cost analysis (RCT)	Infrarenal aortic reconstruction	Hospitalisation, drugs, theatre costs, diagnostic tests, complications, blood	↓ cost (not significant)

Study ID	Design	Indication	Inputs to cost analysis	Cost of cell salvage relative to allogeneic blood transfusion
Huber et al [63]	Modelled cost analysis	Infrarenal aortic reconstruction	Blood costs, complications including costs of infection from BBV, quality of life operative mortality and life expectancy	↑ cost, US$120 794 -$578 275 per QALY
Jackson et al[64]	Cost-utility model	Joint arthroplasty	Treatment, life expectancy, quality of life, risk of BBV	↑ cost, US$5.7million per QALY
Markovic et al[65]	Trial-based cost analysis (cohort study)	Aortoiliac occlusive disease, aortic aneurysm	Blood only	↓ cost for aneurysm patients, ↑ cost for AOD
Munoz et al [66]	Case note review	Knee arthroplasty; post-operative cell salvage	Blood, operating costs, hospitalisation costs	Depending on model, ↑ cost or ↓ cost
Murphy et al[67]	Trial-based cost analysis (RCT)	Coronary artery bypass grafting	Operating room materials, hospitalisation, blood, complication management	↑ cost (not significant)
Odak et al[68]	Trial-based cost analysis (prospective observational study)	Pelvic trauma surgery	Blood only	↓ cost
Samnaliev et al[69]	Modelled cost analysis	Paediatric patients, mostly orthopaedic	Blood, medical treatment for adverse events	↓ cost
Savvidou et al[70]	Trial-based cost analysis (RCT)	Posterior lumbar instrumented spinal fusion	Blood only	↓ cost
Solomon et al[68, 71]	Trial-based cost analysis (prospective observational study)	Emergency room at two hospitals; mostly trauma and obstetric	Blood only	↑ cost (small)
So-Osman et al[55, 72]	Trial-based cost analysis (RCT)	Knee or hip arthroplasty; intra and post-operative cell salvage	Blood, hospital stay	↑ cost
Tawfick et al[73]	Trial-based cost analysis (prospective observational study)	Open abdominal aortic aneurysm repair	Blood, hospitalisation, overall inpatient costs	↓ cost
Thomas et al[74]	Trial-based cost analysis (RCT)	Knee arthroplasty: post-operative cell salvage	Blood, staff time, capital and servicing, readmission, GP consultation	↑ cost

AOD, aortoiliac occlusive disease; BBV, blood borne virus; GP, general practitioner; RCT, randomised controlled trial; QALY, quality adjusted life year

Studies approached costing with various methods; one study used incremental cost effectiveness rations (ICERs) and calculated a cost-per-QALY gained for cell salvage, however most did a simple comparison of the cost of cell salvage versus the cost of allogeneic transfusion, with various inputs to the cost analysis. Some studies included just the cost of the cell salvage procedure and allogeneic blood transfusion, while other studies added various components to the cost of both types of transfusion, including cost and maintenance of the machine, staffing, hospital stay, intensive care stay, and treatment for complications. Many of these studies indicated that they were reporting cost effectiveness analyses but misrepresented the results - the increment in costs was calculated but not the increment in health outcomes.

Several studies that used decision analytic models to determine the cost effectiveness of cell salvage also appropriately considered the likelihood of acquiring a blood borne virus and other serious transfusion complications. Given the rarity of these outcomes in Australia and New Zealand, it is possible that these factors would have limited overall cost and health impact; although, this would need to be analysed formally. A selection of studies is presented by clinical indication below.

Knee and hip arthroplasty

The most recent study, a large RCT in patients receiving a primary knee or hip arthroplasty, or revision of the procedure, was conducted in the Netherlands.[55] The patients were enrolled between 2004 and 2008 and were split into two groups based on their pre-operative haemoglobin level, 10-13 g/dL or >13 g/dL.

Patients in the lower haemoglobin group (n=683) were randomised to receive erythropoietin or not, and then further randomised to cell salvage or no cell salvage. These lower haemoglobin patients receiving hip arthroplasty could receive either intra or post-operative cell salvage, while knee arthroplasty patients only received post-operative cell salvage. Patients in the higher haemoglobin group (n=1,749) were also randomised to cell salvage or no cell salvage, with the use of intra or post-operative cell salvage according to their surgery type, as in the lower haemoglobin group.

In the analysis of this study, the results of patients receiving either intra-operative or post-operative cell salvage were combined. It was determined that patients with a higher haemoglobin level receiving autologous blood through cell salvage had a similar requirement for allogeneic blood as those who did not have cell salvage. Cell salvage patients had a small but statistically significant increase in length of stay in hospital compared to patients who did not receive cell salvage, meaning that cell salvage was more expensive. In this study fewer than 10 per cent of patients required a transfusion, and the amount of blood salvaged and reinfused was relatively small. In the subset of patients undergoing revision surgery (n=114) the blood loss was greater but it was not reported whether there were differences between the cell salvage and allogeneic blood transfusion

arms of this subset. Costs considered in this trial include those associated with hospital stay, allogeneic blood and cell salvage unit costs. The mean cost per patient in the cell salvage group was €3,992 compared to €3,694 in the control group. The cost per transfusion avoided was €51,000.[55] In the group with lower haemoglobin, erythropoietin reduced the need for transfusion irrespective of cell salvage. The cost of cell salvage was similar, with the cost for patients receiving intra or post-operative cell salvage €537 more than the control group. Results were not presented by erythropoietin group. Again, a slightly increased length of hospital stay for the cell salvage group lead to the increase in cost.[55] The authors concluded that cell salvage was not justified on the basis of effectiveness or cost in this population.

An RCT conducted in the UK in 2001 came to similar conclusions when comparing post-operative cell salvage with allogeneic blood transfusion in total knee arthroplasty (TKA) patients.[74]

One more recent case note review from Spain also investigated the costs associated with post-operative cell salvage in TKA patients.[66] The authors conducted modelling using the various cell saving devices and patient indications. Cost inputs to the model were very thorough, including acquisition of red cells for transfusion (derived from a model that included direct and indirect costs), cell salvage and reinfusion, and hospital stay. This study provided the most detail on the costs of allogeneic blood, including in its cost calculations variables such as collecting donor blood, testing of the donor blood, storage and delivery and societal costs. The study found considerable variation according to the variables used in the models, with cell salvage being cost-saving in some scenarios and having a net incremental cost in others. The models were particularly sensitive to the length of stay in hospital (for those transfused) and to transfusion rate in the control group. Cost savings for cell salvage generally increased as the length of stay increased in the allogeneic blood transfusion group because the allogeneic transfusion rate was lower in the cell salvage group. For both models of cell saver machine, a higher preoperative haemoglobin level (above 15 g/dL) was associated with net incremental cost, and, unsurprisingly, cost savings were greatest when the allogeneic transfusion rate was low in the cell saver group and higher in the control group. The authors concluded that their model indicated a benefit for patients receiving cell salvage in terms of a reduced allogeneic transfusion rate and reduced costs if their pre-operative haemoglobin was between 12 and 15 g/dL; over 15 g/dL there was an incremental cost and below 12 g/dL, patients would benefit from blood saving methods additional to cell salvage.[66]

A Markov model published in 2000 used various inputs including risks of transmission of viral diseases and subsequent treatment costs and effects on quality of life.[64] They concluded that, in a hypothetical cohort of patients undergoing total joint (knee and hip) arthroplasty, post-operative cell salvage extended quality-adjusted life expectancy by five

minutes at a net cost of $53, which across the US would represent a cost of US$5.7million per QALY. The model was sensitive to the direct costs of salvaged and allogeneic blood and to the volume of blood salvaged; such that the cost effectiveness calculation remained in excess of US$50 000 per QALY unless the volume of returned blood exceeded 200 mL. The authors concluded that post-operative cell salvage for joint arthroplasty would only become cost effective if the cost of the cell salvage device dramatically decreased or there were sufficient patients with a high drainage volume. The study acknowledged that the only risks modelled were those related to blood borne viruses, and allogeneic complications such as transfusion reactions were not considered.[64]

Cardiovascular surgery

Several studies concerning different types of cardiovascular surgery were identified. A small RCT from the UK published in 2005 investigated intra-operative cell salvage in patients undergoing off-pump coronary artery bypass grafting.[67] Cost calculations included operating room materials, bed occupancy, transfusion products and post-operative complication management, but not professional fees, pre-operative costs, surgical theatre costs, perfusionist staff costs or drug costs. The mean cost of cell salvage was more expensive than the control group receiving allogeneic blood transfusion (US$10,100.34 versus US$8,423.00). The difference was attributed to the cell salvage consumables, and the authors also mentioned that this cost was minimised by not processing small volumes of blood, although this was not further explored. The cell salvage group incurred greater expenses in bed occupancy and complication costs, but saved on transfusion costs. The authors concluded that there was modest clinical benefit without significantly increased costs from cell salvage.[67]

A slightly older RCT also from the UK (the Autologous Transfusion in Surgery trial) investigated patients undergoing elective infrarenal aortic reconstruction surgery.[62] Patients were randomised to acute normovolaemic haemodilution and intra-operative cell salvage or standard transfusion practice. Theatre costs including time, staff and consumables, transfusion-related costs including devices, consumables, transfusion nurse and allogeneic blood, ward stay and complications were all included in the costing analysis. Basing the calculations on a usage of 50 patients per annum, the study found no significant difference in the mean cost of treatment for cell salvage patients (£5,384) relative to control patients (£5,859). The authors noted that greatest costs related to intensive care ward stays while the transfusion component only accounted for six per cent of the control group costs and seven per cent of the cell salvage group costs. This study also noted, through sensitivity analyses, that having a dedicated operator for cell salvage, or increasing or decreasing the number of operations in a year, made little difference to the costs.[62]

A study of patients undergoing surgery for aortoiliac occlusive disease (AOD), elective abdominal aortic aneurysm (AAA) repair or ruptured AAA repair using historical controls was

conducted in Serbia.[65] Historical controls were used as intra-operative cell salvage was routine in the hospital in which this study took place. A simple cost comparison between cell salvage and allogeneic transfusion was conducted but was limited by the exclusion of costs associated with the cell salvage machine and its maintenance. The study found that there needed to be reinfusion of the equivalent of three units of salvaged blood for the cell salvage to be financially beneficial. This level of use was achieved in this study but varied by clinical indication. Only a minority of patients in the AOD group required three or more units of salvaged blood and cell salvage was not considered financially beneficial. In the two AAA groups, the amount of blood reinfused was deemed sufficient to declare cell salvage financially beneficial.[65]

In another more recent prospective study from Brazil, patients undergoing cardiovascular surgery with cardiopulmonary bypass were divided into two groups; one with intra-operative cell salvage and the other without.[58] A simple cost comparison showed that in the cell salvage group, the cost of the consumables for the cell salvage system and any allogeneic blood was R$1,946 and in the control group the cost of allogeneic blood was R$1,552. The authors concluded that although cell salvage did reduce the number of allogeneic units transfused, it was not cost effective.[58] It should be noted that this was not a cost effectiveness analysis.

Two older studies also considered cardiovascular patients. A study from Ireland reviewed nine years of practice treating patients who underwent open AAA repair, some with cell salvage and some without.[73] A simple cost comparison including the cost of setting up and maintaining the cell salvage system, allogeneic blood and hospital stay including time in the intensive care unit. The study found that the overall mean inpatient cost was €13,780.27 for cell salvage patients and €19,016.77 for control patients, a mean saving of €5,236.60 per patient. The authors commented that the system was expensive to set up but proved to be more cost-effective when used on a continuous basis in a mixed emergency and elective repair service.[73] Another study used decision analysis to model complications associated with red blood cell replacement during infrarenal aortic reconstruction surgery for AAA and AOD.[63] The model included risks of transfusion such as reactions and blood borne viruses and their subsequent treatments. The study found intra-operative cell salvage to be cost ineffective during elective infrarenal aortic reconstructions, and concluded it should be reserved for the patients in which larger salvage volumes are expected.[63]

Emergency procedures

Three studies were identified that used cell salvage in emergency procedures. In an RCT from South Africa, patients presenting to emergency with a penetrating torso injury requiring a laparotomy, and in whom there was significant blood loss, were randomised to intra-operative cell salvage plus allogeneic blood if required, or control (allogeneic blood transfusion), with all blood given at the discretion of the medical staff.[59] The patient group

was young (median 30 years, range 20-54 years) and 91 per cent were male. This was a group of severely injured patients; only about a third of the patients in each arm survived, and this did not differ between the two arms of the study. The costing analysis in this trial included the costs of allogeneic blood and cell salvage consumables, and it found the mean cost to be £812.33 in the cell salvage group and £990.04 in the control group, a non-significant difference. The authors concluded that using cell salvage was cost neutral but that adding the cost of a dedicated operator would make the cost unfavourable. If the machine is used by other practitioners (such as anaesthetists) who receive training then additional staff costs are not incurred.[59]

An observational study (2013) in the UK of patients with pelvic trauma investigated the costs associated with intra-operative cell salvage in patients in whom significant intra-operative blood loss was anticipated, according to the injuries sustained (type C pelvic ring injuries and/ or acetabular fractures or fracture dislocations).[68] Thirty patients were included in the study. Based on intra-operative blood loss and according to the hospital's transfusion policy, the expected number of allogeneic units of blood required was calculated for each patient and compared to the actual blood transfused. It was calculated that 34 units of allogeneic blood were saved at a cost of £2,572 or £86 per patient. This was based on the average cost of running one cycle of cell salvage per procedure; in this study, as the capital cost of the machine had been recouped, this was only £65. This cost did not include the cost of the transfusion nurse, maintenance of the machine or cross matching. The authors concluded that intra-operative cell salvage was cost effective in this patient group.[68]

A prospective study in South Africa of patients at two hospitals was conducted from July 2012 to June 2013.[71] Data collection relied on the cooperation of the cell salvage doctors and was voluntary; no response rates were supplied. Of the 144 episodes for which data was collected, the majority were emergencies (92%), predominantly trauma and obstetric patients. Consumables associated with cell salvage alone and with machine costs were considered in the comparison with the equivalent cost of allogeneic blood in terms of the volume reinfused. The total cost over the study period of equivalent allogeneic blood was South African R258,445 compared to the cost of cell salvage consumables only at R221,978 and consumables plus machine R263,478. The authors noted that cell salvage costs could be reduced with more stringent guidelines on when cell salvage should be contemplated.[71]

Spinal surgery

Two studies considered intra-operative cell salvage in lumbar fusion. An RCT from Greece randomised patients undergoing posterior lumbar instrumented spinal fusion into groups where perioperative cell salvage or allogeneic blood transfusion was offered.[70] A simple cost comparison of allogeneic blood versus cell salvage was conducted but no details on the cost items were provided. The cost per patient in the cell salvage group was €995 and in the control group €1,220. The authors concluded that cell salvage during lumbar spine fusion

was cost effective.[70] Conversely, a case note review and modelled analysis on a similar population in the US calculated the ICER using transfusions avoided as the health outcome measure.[61] Cost inputs were related to the set up and running of cell salvage and allogeneic transfusion only. The result for cell salvage was US$5,553,846 per QALY gained, well above the author's stated willingness-to-pay threshold of US$100,000. Assuming a QALY improvement of 0.01, as used in the study, the cost of using cell saver would need to be US$13 or less for the ICER value to fall below the threshold. The authors concluded that cell salvage was not cost effective in this patient group.[61]

Other clinical indications

A study in paediatric surgery in the US used decision analytic modelling to estimate the transfusion-related costs of four transfusion strategies including combinations of preoperative autologous blood, cell salvage and allogeneic blood. Patients were predominantly orthopaedic patients with a mean age of 14.1 years. The costing analysis included the cell salvage machine, consumables and labour, allogeneic blood and autologous blood processing and medical treatment costs in the event of adverse events, including transfusion associated infection from viruses. Transfusion related costs were lowest for cell salvage and allogeneic blood (US$883.30), followed by cell salvage and autologous transfusion (US$1,269.70); allogeneic transfusion alone (US$1,443.00) and autologous transfusion alone were the most expensive (US$1,824.70). Cell salvage was associated with statistically significant cost savings compared with allogeneic transfusion alone and autologous transfusion alone.[69]

In a similar decision model from the US, the cost of cell salvage in women undergoing caesarean section was investigated.[57] The model included costs of short and long term complications as well as cell salvage and allogeneic blood, and hospital stays. The results showed that intra-operative cell salvage was not cost-saving, and cost on average US$223.80 more per caesarean delivery. Monte Carlo simulations showed that the routine setup of intra-operative cell salvage was cost-saving only six per cent of the time. The authors concluded that routine intra-operative cell salvage for caesarean section would increase health costs but could be cost neutral or cost saving in particularly high risk groups where the probability of transfusion is greater, ie repeat caesarean deliveries or in cases of suspected abnormal placentation.[57]

<u>Key research question</u>: 4. What are the costs of outsourcing of cell salvage compared to the strategy of maintaining a program in a hospital (e.g. hospital-owned equipment (i.e. not leased) and 'in-house' trained personnel)?

Summary: No literature that could inform this question could be located. A full economic analysis using Australian data may be warranted.

The literature search did not locate any studies that could help answer this question. Although some of the included studies mentioned having dedicated staff to operate the cell salvage machine, most of them mentioned it in regards to the difference between having a dedicated perfusionist and having existing theatre staff (namely anaesthetists) operate the machinery; nowhere was 'outsourcing' mentioned. Some papers also mentioned they leased the machinery or were given it by the manufacturers, but no details were provided and it does not help inform the answer to this question.

As with the previous question, only a full economic analysis under Australasian conditions will be able to assess the best way for cell salvage to operate in our health systems.

Search Strategy

Search criteria to be used (MeSH terms)

Search terms*
MeSH Operative blood salvage; Blood transfusion, autologous **Text words** “cell salvage”; “operative cell salvage”; “operative blood salvage”; “autologous blood transfusion” **Limits** English; Systematic Reviews; Meta-Analysis; Guideline; Practice Guideline; Human

*Terms based on a PubMed platform. These were adapted to sequentially search the Cochrane Database of Systematic Reviews, PubMed and Embase.com

HTA sites

AUSTRALIA	
Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S)	http://www.surgeons.org/for-health-professionals/audits-and-surgical-research/asernip-s/
Centre for Clinical Effectiveness, Monash University	http://www.med.monash.edu.au/sphpm/divisions/mars/cce.html
Centre for Health Economics, Monash University	http://www.buseco.monash.edu.au/centres/che/
AUSTRIA	
Institute of Technology Assessment / HTA unit	http://www.oeaw.ac.at/ita
CANADA	
Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS)	http://www.aetmis.gouv.qc.ca/site/home.phtml
Alberta Heritage Foundation for Medical Research (AHFMR)	http://www.ahfmr.ab.ca/publications.html
Alberta Institute of Health Economics	http://www.ihe.ca/
The Canadian Agency for Drugs And Technologies in Health (CADTH)	http://www.cadth.ca/index.php/en/
Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database	
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org
Centre for Health Services and Policy Research (CHSPR), University of British Columbia	http://www.chspr.ubc.ca
Health Utilities Index (HUIs)	http://www.fhs.mcmaster.ca/hug/index.htm
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca
DENMARK	
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	http://www.sst.dk/english/dacehta.aspx?sc_lang=en
Danish Institute for Health Services Research (DSI)	http://dsi.dk/english/
FINLAND	
Finnish Office for Health Technology Assessment (FINOHTA)	http://www.thl.fi/en_US/web/en
FRANCE	
L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)	http://www.anaes.fr/
GERMANY	
German Institute for Medical Documentation and Information (DIMDI) / HTA	http://www.dimdi.de/static/en/index.html
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de
THE NETHERLANDS	
Health Council of the Netherlands Gezondheidsraad	http://www.gezondheidsraad.nl/en/
Institute for Medical Technology Assessment (Netherlands)	http://www.imta.nl/
NEW ZEALAND	
New Zealand Health Technology Assessment (NZHTA)	http://www.otago.ac.nz/christchurch/research/nzhta/
NORWAY	

Norwegian Knowledge Centre for the Health Services	http://www.kunnskapssenteret.no
SPAIN	
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III"l/Health Technology Assessment Agency (AETS)	http://www.isciii.es/
Andalusian Agency for Health Technology Assessment (Spain)	http://www.juntadeandalucia.es/
Catalan Agency for Health Technology Assessment (CAHTA)	http://www.gencat.cat
SWEDEN	
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/
SWITZERLAND	
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/
UNITED KINGDOM	
National Health Service Health Technology Assessment (UK) / National Coordinating Centre for Health Technology Assessment (NCCHTA)	http://www.hta.ac.uk/
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/
The European Information Network on New and Changing Health Technologies	http://www.euroscan.bham.ac.uk/
University of York NHS Centre for Reviews and Dissemination (NHS CRD)	http://www.york.ac.uk/inst/crd/
UNITED STATES	
Agency for Healthcare Research and Quality (AHRQ)	http://www.ahrq.gov/clinic/techix.htm
Harvard School of Public Health	http://www.hsph.harvard.edu/
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org
Minnesota Department of Health (US)	http://www.health.state.mn.us/htac/index.htm
National Information Centre of Health Services Research and Health Care Technology (US)	http://www.nlm.nih.gov/hsrph.html
Oregon Health Resources Commission (US)	http://www.oregon.gov/oha/OHPR/HRC/Pages/index.aspx
Office of Health Technology Assessment Archive (US)	http://fas.org/ota
U.S. Blue Cross/ Blue Shield Association Technology Evaluation Center (Tec)	http://www.bcbs.com/blueresources/tec/
Veteran's Affairs Research and Development Technology Assessment Program (US)	http://www.research.va.gov/default.cfm

Number of studies included

All evidence included for assessment in this New and Emerging Health Technology Report has been assessed according to the revised NHMRC levels of evidence. A document summarising these levels may be accessed via the HealthPACT web site.

Total number of studies: 10

Total number of Level 1 studies: 5

Systematic reviews presenting mixed levels of evidence: 5

Ongoing research

A search of the Australian and New Zealand Clinical Trials Registry yielded only one trial of potential relevance, but appeared to be primarily focused on *in vitro* outcomes (i.e. the trial aims to investigate clotting as measured by thromboelastometry after reinfusion of unwashed salvaged blood in THA; trial ID: ACTRN12612000691842). There is insufficient detail to indicate whether the trial will report on additional outcome measures of relevance to patients and the health system.

In contrast, a search of ClinicalTrials.gov identified several ongoing (recruiting) trials investigating the use of cell salvage in a number of surgical settings. Notable examples include adult cardiac surgery (trial ID: NCT02058134; NCT01435304), and surgery for scoliosis in adolescents (trial ID: NCT02112409). The listing of completed trials is more extensive; investigations of cell salvage applied in cardiac and orthopaedic surgery are prominent on the list.

Appendix A:

Profiles of studies of patient indications considered in this report

Study	Population	Intervention(s)	No. studies reporting on cell salvage as sole intervention/ N patients	Relevant outcomes
Carless 2010[7]	6025 patients (k=75 RCTs) undergoing various orthopaedic, cardiac and vascular surgeries	Cell salvage compared to active controls and non-active controls	All studies	Incidence of allogeneic transfusion, volume of blood transfused, complications
[b]Dhariwal 2014[12]	Women undergoing caesarean section (N not reported, k=6 studies)	Cell salvage with or without comparison to standard medical treatment	6 studies, including one small controlled trial, one retrospective cohort study and 4 case series/ N not reported	Rate of blood transfusion; complications
Gurusamy 2012[9]	617 patients (k=10 RCTs) undergoing liver resection	Cardiopulmonary interventions to decrease blood loss and allogeneic transfusion versus control (no cardiopulmonary intervention)	1 RCT/ 80 adult patients undergoing liver resection (donor retrieval)[a]	Mortality; transfusion requirements, peri-operative morbidity; hospital stay; blood loss; results of liver function tests
Kumar 2014[10]	912 patients (k=23 studies) undergoing surgery for various cancers[c]	Intra-operative cell salvage versus control (no cell salvage)	23 studies, including prospective and retrospective cohort studies and case series/ 912 patients	Biochemical recurrence; distant metastasis; allogeneic blood requirements; post-operative complications; tumour recurrence; survival
Li 2014[4]	1,574 patients (k=12 RCTs) undergoing THA	Cell salvage using ABT drainage[d] in THA versus no drainage or closed-suction drainage	12 RCTs/ 1,574 patients	Post-operative haemoglobin levels; allogeneic transfusion rate; post-operative swelling; post-operative haematoma; post-operative pain; length of hospital stay; post-operative complications including DVT, PE, wound healing, persistent drainage, trochanteric fracture, surgical revision and death
Markar 2012[5]	650 adult patients (k=6 RCTs) undergoing TKA	Cell salvage using ABT drainage (presumably post-operative)[e] in TKA vs suction drainage	6 RCTs/ 650 patients	Number of patients requiring allogeneic transfusion; average number of allogeneic blood units transfused per patient; post-operative haemoglobin levels; drainage volume; length of hospital stay; post-operative wound infection; DVT

Study	Population	Intervention(s)	No. studies reporting on cell salvage as sole intervention/ N patients	Relevant outcomes
Shantikumar 2011[8]	1,994 patients (k=23 studies) undergoing elective or emergency AAA repair	12 studies compared washed cell salvage versus control and 6 studies compared cell salvage plus pre-deposited autologous blood donation and/ or ANH vs control; 5 non-comparative studies reported results for cell salvage alone	17 studies, including 3 RCTS, 9 non-randomised trials and 5 'uncontrolled studies' (presumably case series)/1,595 patients	Allogeneic transfusions (mean number of red cell units and proportion of patients transfused); RR for no. of patients requiring allogeneic transfusion (cell salvage vs control groups); length of ICU and hospital stay
Tavare 2011[38]	888 patients (k=10 studies) undergoing elective AAA repair	8 studies compared cell salvage versus control, 1 study compared cell salvage plus ANH versus control, and 1 non-comparative study reported results for cell salvage plus ANH	8 studies, including 5 RCTs, 2 retrospective cohort studies and 1 case series/ 633 patients	Length of hospital stay; complications including the development of SIS, chest sepsis, post-operative infections, cardiac events, haemorrhage requiring reoperation, pneumonia, coagulopathy, renal dysfunction/ failure, and respiratory dysfunction; liver function; mortality
Waters 2012[11]	2,251 patients (k=11 studies) undergoing surgery for various cancers[f]	Intra-operative cell salvage versus control (no cell salvage)	11 studies of which 3 were prospective cohort studies and the remainder were retrospective cohort and historical case control studies/ 2,251 patients	Cancer recurrence
Zhao 2013[6]	829 patients (k=6 RCTs) undergoing TKA or THA	Cell salvage using post-operative autologous transfusion drainage versus control (standard drainage without reinfusion of autologous blood)	6 RCTs/ 829 patients	Number of patients requiring allogeneic blood; number of RBC units transfused per patient; total blood loss; post-operative haemoglobin levels; complications including transfusion reactions, infections, and DVT; length of hospital stay

AAA, abdominal aortic aneurysm; ABT, autologous blood transfusion; ANH, acute normovolaemic haemodilution; DVT, deep vein thrombosis; ICU, intensive care unit; PE, pulmonary embolism; RCT, randomised controlled trial; RBC, red blood cell; RR, relative risk; SIRS, systemic inflammatory response syndrome; THA, total hip arthroplasty; TKA, total knee arthroplasty

[a] The intervention for this study was described as "pre-operative autologous blood donation" in Gurusamy 2006[9]. However, the original trial[48] reported that "intra-operative blood salvage" was the intervention and suggested that pre-deposited autologous blood donation had occurred among some patients (a confounding factor that was claimed to have been adjusted for in the analysis). Based on the description of the methods in the trial, the conservative decision was made to include rather than exclude the results of Hashimoto 2007[48] as per Gurusamy 2012[9].

[b] The study presented by Dhariwal et al cannot be truly considered as a systematic review as the terms used to search the chosen databases were not specified; however, criteria for the selection of studies were specified, and a limited appraisal of study quality was conducted. The review was conservatively included as a best attempt to include a collated body of available evidence on the use of cell salvage in obstetrics (caesarean section), given no other reviews of even a quasi-systematic nature which reported on the technology in this clinical setting were identified.

[c] Cancer surgeries included were gynaecological, hepatobiliary, gastrointestinal, urological and lung.

[d] In THA, this procedure may be performed intra-operatively or post-operatively; the meta-analysis did not make the distinction as to whether one modality, or both, were involved

[e] In TKA, this procedure is most likely to be performed post-operatively, given that TKA is usually done under tourniquet.

[f] Surgeries were for hepatocellular carcinoma, cervical cancer, prostate cancer and gastrointestinal cancer.

Appendix B:

Profiles of studies reporting on costs and economic evaluations of cell salvage

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Albright 2014[57]	USA	Modelling exercise using decision analysis	Intra-operative cell salvage during caesarean section	NA	Total expenditures related to blood replacement in women undergoing caesarean delivery under a variety of clinical circumstances; model accounts for short and long term complications such as severe allergic reaction and viral infection.	On average, using intra-operative cell salvage costs $223.80 more; unless the cost of cell salvage is implausibly low, routine set up of cell salvage is not cost-saving. Model is sensitive to the probability of transfusion and number of units transfused - as these increase, cell saving trends towards cost saving. Cell salvage is only cost saving where risk of transfusion is high (more than 50%) and transfusion requirement is at least 3 units.
Almeida 2013[58]	Brazil	Trial-based cost analysis (non randomised prospective study)	A group of consecutive patients who underwent cardiovascular surgery with cardiopulmonary bypass; half used cell salvage. Patients aged 26-84 years, mean in cell salvage group 60.55 years and 64.15 years in no cell salvage group; transfusion trigger haemoglobin <7 or 8 g/100mL with haemodynamic instability	N=100, n=50 with cell salvage and n=50 without cells salvage	Limited to cost of allogeneic blood, and cost of disposables for cell salvage	Cost per patient in cell salvage group R$1946 and without cell salvage R$1552. Authors concluded cell salvage was not cost effective based on simple comparison of these costs.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Bose 2011[60]	USA	Case note review	Patients who underwent consecutive, primary, unilateral TKA between January 2003 and February 2009; cell salvage using OrthoPAT used ad hoc but generally was triggered when preoperative haemoglobin was <13 g/dL or patients older than 72 years. Cell salvage used post-operatively only.	N=833, n=285 using OrthoPAT and n=548 controls.	Cost of therapy for blood salvage, cost per unit of allogeneic blood transfusion, including costs of blood product and laboratory procedures. Did not include nursing productivity, tubing, saline.	OrthoPAT significantly added to the cost of surgery; blood management cost using blood salvage was $283.16 compared to $87.62 for surgeries without. Difference in costs was much less in subgroup of patients weighing <75 kg ($333.18 for blood salvage and $213.88 for controls) Serious concerns about patient selection in this study; blood salvage likely to be used in patients who needed it most therefore most likely to require transfusions.
Bowley 2006[59]	South Africa	Trial-based cost analysis (RCT)	Patients who underwent emergency surgery for penetrating torso injury requiring a laparotomy and where there was significant blood loss.	N=44, n=21 in cell saver and n=23 in control group	Few details given; included costs for homologous blood and cell saver consumables. Did not consider capital and maintenance costs, nor the cost of a cell salvage operator.	Mean cost for cell salvage group was £812.23 and £990.04 for control group; not statistically significantly different. Authors concluded cell salvage was cost neutral, but adding cost of operator would change this.
Canan 2013[61]	US	Case note review and modelled cost analysis	Random selection of patients aged 18 years and older who underwent posterior lumbar decompression and fusion surgery	N=180 randomly selected from n=587 who met inclusion criteria.	All patient-relevant costs considered, but only setting up blood salvage machine, infusing salvaged blood, transfusing allogeneic blood were specifically mentioned.	ICER was calculated at $55,538.46 per transfusion averted, and $5,555, 380 per QALY gained. Authors concluded high cost of cell saver and low complication of allogeneic blood transfusion suggests it should not be used.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Haynes 2002[62]	UK	Trial-based cost analysis (RCT)	Patients underwent infrarenal aortic reconstruction; aged 30-85 years. Patients with potential complicating factors like myocardial infarction in previous 6 months and severe angina excluded from study. Recruited over 30 months	N=145; n=74 to autologous transfusion using intra-operative cell salvage, n=71 to standard transfusion	Ward and ICU stay costs, drugs, theatre costs (duration, staffing, consumables), diagnostic tests, treatment of complications, homologous blood and cross matching, transfusion consumables, cell salvage machine costs (consumables, staff, capital cost and maintenance)	No significant difference found between groups; cost for treatment of homologous transfusion £5,859, autologous transfusion £5,384. Majority of cost due to intensive care and ward stays, transfusion only accounted for 6-7% of total cost. Having a dedicated cell salvage operator had no influence on overall results.
Huber 1997[63]	US	Modelled cost analysis	Used data from case records of patients who underwent infrarenal aortic reconstruction. Focus on risks of infection from blood borne viruses.	NA	Costs (allogeneic blood, cell salvage, complications including costs of infection from blood borne viruses), quality of life (living with symptoms of a blood borne virus), operative mortality and life expectancy post-transfusion	Routine use of cell salvage not cost-effective according to model; cell salvage cost an additional $263.75 but saved only 0.00218 QALYs, at a rate of $120,794 per QALY, well above the $50,000 per QALY threshold set for cost effectiveness. Cell salvage becomes cost effective when more than 5 units of blood are salvaged; authors concluded that cell salvage could be justified in a select group of patients with sufficiently high blood loss.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Jackson 2000[64]	USA	Modelled cost analysis	Hypothetical cohort of patients undergoing total joint arthroplasty, mean age 65 years (20-85 y ears)	NA	Treatment costs, life expectancy, quality of life on the basis of the risk of contracting HIV, HBV, HCV or HTVL from allogeneic blood.	Analysis found use of post-operative salvage device would extend quality-adjusted life expectancy approximately 5 minutes per device; for all of the US (in 2000) this would represent an average cost of $5.7million per QALY. Model sensitive to direct costs of salvaged versus allogeneic blood. Model showed cell salvage was cost saving if red blood cell recovery exceeded 200 mL.
Markovic 2009[65]	Serbia	Trial-based cost analysis (prospective cohort study)	Consecutive patients undergoing surgery for AOD, AAA (elective or rupture repair) all using cell saver. Chart review of historical controls who underwent same surgeries before cell saver was implemented in the hospital.	N=90 prospective using cell saver, n=90 historical controls	Only considered cost per unit of cell saver blood and allogeneic blood. Cost of cell saving device or machine maintenance not included as hospital received these for free.	Analysis based on amount of blood required for transfusion; cell saver deemed to be less costly for elective and rupture repair AAA patients but not AOD patients. Authors concluded that cell salvage is less costly where patients have more than three units of autologous blood reinfused.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Munoz 2013[66]	Spain	Case note review	Patients who underwent primary knee arthroplasty; blood collected immediately post-surgery and reinfused within 6 hours	n=1093, n=763 had cell salvage with n=488 reinfused; n=330 no cell salvage	Supply of blood, supply of cell salvage components; operating costs; hospitalisation costs	Depending on type of cell salvage used in model and length of stay, cost savings ranged from as much as €106 per patient to €4.60 per patient, and in some models a cost of up to €51.10 was incurred. Procedure cost-neutral for all pre-operative Haemaglobin levels using one model; but significant incremental costs using other model for patients with pre-op Haemaglobin ≥13 g/dL. Authors concluded cell salvage reduces costs in patients wtith 12 g/dL>pre-op Haemaglobin <15 g/dL, but incremental costs and no benefit on reduction of allogeneic transfusion rate in patients with pre-op Haemaglobin >15 g/dL.
Murphy 2005[67]	UK	Trial-based cost analysis (RCT)	Patients who underwent first time off-pump coronary artery bypass grafting; excluding patient opposed to receiving blood, receiving systemic anticoagulant drugs, with congenital haematological disorders, ongoing or recurrent sepsis. Patients mean age 62.3 in cell salvage group and 66.4 in control group.	N=61, n=30 in cell salvage group and n=31 in control group.	Direct costs only included: operating room materials, bed occupancy (including nursing costs), transfusion products, post-operative complication management Did not include: professional fees, preoperative costs, theatre or perfusionist staff costs, drug costs, indirect costs such as hospital administration, building and maintenance costs.	Median operative cost per patient significantly higher in cell salvage group, attributed to cost of consumables; effect minimised by not processing small volumes of blood. No difference in bed or nursing costs or costs of managing complications. Transfusion costs were less in cell salvage group. Mean total cost per patient in cell salvage group $10,100.34 and $8,938.60 in control group, not significant.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Odak 2013[68]	UK	Trial-based cost analysis (prospective observational study)	Patients underwent surgery for pelvic trauma; cell salvage used in all patients in whom significant blood loss was expected. Analysis based on expected allogeneic transfusion amount given intra-operative blood loss compared to actual allogeneic transfusion amount.	N=30	Direct costs of cell saver and allogeneic blood; did not include costs of transfusion nurse, regular maintenance of machine or cross matching.	Simple analysis where expected allogeneic transfusion amount was calculated based on intra-operative blood loss and compared to actual allogeneic transfusion amount; cost saving of £86 per patient found.
Samnaliev 2013[69]	US	Modelled cost analysis	Paediatric patients who underwent cardiac or orthopaedic surgery; compared four transfusion strategies of cell salvage followed by allogeneic transfusion, cell salvage followed by autologous transfusion (preoperative blood donation), allogeneic transfusion alone and autologous transfusion alone.	Reference population for cell salvage was n=478; populations without cell salvage were modelled.	Cell salvage costs (machine, supplies and labour), allogeneic blood costs, medical treatment costs in the event of allogeneic transfusion related adverse events.	Transfusion related costs were lowest for patients receiving cell salvage and allogeneic blood ($883.30 per patient) followed by cell salvage and autologous transfusion ($1269.70), allogeneic transfusion ($1,443) and autologous transfusion alone ($1,824.70). Use of cell salvage associated with statistically significant cost savings compared to allogeneic transfusion alone. Authors concluded results driven by relatively low additional costs of using cell salvage compared with savings from reduced used of blood products and associated costs.
Savvidou 2009[70]	Greece	Trial-based cost analysis (RCT)	Consecutive patients scheduled for posterior lumbar instrumented spinal fusion; half randomised to perioperative cell salvage and half without cell salvage. Same transfusion protocol for both groups.	N=50, n=25 randomised to cell saver and n=25 to no cell saver	Only considered cost per unit of cell saver blood and allogeneic blood.	Cost of blood transfusion was €995 ± 447 for cell saver group and €1,220 ± 269 for no cell saver group, $p<0.05$.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
So-Osman 2014[55, 72]	Netherlands	Trial-based cost analysis (RCT)	Patients who underwent primary or revision TKA or THA; patients stratified by preoperative haemoglobin and those under 13 g/dL randomised first to erythropoietin or control and then to intra or post-operative cell salvage or control, those over 13 g/dL randomised to intra and/ or post-operative cell salvage or control (no intra-operative salvage for TKA patients)	N=2442 evaluated, n=683 in erythropoietin trial group (erythropoietin and cell salvage, n=214, erythropoietin and control, n=125, control and cell salvage n=206, control and no cell salvage, n=138) Higher haemoglobin group n=1,759, cell salvage n=1,061, control n=698); Intra and post-operative cell salvage considered together.	Limited detail: cost of erythropoietin, intra and post-operative cell salvage, allogeneic blood, intensive care unit and general ward hospital stay. Total cost of allogeneic blood estimated at four times the actual product price.	Using cell salvage was associated with an average increased cost of €298 per patient, attributed to an increased length of stay in general wards. A small non-significant decrease in proportion of patients requiring allogeneic transfusion in the cell salvage group meant that the cost of cell salvage was €51,000 per avoided transfusion. Erythropoietin reduced the need for transfusion but cell salvage made no difference in this part of the study, and it was expensive.
Soloman 2013[71]	South Africa	Trial-based cost analysis (prospective observational study)	All patients who had cell salvage set up in theatres and ICU in two South African hospitals for one year. Most patients trauma and obstetric.	N=144	Cost of allogeneic blood, consumables associated with cell salvage, cost and maintenance of machine	Cost of cell saver machine and consumables over study period was R263,487; equivalent cost of allogeneic blood would have been R258,445. Authors noted that anaesthetic staff controlled the machine; extra staff to do so would cost more.

Study	Country	Study design/ analysis method	Population/ procedure	N patients	Cost components	Results
Tawfick 2008[73]	Ireland	Trial-based cost analysis (prospective observational study)	Patients who underwent open abdominal aortic aneurysm repair, both elective and emergency. Cell salvage used if haemovigilance technician was available. In all patients in whom cell saver was used, red cells were reinfused once 15 mL of packed red cells became available ie no transfusion protocol for cell saver; allogeneic blood transfused in all patients if haemoglobin ≤8.5 g/dL or patient haemodynamically unstable	N=187 in review, cell saver used in n=101	Cost of setting up and maintaining cell saving equipment; total amount of blood reinfused, length of hospital stay, length of ICU stay, overall inpatient costs	Mean cost per patient was €13 780.27 for cell saver patients and €19 016.77 for no cell saver patients. Saving related to reduced ICU and overall hospital stay.
Thomas 2001[74]	UK	Trial-based cost analysis (RCT)	Patients who had TKA. Cell salvage patients transfused with salvaged blood if volume was greater than 125 mL. Both groups transfused if haemoglobin fell below 9 g/dL	N=231, n=115 randomised to cell salvage and n=116 to allogeneic transfusion	Limited detail: cost of allogeneic blood, staff time, capital and servicing, disposables, readmission, GP consultation	Total per patient cost £64.90 in allogeneic group and £178.16 in cell salvage group.

AAA, abdominal aortic aneurysm; AOD, aortoiliac occlusive disease; GP, general practitioner; ICU, intensive care unit; NA, not applicable; RCT, randomised controlled trial; THA, total knee arthroplasty; TKA, total knee arthroplasty; QALY, quality adjusted life year

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