Challenges in the management of the blood supply

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Although blood suppliers are seeing short-term reductions in blood demand as a result of initiatives in patient blood management, modelling suggests that during the next 5–10 years, blood availability in developed countries will need to increase again to meet the demands of ageing populations. Increasing of the blood supply raises many challenges; new approaches to recruitment and retaining of future generations of blood donors will be needed, and care will be necessary to avoid taking too much blood from these donors. Integrated approaches in blood stock management between transfusion services and hospitals will be important to minimise wastage—eg, by use of supply chain solutions from industry. Cross-disciplinary systems for patient blood management need to be developed to lessen the need for transfusion—eg, by early identification and reversal of anaemia with haematonics or by reversal of the underlying cause. Personalised medicine could be applied to match donors to patients, not only with extended blood typing, but also by using genetically determined storage characteristics of blood components. Growing of red cells or platelets in large quantities from stem cells is a possibility in the future, but challenges of cost, scaling up, and reproducibility remain to be solved.

The challenge of matching supply with demand

Efforts in blood transfusion over the past 20 years have focused on improving viral safety and on randomised trials to establish when transfusion provides clear patient benefits. Although these efforts must be maintained, there is now also a need to develop plans to ensure that the blood supply is adequate to provide for ageing populations. In this review we aim to outline the issues facing blood suppliers in high-income countries, and we will discuss possible present and future solutions. A full discussion of the challenges facing developing countries is beyond the scope of this paper.

Health-care systems will be managing the so-called grey tsunami of ageing populations for decades to come. As a result of medical progress during the past decade, major surgery can be done without donor transfusion—eg, primary joint replacement and coronary-artery bypass grafting. However, ageing populations lead to increases in complex surgical procedures for which transfusions are still necessary, such as recurrent joint replacements and combined coronary artery and valve procedures. Success of cancer treatment in older patients and an unavoidable increase in violent trauma in young people together has an estimated increase of more than 10% in the demand for blood over the next decade (MacLennan S, National Health Service Blood and Transplant, personal communication). Another challenge is the difficulty in recruiting and retaining the next generation of blood donors. All high-income countries have to compensate for a steady decrease in regular donors with increased marketing. Issues such as iron deficiency in regular donors have caused regulators to question whether blood services are doing enough to balance donor health with the needs of patients. Finally, even if we can achieve a balance between blood supply and demand, we still have the challenge of transfusion complications in regular patients. In patients who are dependent on lifelong transfusions for thalassaemia or sickle-cell anaemia, alloimmunisation and iron overload are well recognised, but these are also increasing in older patients with acquired anaemia, such as myelodysplastic syndromes.

Therefore, all involved in vein-to-vein delivery of the blood supply need to work together to ensure that blood donation does not compromise donor wellbeing, is used only when clinically indicated, and that wastage and blood going beyond its expiration date in the supply chain is minimised. However, there is an expectation that blood will always be there when really needed; running out is not an acceptable option in countries with developed health-care systems, including during periods of extreme weather, influenza epidemics, and volcanic ash, in addition to normal fluctuations in demand. Fortunately, there are new developments in management systems for blood supply, blood component manufacturing, and donor and patient blood grouping, which can contribute to a streamlined supply chain from donor to patient. Additionally, some countries are now establishing initiatives for patient blood management, which cross health-care boundaries and aim to produce patient-care pathways that minimise the use of blood transfusions.
These are discussed in detail in a separate report in this Series. Preparation for and response to acts of terrorism merits separate exploration, and is not discussed further in this report.

How can we secure the donors of the future?

Donor recruitment and retention in the digital age

Market research experts define the different generations found in the blood donor population, from the World War 2 generation, through baby boomers, to the so-called generations X, Y, and Z, and now the so-called digital natives whose smartphones are ubiquitous. Expectations of each of these groups differ substantially at all stages of contact with a blood service. Not only does the content of advertising have to vary, but also the method by which donors and blood services interact. Donor recruitment has developed from volunteers delivering recruitment leaflets by hand, to postal contact, and now to email and text messaging. Now Facebook, Twitter, Spotify, and interactive websites are the social norms that blood services must use to enlist and retain young donors. An interactive website for donors with discussion boards, online appointment booking, and news sections could increase donor loyalty. With further development, this approach could also allow donors to complete health-check questionnaires online at home, avoiding a wasted journey if they are ineligible to donate.

Donor venues might also need to be reconsidered. The present model in many countries is to reach out to rural communities, meaning blood-collection teams have to travel long distances, and this does not always result in many donors. Although this approach is seen as socially desirable, it might be difficult to continue to justify the costs. Clearly donors should not be asked to make long journeys to give blood, but blood services need to examine whether blood collection efforts can continue to be spread thinly, or should be concentrated in areas where more people are likely to donate. Another factor to be considered is the donation venue. Blood collection in village halls and local schools is possible, but limits what can be done to improve the donor experience. Fixed donor sites potentially offer more digital-age facilities, such as free WiFi and iPod docks at each bed.

Evidence-based donor selection

Donor selection guidelines are there to protect both donors and patients from acute and long-term harm. Although good epidemiological work has underpinned donor selection related to infection transmission, there is scarce evidence for other exclusion criteria. This absence of proper exclusion criteria for donors has resulted in highly risk-averse guidance, which has become a challenge. One good example is the upper age limit for donors, which in the UK was age 66 years. This upper age limit was extended to 70 years, but in an era where 100-year-olds run marathons, even this appeared somewhat arbitrary. Therefore, in the past 10 years, after a careful review of all the evidence, both Canada and the UK abolished the upper age limit for blood donation altogether, joining the USA among other countries. Further monitoring has not found any increase in serious adverse events in these older and highly motivated donors. The UK have started accepting donors who are treated with oral hypoglycaemic drugs (although patients on insulin treatment are not accepted, unlike in some other countries), and extended this to patients on acceptable antihypertensive drugs. Similarly, both the US Food and Drug Administration (FDA) and the UK now accept asymptomatic donors with genetic haemochromatosis with the permission of their treating physician, provided the spirit of altruism is retained, the donor meets all other background selection criteria, and there is a back-up phlebotomy service for times when the donation cannot be taken for clinical use. Such donors are highly motivated and can provide a useful addition to the blood supply. A culture that continually updates guidance based on new evidence is now typical, and one that will resonate with the present generation of donors who are more questioning. One such review of guidelines resulted in the UK Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs recommending changing the lifetime ban from blood donation of men who have had sex with men to a 12-month deferral from last sexual contact. This amendment in the guidelines was implemented in England, Scotland, and Wales in November, 2011, so far without problems. Australia has had a similar experience in changing the deferral period in men who have had sex with men, and other countries are also seeking revisions to their guidelines.

Maintaining donor health and wellbeing

Until recently, there has been little high-quality research done on the complications of blood donation, such as fainting. These complications are common in young donors; the high faint rate seen in donors aged 16 years in the USA has deterred the UK from lowering the present age limit to younger than 17 years. Both Canada and the UK have recently implemented a new criterion for donor acceptance based on estimated blood volume for first-time donors aged 17–23 years, a strategy that has been effective for some US blood operators. Other interventions such as drinking cold water before donation and applied muscle tension during donation have also been effective. Rarely, potentially serious delayed faints can happen after the donor has left the session; their specific cause and prevention is unclear.

Long-term consequences of donation are of concern in many countries, notably the incidence of so-called haemoglobin fails and non-anaemic iron deficiency in blood donors. All donors have their haemoglobin concentrations measured before each donation, and many donors drop below the acceptance thresholds on a regular basis. Even three donations in one year can...
completely use up the body’s iron stores, especially in young premenopausal women with borderline iron intake. Countries vary in the acceptable haemoglobin thresholds. In Europe, the minimum thresholds were increased nearly 10 years ago from 120 g/L to 125 g/L in women and 130 g/L to 135 g/L for men, but this change was not based on systematic evidence. In both Canada and the USA, a universal haemoglobin threshold exists of 125 g/L for both men and women. Studies in the USA have shown an unexpectedly high proportion of donors with non-anaemia iron deficiency, and in 2011, the FDA held a workshop to explore increasing this threshold. Another factor that varies greatly between countries is the frequency of donation, varying from 8 to 16 weeks for men, and from 10 to 16 weeks for women (table 1).

Approaches to prevent donor iron deficiency (panel 1) include the development of algorithms based on red-cell indices to predict the safest interval between donations, including small trials of iron replacement and a new randomised trial on the donation intervals in 50 000 donors in England (INTERVAL, ISRCTN24760606). This trial also aims to gather new information about the mental and physical consequences of non-anaemic iron deficiency, and to explore genetic factors determining susceptibility to iron deficiency. Changing the haemoglobin threshold or personalising the interval between donations are better than medicating healthy people in order for them to donate blood.

Matching the donor base to patient need
A further issue in both donor and stock management is ensuring that there is always sufficient blood to meet the specific blood-type requirements of chronic transfusion recipients. All transfusions are matched for blood group (ABO) and rhesus factor D (RhD)-antigen classification, but the risk of alloimmunisation to the so-called minor blood group antigens, of which there are now known to be more than 300, increases with each transfusion, thus increasing the complexity of finding compatible blood. When genetic typing of donors and patients becomes available, it will be possible to find single nucleotide polymorphisms and other genetic variants; however, their clinical significance will have to be clearly understood because provision of compatible blood could be slowed down by trying to match for variants that are not clinically relevant. Blood services that have well characterised donor panels can deal with most patients who regularly receive blood transfusions. However, owing to differences in blood group distribution across races, and the mismatch seen in most countries between the ethnic mix of the donor and patient populations, it can be difficult to provide adequate supplies of group B red cells, especially if the patient also has many red-cell alloantibodies. This problem could lead to a default position of the use of blood group O RhD-negative blood for such patients, which is clinically safe, but puts great strain on the supply (only 7% of the UK population are O RhD negative). Additionally, minor blood group antigens such as Ss and U are distributed differently across races, so recruitment strategies are needed that engage with minority ethnic communities, patient groups, and their families. Clinical practice in patients with sickle-cell anaemia is extending the use of regular transfusions to prevent stroke. Improving donor–patient matching to include minor blood groups has substantially reduced alloantibody production in patients with sickle-cell anaemia. Now, the use of new DNA-based typing technologies for blood grouping, coupled with sophisticated donor management strategies, have the potential to improve blood provision for these groups.

Further challenges in matching the donor base to recipients arise with the increasing use of massive transfusion protocols for trauma patients. Because it is not always possible to crossmatch the recipient, and time is critical, these patients typically receive O RhD-negative red cells and AB plasma. This practice challenges the
availability of both components for many blood providers, especially with the use of male plasma for transfusion in order to reduce the risk of transfusion-related acute lung injury (TRALI).

The restriction of which donors can be used for manufacture of particular components of blood is sometimes needed for safety reasons. For example, the USA, Canada, and the UK have mandated that fresh frozen plasma be manufactured only from male donors, to minimise the risk of TRALI caused by donor HLA antibodies. However, plasma from female donors is still acceptable for fractionation into plasma products, such as immunoglobulin, and the red cells from women are essential to the blood supply. TRALI can also be caused by the plasma in platelet concentrates, but it is not feasible to source 100% of apheresis platelets from men. Therefore, another strategy has to be used, such as testing the donors for HLA antibodies; however, this process adds to cost, complexity, and the loss of up to 15% of donors (MacLennan S, National Health Service Blood and Transplant, personal communication).

**Effect of manufacturing and storage limitation on blood supply management**

In blood systems in high-income countries, transfusion is usually of specific components (eg, red cells, platelets, fresh frozen plasma) rather than whole blood, although there is renewed interest in the possibility that whole blood donation or apheresis procedures, such as immunoglobulin, and the red cells from women are essential to the blood supply. The testing and manipulation of donations form the core processes in component manufacture. The collection and preparation of transfusion products, either by whole blood donation or apheresis procedures, generates products that have limited shelf lives, defined by the ability of storage protocols and containers to maintain the quality of the functional elements (table 2). Therefore, the resulting supply chain is highly varied, with potentially dozens of different product lines, combining donor’s ABO and RhD groups and cytomegalovirus (CMV) status, the type of component, and additional manipulations such as irradiation, pathogen reduction, or washing. Management of the supply chain against this backdrop is challenging, especially when the unstable nature of cellular blood components is added to the mix.

The management of the supply of ready-to-use transfusion products has developed to minimise product wastage, with most blood systems using a “first in, first out” management system.26 The main deviation from this practice, other than individualised products such as HLA-matched platelets, is the use of fresh red blood cells for neonatal transfusion because of concerns about the accumulation of potassium in the product supernatant during the storage period. Whether transfusion of older red blood cells is the cause of hyperkalaemia-associated cardiac events or simply associated with them has yet to be determined.27 For some time, management of the blood supply to accommodate these patients has been a standard practice for most blood operators. Of greater concern is the increasing evidence that suggests that for some adult patients, clinical outcomes could be affected by the age of transfusion products. This concern also exists for paediatric transfusion,28 but the only randomised clinical trial of the age of blood in neonates has shown no effect of the age of blood.29 Little level 1 evidence exists to support this result, and retrospective studies have contradictory findings; however, within the next 2 years, several continuing clinical studies comparing fresh blood and older blood should be completed, such as the randomised controlled trial TRANSFUSE (NCT01638416), RECESS (NCT00991341), and the ABLE (ISRCTN44878718) trial of the resuscitation of critically ill patients. If these studies show that the shelf life of blood should be reduced, the level of wastage should be monitored because modelling studies suggest that, although lowering the expiration date for red blood cells is important, there is a point at which blood shortages will be inevitable.30

Products that have been manipulated after production typically have further restrictions on their allowable storage period, which need extra effort to ensure that products do not go to waste. Examples include irradiated red blood cells, volume-reduced products, and any product for which there is concern about sterility.

Research efforts into blood components, driven to some extent by research and development investment by the military, have begun to improve the situation. The development of synthetic additive solutions for the suspension of platelets or red cells might minimise transfusion reactions without the need to wash off the plasma. New storage systems promise extended storage life of red blood cells with good maintenance of product quality and changes to the storage conditions for platelets or plasma (ie, frozen or lyophilised) could similarly reduce the expiration rates and utilisation management of these components. Developments in processing technology have substantially improved the

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<th>Storage time for transfusion products</th>
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<td><strong>Table 2:</strong> Storage time for transfusion products</td>
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<th>Allowable storage period</th>
<th>Factors affecting storage</th>
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<td>Red blood cell concentrate 5–49 days depending on each country’s regulations for adults and paediatric recipient</td>
<td>Composition of storage container, presence of additive solution, post-production manipulation such as γ-irradiation, intent of use—eg, exchange transfusion</td>
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<td>Platelet concentrate 3–7 days</td>
<td>Some countries allow additional days of storage up to day 7 if the product has been tested for bacteria or bad pathogen-reduction technology</td>
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<td>Fresh frozen plasma 1 year (frozen) 24 h to 7 days (thawed)</td>
<td>Freezer temperature, Liquid vs frozen state</td>
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<td>Cryoprecipitate 1 year (frozen) 4–6 h (thawed)</td>
<td>Method of manufacture, Liquid vs frozen state</td>
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consistency and reliability of components; however, the biological variation among blood donors means that manufacturing practices alone cannot optimise product quality.

Without specific attention to optimising production techniques, blood components are highly enriched but are not free of other blood elements. For example, without careful separation techniques or the use of leukoreduction filters, white blood cells might be present in any component, or platelets might be present in plasma or products of red blood cells. Some think that the contaminating platelets present in plasma products are a source of the tumour necrosis factor CD40L, which could cause adverse events in recipients; however, other studies do not support a role for CD40L in transfusion reactions or TRALI. Pathogen reduction is an additional development that might have an effect on blood supply management because it is more fully implemented. Techniques typically include use of a chemical that binds to nucleic acids, coupled with a photoactivation step, and in some cases, removal of the chemical at the end of the process. Some regulatory authorities allow extended storage of platelets if they are pathogen reduced, because of the reduced risk of bacterial growth during storage, potentially offsetting some of the additional costs by a reduction in the discard rate. However, these technologies cause changes in the platelet product. A recent meta-analysis of trials concluded that a common theme was reduced rises in platelet count after transfusion, although this did not result in increased bleeding. If large-scale implementation was associated with increased demand for platelet transfusions to compensate, this would increase costs, and potentially restrict the overall benefit of the technology.

Management of the blood supply stock
A nation’s blood supply is distributed between the organisations that prepare blood components and the institutions that use them. In some cases, these might be one and the same. Ideally, both the producers and the users should have inventory-management systems that minimise wastage of blood products and provide immediate line of sight to the status of full blood supply. However, in some jurisdictions, producers and users do not have shared management systems to assess the blood supply. Although information technology solutions to do this exist, there are substantial hurdles, financial and otherwise, to their implementation. Interesting examples exist of integrated supply-chain management, especially where a blood operator is both the producer and the operator of the local transfusion service to patients. Although present practices have developed empirically, blood supply systems are beginning to apply operational research to improve product ordering and inventory management. This type of management system suggests an increasing appreciation of the alignment of many activities within a blood system to those of the traditional manufacturing sector, and recognition of the role that industrial engineering has in improving practices in the manufacturing sector. The scientific literature on blood inventory management has recently been reviewed in detail.

An important factor in the management of blood stocks is accurate prediction of the demand. This type of management can be restricted by insufficient information given to blood providers when a hospital changes its service provision. This can simply result in different distribution of the same number of donations in the system. However, changes to medical practice, such as approval of new chemotherapy or stem-cell transplant regimens, are more likely to affect demand for blood supply. Collection of blood that will not be used is expensive and wasteful, but undercollection of blood leads to shortages and surgery cancellations. Forecasting of blood demand tends to be based on historical patterns of use. Although this approach is generally viable, it sometimes leads to failure to see the consequences of changes in other areas of medical practice that will also affect the blood supply. An example is the rapid uptake of massive transfusion protocols from the military, which caught many hospital transfusion specialists and blood operators unaware. The proposed early so-called formula replacement with high ratios of fresh frozen plasma and platelets to red cells, with the development of shock packs with many components readily available for incoming trauma victims. This approach has led to challenges with adequate collection of group O RhD-negative red cells and group AB fresh frozen plasma for some countries, although in the UK only 5% of blood group O RhD-negative units are issued as emergency. To minimise wastage of fresh frozen plasma in emergency situations, in 2004, the UK allowed the extension of the post-thaw shelf life from 4 h to 24 h. Other strategies to improve the accessibility of products for trauma treatment include prescreening of platelets for high titre anti-A or anti-B antibodies; ABO incompatible platelets with low titres can safely be used in trauma packs.

The best quality data for forecasting of blood demand is found in a system of vein-to-vein monitoring of blood use, such as that implemented in Oxford, UK. In the absence of such a system, there are substantial challenges in combined assessment of hospital transfusion records, sales records between the blood supplier and the hospital, and the supplier’s own inventory-management system.

In view of the importance of appropriate blood inventory management, some countries (including the UK) have established formal national blood-stock management schemes, which feed back wastage data to hospitals and allow them to compare themselves with other management systems.

Effective management of blood inventories needs to be done in a holistic manner by both the blood product provider and the hospital blood transfusion service. The
role of the transfusion service cannot be underappreciated. Decisions made by individual hospital blood banks ultimately affect the entire system’s ability to meet demand, so considering the whole picture is important to the successful balance between adequate supply and minimum wastage. Within a single institution, this focus consists of having appropriately experienced personnel making decisions about ordering with the blood bank, a line of sight on all blood inventory in the hospital including other locations such as the emergency ward, and standard protocols to minimise so-called just-in-case ordering behaviour. Like blood providers, the hospital blood bank should manage stocks with strategies to avoid blood passing its expiration date or the unnecessary use of specialised products, such as CMV-negative blood. Strategies such as issuing the oldest units first and implementing restocking practices of frequent small orders, rather than receiving a large stock of blood products all of a similar age are important. Implementation of electronic crossmatching has become more common and is an important way to reduce unnecessary wastage of blood. This electronic system involves establishing the patient’s ABO and RhD group by conventional blood typing, and screening the patient’s plasma for antibodies. When blood is needed, a computer check allows the selection of suitable donations within the present supply without the need for physical cross-matching of donor and patient’s blood.

Hospitals and blood providers could also work together to manage inventory through the use of return or reissue programmes that are designed to minimise expiration of blood products. Such programmes can be helped by the use of information technology solutions, such as radio-frequency identification technology. Platelet concentrate products are a particular challenge for inventory management because they have a short shelf life, varying from 3 to 7 days depending on local regulatory standards. An adequate dose of platelets for an adult patient can be obtained either from one donor via an automated apheresis procedure, when the red cells are returned to the donor, or by combining Buffy coats from four to six whole blood donations, then separating the platelets by centrifugation. There is no difference in the functionality of these products in preventing or treating bleeding, and blood services vary in the ratio of apheresis-whole blood platelets they produce. However, because of the small risk of transfusion transmission of variant Creutzfeldt-Jakob disease, the UK Advisory Committee on the Safety of Blood, Tissues and Organs has recommended that 80% of platelet doses are sourced from apheresis to minimise donor exposure. The time needed to produce a platelet concentrate product and obtain all the donor test results generally means that platelets are not released for use until at least 2 days after production. The very short shelf life of plasma concentrates means that a high proportion of platelets expire before use, either at the blood supplier or in the hospital blood bank. Typical combined blood service and hospital expiration rates of plasma concentrate in countries with a 5-day shelf life can reach 25%. The short shelf life also creates inventory challenges during holiday periods. Strategies to minimise such wastage include bacterial screening of platelets combined with extension of the shelf life, and accepting that leucocyte-reduced red cells and platelets are CMV-safe, thus removing the need for a separate CMV-negative stock. In 2011, the UK Department of Health Advisory Committee on the Safety of Blood, Tissues and Organs published a position paper stating that leucocyte-depleted red cells and platelets were adequate to protect most patients at risk of transfusion-transmitted CMV, except for pregnant women and neonates, in whom monitoring and treatment is challenging. A further challenge to platelet inventory is bacterial screening, which is not normally done until 24 h after donation. Therefore, the retention of a 5-day shelf life will narrow the window of availability for tested platelet products and might increase the challenges of platelet inventory management. In England, bacterial screening has allowed the extension of the shelf life to 7 days, resulting in a reduction of expired product in blood centres from 9% to 7% (MacLennan S, National Health Service Blood and Transplant, personal communication). Additional platelet inventory can be obtained by optimising the preparation of platelet concentrations from whole blood donations, or ensuring that apheresis donors have starting platelet counts that ensure the collection of multiple products from a single procedure. On the other hand, new focus is being applied to platelet dosing as well as the need for prophylactic platelet transfusion in some patient groups. Results of some of these studies suggest that we might be transfusing platelets more than is clinically necessary.

Management of the patient

Progress in the past decade

Since 1998, there have been three health service programme circulars in the UK to define a series of actions to optimise blood usage and delivery without errors to patients. Much has been achieved in the past 15 years by the combined efforts of hospital-based transfusion leaders and the UK blood services. Overall, blood use fell by nearly 16% between 2001 and 2007, and international benchmarking in 2008 put both the UK and Canada at the lower end of blood use worldwide (about 32–36 per 1000 population per year), compared with 48 per 1000 population in the USA. Recent efforts to address the optimisation of blood use in the USA combined with the economic downturn have led to a substantial decrease in red cell use in the country. Despite this change, there is still much to do to ensure that every transfusion is necessary and appropriate. The notable reduction in red cell use has stalled in the UK, and national comparative audits continue to show red cell transfusion being used outside guidelines in as many as 15–20% of patients.
The overall fall in blood use was achieved by a 40% reduction in peri-operative transfusions, but use in medicine, obstetrics, and gynaecology in the same time period did not change. Therefore, a refresh of the UK approach is therefore needed.

The concept of patient blood management
Optimum management of the patient at risk of transfusion needs a broader systems approach to the issue than is presently applied. This approach to patient management has led to the concept of patient blood management (panel 2), which has three key rules: optimisation of the blood volume and red cell mass without transfusion with the use of haematinics or substances that expand blood volume when appropriate; minimisation of blood loss with surgical technique and antifibrinolytics when needed; and optimisation of tolerance of anaemia. In the USA, the application of programmes for patient blood management is beginning to have a substantial effect on blood demand. A seminar on patient blood management, co-sponsored by the Chief Medical Officer’s National Blood Transfusion Committee and NHS Blood and Transplant, was held in London in June, 2012, and several strategies were agreed on.

What resources are needed for patient blood management?
Experience in Australia and the USA confirms that for patient blood management to be successful, there has to be acceptance and input from senior leaders across the health-care system; this is because changes might be needed across the whole patient pathway, including in primary care. Within hospitals, resources are needed for 24-h availability of cell salvage and upper gastrointestinal endoscopy (for management of acute haemorrhage); and for dedicated nursing, medical, and administrative time for blood management. Production and delivery of evidence-based guidelines is also important. These guidelines have to be targeted to the right staff group because most transfusions are prescribed by junior doctors. For example, a national comparative audit of platelet usage showed a tendency for many patients to be prescribed two adult doses as routine. A targeted poster campaign for junior doctors is reversing this trend. Changing care pathways to optimise transfusion use will probably work best if the pathway is being reviewed for other purposes, so opportunities should be sought to join existing pathway improvement programmes, perhaps incorporating standard methodology for clinical practice improvement.

Information technology challenges in patient blood management
Information technology is one of the most challenging aspects of the whole initiative. Ideally, there would be an association between hospital management and laboratory systems to link information on diagnoses and procedures in patients to blood usage. However, this approach will only happen if electronic linkage exists between the hospital patient information system and the transfusion laboratory computer, so that information on patient diagnoses and blood usage can be linked. Electronic order systems could also capture diagnostic information through a menu-driven order form, and be a method for delivering best practice guidance, perhaps through a smartphone app.

Blood transfusion in patients with medical disorders
Management of anaemia in patients with chronic renal failure has been transformed by the use of recombinant erythropoietin and other erythropoiesis-stimulating drugs. However, recent trials have shown safety issues with these medications, such as an increase in stroke or cancer. Data from the USA over the past 5 years show a reduction in the prescription of erythropoiesis-stimulating drugs for patients with chronic renal failure, but an increase in the use of intravenous iron and blood transfusions for this patient group. These data might suggest both relative cost and safety concerns regarding erythropoiesis-stimulating drugs, but this shift has not been negatively associated with effect on blood stocks. A further treatment that might provide benefit is tranexamic acid. The international CRASH-2 randomised controlled trial in patients with trauma showed a clear reduction in mortality in the group treated with tranexamic acid, and a systematic review of its use in surgery showed a 40% reduction in both mortality and transfusions.

Gastrointestinal haemorrhage has also become the focus of new research to establish the appropriate transfusion threshold for best patient outcomes. A recent randomised trial from Spain showed improved survival in 421 of the 444 patients in the restrictive transfusion group (95%; threshold of 70 g/L compared with those transfused at a threshold of 90 g/L (91%; hazard ratio 0.55,

Panel 2: Practice points for patient blood management
Although the evidence base is not complete on how to reduce blood transfusion, some general points can be made:

- Patient blood management should be built into the care pathway for each major operation or acute medical diagnosis
- Preoperative patients should have their haemoglobin concentration measured as early as possible, so that correction and investigation of iron deficiency can proceed in parallel
- Cell salvage should be available 24 h a day, as should endoscopy for investigation and potentially treatment of upper gastrointestinal haemorrhage
- A postoperative transfusion trigger should be defined; trials of liberal vs restrictive transfusions show no effect with a lower threshold
CI 0·33–0·92). Both rebleeding and adverse events were reduced in the restrictive group, with a striking difference in transfusion rate (15% compared with 51%). A pilot trial of optimum use of blood transfusion in upper gastrointestinal haemorrhage (TRIGGER, ISRCTN 85757829) is also underway in the UK.

What further research is needed?
Panel 3 suggests performance indicators that could be used to assess patient blood management programmes. These programmes have to be underpinned by high quality research, including behavioural studies of prescribing habits. For example, the role of near-patient monitoring of coagulation in reducing fresh frozen plasma and platelet prescription is not yet fully defined, nor is the use of pragmatic preoperative intravenous iron, of which a UK trial (PREVENTT, NCT01692418) will begin shortly.

Future directions
As increasing attention is paid to patient blood management and the need for clear indications for component transfusion, use of fresh frozen plasma could decrease notably because it is usually given to patients without adequate indication.39 Even for patients who need plasma protein treatment, it is likely to be provided by more refined mixtures such as prothrombin complex concentrates, fibrinogen concentrates, and recombinant coagulation factors such as recombinant factor VIIa. In countries where these newer products are being used, some of the older products such as cryoprecipitate are hardly used anymore. Implementation of newer plasma products could come with substantial increases in cost, which might restrict their use in some jurisdictions.

In the past, all donors who were healthy enough to donate and presented no obvious risk to the recipient were able to give blood. Our practice has been to view all donors as providing similar starting material for the production of blood components. However, donorspecific characteristics have a substantial effect on the quality of components during the allowable storage period. In the future, management of the blood supply will probably involve much more sophisticated management of donors than presently. Although we do not know how this approach will affect blood-supply management practices, studies in progress in the UK (PROmPT, ISRCTN56366401) should clearly establish the association between donor characteristics and the outcome of a platelet transfusion. Recent studies have identified similarly predictive markers in healthy participants in radiolabelled platelet survival and recovery studies.39 Recent work has suggested that donor-specific factors including sex have an effect on the storage quality of red blood cells.27 Manufacturers of blood products already stream donors to specific kinds of donations as a strategy to minimise the risk of TRALI. For example, women with history of pregnancy cannot donate apheresis platelets in Canada and in the UK, fresh frozen plasma and platelet donors are either male or those who are negative for HLA antibodies. In the future it might be possible for donors to be characterised by their suitability for component storage, with products labelled for expiration accordingly. This approach would truly stretch our thinking around blood-supply management. As we accumulate additional information on our donor population, we could envision an intersection between enhanced donor management and the methods being developed in the application of personalised medicine. Applied correctly, this approach should lead to high-quality products that have a reduced rate of adverse transfusion events, reduced wastage, and improved overall cost-effectiveness. This approach would need more sophisticated inventory management with information technology than is presently available.

The future is also going to bring new products to the blood transfusion service. The ability to produce a transfusion product in the laboratory from different stem-cell sources has been successfully shown73,74 and such material has been safely given to recipients.75 Large-scale production will need solutions to challenging scientific and bioengineering problems such as blood expansion, renewal, and full red-cell maturation. Likewise, issues of consistency in quality and clinical assessment need to be solved. Although production costs remain prohibitive, these will reduce over time. To begin with, a restricted application of the technology could readily be envisioned for patients for whom compatible blood cannot be found. Expansion of production to meet the needs of wider patient groups could really change the nature of our blood supply chain in the coming decades.

In summary, blood systems exist to ensure that sufficient quality blood products are available when needed. Blood services manage products that are heavily influenced by both the availability and biological characteristics of blood donors. Strategies on how to best use blood products, and the development of processes to improve the quality of blood products will make blood transfusion a safer and more effective treatment.
Contributors
The authors were equal contributors to the conceptualisation and writing of this paper.

Conflicts of interest
LMW declares that she has no conflicts of interest. DVD receives research funding from TerumoBCT and Macopharma. She is a member of the scientific advisory committee of Fresenius-Kabi Transfusion Technologies and has received speaker fees or travel reimbursement for speaking at various conferences including the International Society for Blood Transfusion, the International Association for Biological Standards, the US FDA Blood Products Advisory Committee, Cellular Therapeutics in Trauma and Clinical Care, and the Fresenius-Kabi Advanced Course on Transfusion Technology as well as a number of visiting professorships.

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