MONASH University

Essays on the Economics of Blood

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List of abbreviations

ABLE	Age of BLood Evaluation
AIDS	acquired immunodeficiency syndrome
ANZSCTS	Australian & New Zealand Society of Cardiac & Thoracic Surgeons
APACHE	Acute Physiology and Chronic Health Evaluation
AR	Argentinian Peso
CI	confidence interval
ECMO	extracorporeal membrane oxygenation
EQ-5D-3L	EuroQol 5 dimension 3 level
GLM	generalised linear model
GP	general practitioner
HEV	hepatitis E virus
HIV	human immunodeficiency virus
ICU	intensive care unit
ITT	intention to treat
IVIg	intravenous immunoglobulin
NBA	National Blood Authority
NR	not reported
OR	odds ratio
PBM	patient blood management
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	quality-adjusted life-year
RBC	red blood cell
RCT	randomised controlled trial
RRT	renal replacement therapy
SD	standard deviation
SEK	Swedish krona
SMS	short message service
TRACS	Transfusion Requirements After Cardiac Surgery
TRANSFUSE	STandaRd Issue TrANsfusion versuS Fresher red blood cell Use in intenSive carE
TRICS	Transfusion Requirements in Cardiac Surgery
UK	United Kingdom
US	United States (of America)
USD	United States Dollar
WHO	World Health Organization

Abstract

This thesis examines four research questions relating to the economics of blood.

Chapter 2 presents a systematic review of randomised controlled trials comparing interventions for increasing blood donations. A network meta-analysis was used to pool the results from identified trials. A subgroup analysis was performed in populations of donors and non-donors. The best performing interventions were letter & telephone call, and telephone call only. With considerable uncertainty around the pooled effect, there was no evidence that monetary incentives were effective at increasing donations compared to existing practice. Non-monetary incentives were only effective in the donor subgroup.

Chapter 3 presents the first economic evaluation alongside a full "age of blood" clinical trial with a large population assessing the impact of red blood cell storage duration on quality of life and costs in critically ill adults. Patients were randomised to receive either the oldest available compatible RBC unit (standard practice) or the freshest in the hospital transfusion service. Utility scores were similar at 6 months and there were no significant differences in resource use between the two groups apart from 3.0 fewer hospital readmission days in the short-term storage group. Overall, there were no significant differences in adjusted total costs or QALYs between the storage groups.

Chapter 4 assesses how blood transfusions and patient outcomes in cardiac surgery changed in response to a set of clinical guidelines designed to reduce transfusions using an interrupted time series analysis. The model finds significant reductions in red blood cell, platelet and fresh frozen plasma transfusions after the guidelines were published. There was also a significant reduction in hospital length of stay but no significant impact on cryoprecipitate transfusions, 30-day mortality, 30-day readmissions or intensive care unit length of stay.

Chapter 5 uses the data from red blood cell transfusions during cardiac surgery and a set of clinical guidelines to illustrate methods for assessing changes in variation in care across all hospitals, across all surgeons, and across surgeons within hospitals. After the guidelines were published, variation in care decreased in all scenarios due to a larger response to the guidelines in those hospitals and surgeons with higher pre-guideline transfusion rates. Larger decreases in within-hospital variation occurred in hospitals with high pre-guideline within-hospital variation.

Publications during enrolment

Irving A, Higgins A, Ady B, Bellomo R, Cooper DJ, French C, Gantner D, Harris A, Irving DO, Murray L, Nichol A. Fresh Red Cells for Transfusion in Critically Ill Adults: An Economic Evaluation of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) Clinical Trial. Critical care medicine. 2019 May 24.

Irving AH, Harris A, Petrie D, Higgins A, Smith J, McQuilten ZK. Impact of patient blood management guidelines on blood transfusions and patient outcomes during cardiac surgery. The Journal of thoracic and cardiovascular surgery. 2019 Oct 7.

Irving AH, Harris A, Petrie D, Mortimer D, Ghijben P, Higgins A, McQuilten Z. A systematic review and network meta‐analysis of incentive‐and non‐incentive‐based interventions for increasing blood donations. Vox Sanguinis. 2020 Feb 11.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers published in a peer reviewed journal and one submitted manuscript. The core theme of the thesis is the economics of blood. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Centre for Health Economics under the supervision of Professor Anthony Harris. The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

Publication Title	**Nature and % of contribution**	**Co-author name: Nature and % of Co-author's contribution**	**Monash student**
Chapter 2	Published in Vox Sanguinis		
A systematic review and network meta-analysis of incentive and non-remunerated interventions for increasing blood donations	70% Literature review, analysis, writing	1) Anthony Harris: input into manuscript 5% 2) Dennis Petrie: input into manuscript 5% 3) Duncan Mortimer: concept, screening 10% 4) Peter Ghijben: concept 6% 5) Alisa Higgins: input into manuscript 2% 6) Zoe McQuilten: input into manuscript 2%	No No No Yes Yes No
Chapter 3	Published in Critical Care Medicine		
Fresh red cells for transfusion in critically ill adults: an economic evaluation of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) clinical trial	70% Analysis, writing	1) Alisa Higgins: input into manuscript 5% 2) Anthony Harris: input into manuscript 10% 3) Dennis Petrie: input into manuscript 10% 4) Zoe McQuilten: input into manuscript 5% Clinical trial investigators: Bridget Ady, Rinaldo Bellomo, D James Cooper, Craig French, Dashiell Gantner, David Irving, Lynne Murray & Alistair Nichol	Yes No No No
Chapter 4	Published in the Journal of Thoracic and Cardiovascular Surgery		
Impact of patient blood management guidelines on blood transfusions and patient outcomes during cardiac surgery	85% Concept, analysis, writing	1) Anthony Harris: input into manuscript 5% 2) Dennis Petrie: input into manuscript 5% 3) Alisa Higgins: input into manuscript 2% 4) Julian Smith: consultant 1% 5) Zoe McQuilten: input into manuscript 2%	No No Yes No No
Chapter 5	Submitted to Medical Decision Making		
Assessing heterogeneity in the response to clinical guidelines and subsequent changes in variation in care – the case of blood transfusions during cardiac surgery	85% Concept, analysis, writing	1) Anthony Harris: input into manuscript 5% 2) Dennis Petrie: input into manuscript 5% 3) Alisa Higgins: consultant 1% 4) Julian Smith: consultant 1% 5) Lavinia Tran: consultant 1% 6) Christopher Reid: consultant 1% 7) Zoe McQuilten: consultant 1%	No No Yes No No No No

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I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Prof Anthony Harris

Main Supervisor signature:  **Date:** 12/08/19

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1 The Economics of Blood

1.1 The Market

Economics is concerned with the optimal allocation of scarce resources. Blood as a resource derives its therapeutic value from its ability to be donated, stored and transfused to treat illness. This value gives rise to a market for blood that can be separated into its demand and supply components. The supply side of the market concerns the collection, preparation, distribution and storage of blood products ahead of transfusion. The demand side concerns the prescription of blood products to patients to alleviate ill health. As with many therapeutics, there is uncertainty over blood's effectiveness and questions remain such as how to determine the socially optimal supply of blood when the opportunity cost of donations is unknown, and how to influence a market that largely operates without upstream prices to set demand at the socially optimal level.

1.1.1 History

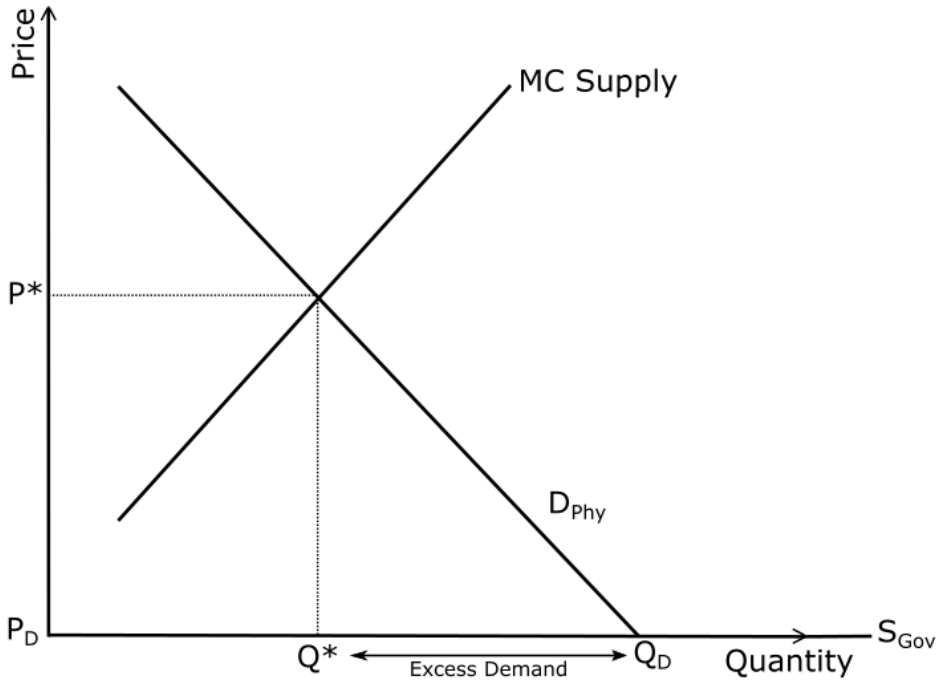
The first human-to-human blood transfusion is usually credited to Dr James Blundell. His 1828 publication in The Lancet describes an invention called "the Gravitator" that collects and transmits blood directly from a supplier to a recipient.[1] Over the next 100 years, technological advances such as sterilisation, blood typing and blood delivery devices vastly improved the safety of the procedure. Improved survival rates increased the average clinical benefit of transfusions and thus shifted the demand curve outwards, increasing the quantity of transfusions performed. Transfusions still required blood to flow directly from supplier to recipient until the 1930s, when the use of sodium citrate as an anticoagulant allowed for extracted blood to be stored for up to 2 weeks. Blood banks were developed to store blood ahead of transfusion, increasing the reliability of the blood supply. This important development dramatically reduced the marginal cost of blood transfusions, again increasing the quantity performed.[2]

The first transfusions were whole blood transfusions to patients who were haemorrhaging, in order to replace lost volume. During the expansion into modern medicine, the discovery that whole blood could be fractionated into its constituent components – red blood cells (RBCs), platelets and plasma – led to more directed use of each donation, improving the effectiveness of transfusions and reducing the marginal cost of supply. Indications for transfusions became more numerous, including anaemia, cancer treatments and natal care. Additional plasma-derived products were developed including clotting factors, albumin and immunoglobulin, with their own indications for haemophilia, shock and immunodeficiency disorders respectively. Advances in surgical techniques allowed for more invasive

operations, increasing the likelihood of significant intraoperative blood loss creating additional demand for RBCs and platelets. Nowadays, RBC transfusions are the most commonly performed procedure on hospitalised patients among all age groups except infants.[3]

1.1.2 Background

We start our discussion on the market for blood using a simplified supply and demand model. In the market for blood and blood products, the end-user – the patient – often relinquishes their autonomy regarding transfusion decisions to their treating physician. Therefore, it is physicians, in response to perceived patient need, who create the demand for blood. Unlike a traditional competitive market, physicians do not usually face explicit prices for the products they demand. Instead, in countries such as Australia, which operates under a social healthcare system, the government maintains a supply of blood sufficient to meet all of the physician-created demand, at significant cost – Australia's National Blood Authority (NBA) spent over $1.2 billion of government funding in 2017/18 to maintain Australia's blood supply.[4] Consequently, because the government and the physicians are not engaged in an open market with explicit prices, there is a disparity between the marginal cost of supply faced by the government (MC Supply), and the government's supply curve (S_{Gov}), highlighted in Figure 1.1. The government will supply any quantity demanded by physicians at zero price – their supply curve is equivalent to the x-axis, despite the government facing a traditional upward-sloping marginal cost of supply.



Q* and P* represent the equilibrium quantity and price if physicians faced the price of blood and their 'perceived' demand curve D_{Phy}
Q_D and P_D represent the actual quantity demanded and price faced by physicians

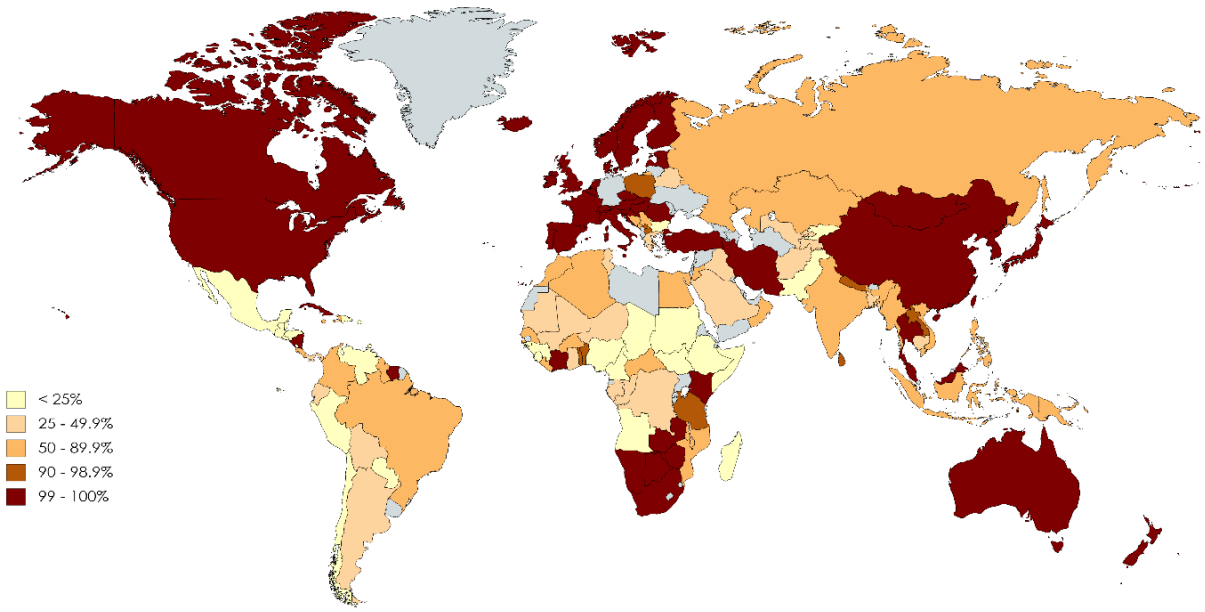
Figure 1.1: Demand & Supply for Blood

The government would prefer to supply blood only to those patients for whom the marginal cost of supply is below or equivalent to the marginal benefit. Given the uncertainty in the effectiveness of blood, the true societal marginal benefit curve remains unknown. However, if physicians were exposed to a price, they would face their 'perceived' physician demand curve (their perceived value of blood for different patients, D_{Phy}) and would prefer to demand blood only for those patients for whom they perceive the marginal benefit is above the price of blood. In a competitive market where the price physicians observed was equal to the true marginal cost of supply, then given these two competing forces, the market would clear where marginal benefit equals marginal cost at quantity Q* and price P*. However, given that physicians face a zero price at any quantity demanded, they will demand all of the blood for which they believe there is a positive marginal benefit, represented by Q_D. As there is no incentive for physicians to prescribe blood only to those patients for which the marginal benefit exceeds the marginal cost of supply, there is an excess demand for blood in society, represented by $Q^* - Q_D$.

In order to reduce this excess demand for blood, governments intervene in the market. Demand-side interventions are designed to reduce physician demand either via price or non-price signals, which we discuss shortly. First we consider the nature and key components of the supply curve and supply-side interventions designed to reduce the marginal cost of supply.

1.2 Supply

A blood supply is the network of individuals, organisations, infrastructure and systems that begins with recruiting donors and ends when blood is transfused to a patient to fulfil a prescription. As well as the donation phase, the blood supply incorporates screening, processing, distribution, storage ahead of transfusion, tracking of prescriptions and the discard of any expired product. Blood supplies are generally organised at the national level with significant government intervention to maintain their safety and stability. The World Health Organization (WHO) describes access to sufficient, secure supplies of blood as an essential part of a strong health system and the responsibility of every national government.[5] Nowadays most developed nations maintain their supply of fresh blood through volunteer non-remunerated donations, highlighted in Figure 1.2. Next, we briefly discuss the various phases of the supply chain.



Source: World Health Organization. Global Status Report on Blood Safety and Availability 2016.

Figure 1.2: Proportion of Blood Donations Collected via Volunteer Non-remuneration

1.2.1 Donation

In 1970, Richard Titmuss argued in his seminal book, *The Gift Relationship*, that blood is a public good and that providing extrinsic rewards such as monetary payments would crowd-out intrinsically motivated donors, reducing the blood supply.[6] Titmuss theorised that individuals at high risk of carrying transfusion-transmissible infections such as injecting drug users and the homeless would be disproportionately attracted by the extrinsic reward, compromising the safety of the blood supply. In response, Solow[7] and Arrow[8] argued that blood is a normal, private good and that increasing the price paid per donation would lead to greater supply – the effect of the extrinsic reward simply adding to the intrinsically motivated donations. To this day, the debate continues, and no analytical framework nor conclusive empirical evidence has been developed to conclusively prove or disprove either claim. In response to this debate on blood supply safety, the WHO issued a directive in 1975 which remains in place today to promote 100% non-remunerated volunteer blood donations.[9]

The extent to which Titmuss' argument holds true relies on the role in which altruism plays in the decision to donate blood. In the social sciences, altruism is defined as unpaid voluntary behaviour that sacrifices the altruist's utility for the utility of another, the beneficiary.[10] The pure altruism model dictates that the altruist gains utility solely through the gain in utility of the beneficiary while the impure model of altruism allows the altruist to directly gain additional utility through the act of donating itself, independent of the beneficiary's utility gain. Some suggested motives[11, 12] that could provide the additional utility to donors in support of the impure model of altruism are:

1. Warm glow altruism – the act of giving itself improves either the self-perception of the altruist or the altruist's belief about how others perceive their actions.
2. Reciprocal altruism – the altruist's utility depends on the beneficiary's altruism in return.
3. Salient altruism – the altruist's utility is enhanced by their recent experiences, in the case of blood donation this could be either themselves or someone close to them recently receiving a transfusion.
4. Income related altruism – the altruist's utility is influenced by the difference between their own and the beneficiary's income, which could be related to inequality aversion.

The popular explanation for the behaviour of blood donors was suggested by Andreoni in his warm-glow theory where donors gain utility from the act of giving.[12] However, a recent survey found that reciprocity was the most frequently stated reason for giving blood.[13] Given the multidimensional nature of these decisions, an altruists' utility function is likely to be unique and made up of a combination of motives. We can adapt the altruism model proposed by Rodríguez & Hita[14] to describe the utility function of an altruist:

$$U_i = U_i\left(X_i, g, U_j(g)\right)$$

Where, U_i is the altruist's utility representing their preferences that depend on the set of goods X_i and U_j is the utility function for the beneficiary j which depends on the good to be donated g. When the altruist donates g they forgo utility $u_i(g)$ from the loss of the good but gain utility $u_i\big(U_j(g)\big)$ through the utility function of the beneficiary. Therefore, an altruist will give g when the utility gained via the beneficiary exceeds the loss from donating g. The weights given to these two factors are complementary and can be understood as an individual's degree of altruism.[14] Individuals with higher degrees of altruism assign greater weight to the utility gained via the beneficiary's utility function. We can consider health transfers such as blood or organ donations a special case of the basic altruism model, expanded to include the donor's health loss.

$$U_i = U_i\left(X_i, g, H_i(g), U_j(g)\right)$$

In this expanded model, $H_i(g)$ represents the loss of health for the altruist upon donation. An individual will now donate when the utility gained via the beneficiary's utility function outweighs the combination of the loss of utility from donating g and the subsequent loss of health. The loss of health from donating blood is mild and temporary, without long-term negative health consequences for the donor. However, in the case of organ donations, the loss of health is permanent and may be significant as to impair the life of the donor. It is therefore common for blood services to highlight the altruistic benefits of blood donation when attempting to increase donations. Under Titmuss' hypothesis,

providing an extrinsic reward would crowd out intrinsically motivated individuals. We can expand our altruism model to include an extrinsic reward p:

$$U_i = U_i\left(X_i, g, H_i(g), p, U_j(g)\right)$$

An individual will now donate if the sum of the utility gained via the beneficiary's utility function plus the extrinsic reward outweighs the combination of the loss of utility from donating g and the subsequent loss of health:

$$u_i\big(U_j(g) + p\big) > u_i\big((X_i - g), H_i(g)\big)$$

If Titmuss' hypothesis regarding the altruistic nature of donating blood is correct then for intrinsically motived individuals, $u_i\big(U_j(g)\big)$ will diminish as a result of receiving p. If the utility gained from the extrinsic reward, $u_i(p)$ is insufficient in magnitude to substitute for the reduction in the utility gained via the beneficiary's utility function, $u_i\big(U_j(g)\big)$ then the overall utility received from donating will have decreased. Using this framework, we can define intrinsically motivated individuals as those for which $u_i\big(U_j(g)\big) > u_i(p)$ and extrinsically motivated individuals are those for which $u_i\big(U_j(g)\big) < u_i(p)$. Increasing the price paid per donation will increasingly dissuade more intrinsically motivated individuals from donation while increasingly persuade extrinsically motivated individuals to donate. Deciding whether to recruit intrinsically or extrinsically motivated donors rests heavily on Titmuss' secondary hypothesis – that extrinsically motivated donors were more likely to carry transfusion-transmissible infections and compromise the safety of the blood supply. While potential donors are screened for risky behaviours such as injecting drugs before donating, providing an extrinsic reward presents an incentive and opportunity for potential donors to answer screening questions deceptively in order to avoid rejection and receive the reward.[15] A number of studies have attempted to quantify the relative risk of transfusion-transmissible infections between paid and unpaid donations. Overall, research indicates that paid donations have higher risk of transfusion-transmissible infections with paid donors being more likely to donate during the 'window-period' when viral load is below the minimum threshold for detection by screening tests.[15, 16] Given these findings, and the fact that modern blood services in the developed world have been successful at maintaining a safe and reliable supply of blood based on volunteer donations, there has been little impetus for change regarding the widely adopted policy of not remunerating blood donors.

Volunteer collection regimes can be organised by a humanitarian, non-government organisation such as the Red Cross, by state-run health services or by independent hospital blood banks. A comparison of the various regimes operating in Europe concluded that state-run systems have a larger than average donor base with fewer higher frequency donors compared to Red Cross systems that rely on

smaller pools of highly active donors.[17] Independent hospital blood banks exhibited the most variability in donation rates. The authors concluded that, compared to state or blood bank systems, Red Cross regimes are better able to embed altruism and tap into intrinsically motivated donors. Australia uses a Red Cross donation regime which collected over 1.3 million voluntary blood and plasma donations from just over 460,000 donors during 2017/18.[18] Comprising a wide network of donation, processing and distribution centres, the Australian Red Cross Blood Service (ARCBS) expended nearly $40 million in collecting these donations. A number of different routine interventions are available to blood services to recruit and retain donors – from monetary or non-monetary incentives to reminder letters or telephone calls, and it is important to know the relative effectiveness of each option. Chapter 2 presents a systematic literature review and network meta-analysis of incentive and non-remunerated interventions for increasing blood donations in order to answer this research question.

Another option for increasing the supply of blood is to shorten the mandatory period of time that donors must wait between donations to replace the volume of blood donated. In Australia, whole blood donors can donate every 12 weeks and, due to modern apheresis techniques, plasma and platelet donors can donate every 2-3 weeks. However, there is uncertainty over the appropriate inter-donation interval. To answer this research question, a large randomised controlled trial was conducted comparing different inter-donation intervals: 12 vs 10 vs 8 weeks for men and 16 vs 14 vs 12 weeks for women.[19] Over the 2-year trial period, the shorter interval groups were associated with a significant increase in the mean amount of blood collected per donor without any significant differences in quality of life, physical activity or cognitive function. However, more frequent donation did result in more donation-related symptoms, deferrals and iron deficiency.

Other questions regarding blood services' interventions for recruiting and retaining donors remain unanswered. It is implicit in their ambition of maintaining supply that blood services do so at minimum cost. Therefore, though rarely studied, an understanding of the relative cost effectiveness of alternative interventions to recruit and retain donors would be valuable information. For example, a study has shown that extending opening times to evening and weekends may be a cost-effective intervention for static donation centres.[20]

Published studies comparing alternative interventions for increasing donations do not usually account for the donor's opportunity cost of donating. Individuals with high degrees of altruism such as regular blood donors may substitute time engaged in other altruistic behaviours such as charity work or other volunteering when asked to donate more frequently. While little empirical work has been performed in this area, there is evidence to suggest that a substitution effect exists in the context of charitable

donations using data from a Catholic church.[21] Therefore, while recruiting more donors or encouraging more frequent donations may increase the blood supply, it is not clear that this represents a socially optimal allocation of the donor's time among possible altruistic activities.

A shortage in the blood supply occurs when demand exceeds supply. Under these circumstances, blood services traditionally contact existing or lapsed donors with an emotive plea to help alleviate the shortage. Research has found these messages are effective at eliciting donations in the short-term[22] – presumably through increasing the altruistic benefit for donors by instilling a sense that their donation during the time of shortage is more valuable and therefore increasing the utility they receive for their donation. Blood supply shortages, while uncommon in the developed countries with efficient blood supply chains, are still a regular occurrence in developing nations.[23] Indeed developing nations face a number of additional challenges in maintaining a safe and reliable supply of blood including insufficient donor bases, higher rates of transfusion-transmissible disease and a general lack of funding for blood services which often do not take priority within the healthcare system.

Although a rare occurrence, the health consequences of national emergencies such as earthquakes or tsunamis create a demand shock for blood, quickly shifting the demand curve outwards and creating an acute shortage. In these situations, blood services need to respond by increasing their supply in a short space of time. Thankfully, perhaps motivated by a sense of civic cohesion and duty in response to crisis, survivors appear very willing to donate with large increases in individuals presenting to donate after the terrorist attack on September 11th 2001[24] or after the earthquake in Pakistan in 2005.[25] Instead of motivating donors, the challenges in these unfortunate circumstances largely relate to continuity of the infrastructure of the supply chain – donation centres, screening and processing centres, transport links for distribution, blood banks and hospitals. Unfortunately, misinformation can lead to an oversupply of donations in response to a crisis – the American Red Cross reportedly discarded over 500,000 surplus units of red blood cells donated in response to the urgent appeal broadcast after September 11th 2001.[26]

1.2.2 Screening

During the blood contamination crisis of the 1980s, thousands of blood product recipients, including many with haemophilia, were inadvertently infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). A number of safety protocols were introduced in response including donor screening questionnaires, donor deferrals and universally screening donations for a range of transfusion-transmissible infections.

Prior to donation, blood services screen potential donors using a questionnaire against strict eligibility criteria (e.g. needle use, HIV status). Donors who do not meet the eligibility criteria are 'deferred' and not permitted to donate. Blood services adopt almost excessively strict eligibility criteria to ensure the security of their blood supply. There are indefinite deferrals in countries such as Australia, Canada, New Zealand and the United States for anyone who spent time in parts of Europe such as France or the United Kingdom during the 'mad cow' crisis from 1980 to 1996. While the risk of infection with variant Creutzfeldt-Jakob disease is incredibly low, there are no blood screening tests available and the proportion of eligible donors deferred in those countries with permanent deferrals does not jeopardise the reliability of the blood supply. In similar fashion, men who have sex with men have been indefinitely deferred based on their higher prevalence of HIV and hepatitis. This was introduced during the initial acquired immunodeficiency syndrome (AIDS) epidemic however, given the modern screening technologies available today, it has been criticised as outdated and unjustly discriminatory.[27] While some blood services have introduced finite deferral periods for this population[28] there remains a reluctance for a widespread policy change, potentially due to the memories of the blood transfusion HIV crisis.

Given the significant costs involved in implementing screening programmes for donated blood, a large body of literature has been devoted to assessing their economic value, from an early cost-benefit study of HIV screening published in 1988[29] to the current debate surrounding the cost effectiveness of universal versus selective screening for Hepatitis E virus (HEV).[30] Assessing the appropriateness of a screening programme involves comparing the risk of transfusion-transmitted infection and its associated cost with and without the screening programme. In the case of HEV, infection is usually mild, asymptomatic and self-limiting – one that resolves itself without specific treatment. In these patients, the cost of an infection is low, although immunocompromised patients who become infected with HEV are at risk of developing chronic hepatitis for which treatment, potentially liver transplantation, is very expensive. As a result, the cost effectiveness of the screening programme is also dependent on the immune status of the blood recipient. This risk dichotomy in blood recipients has led to selective screening of blood intended for high-risk patients in countries such as France and Germany, while universal screening for HEV has been implemented in other countries such as the UK and Ireland. Conclusions from cost-effectiveness analyses assessing the two strategies are dependent on understanding the minimum infectious dose of HEV, which remains uncertain.[31] Therefore, it is not clear whether universal or selective screening for HEV represents the most cost effective strategy.[30]

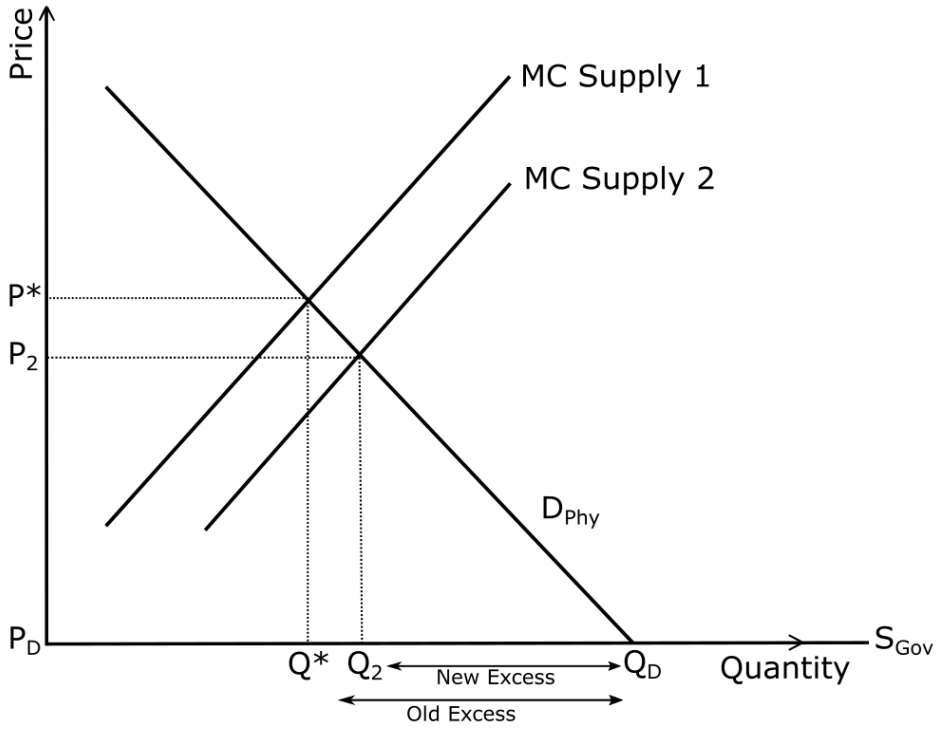
Nucleic acid test (NAT) screening is another example of the debate concerning the value of potential blood donation screening programmes. This technology reduces the 'window-period' for detecting infectious diseases such as HIV and HCV. Earlier detection of infected donations will improve the

security of the blood supply however, NAT screening is more expensive than traditional serologic tests for the same infectious diseases. Published cost-effectiveness analyses have found NAT screening to be beyond traditional thresholds, although conclusions are based on the ability to pay (higher in developed economies) and the prevalence of disease (higher in developing economies).[32, 33] The cost effectiveness of screening programmes for infectious disease will change over time in line with movements in disease prevalence in the donor pool. The proliferation of global travel has increased the likelihood of a donor carrying an unscreened infectious disease contracted abroad (e.g. Zika virus) and travel history is now part of many blood services screening questionnaires. Furthermore, climate change may introduce disease-spreading mosquitos into new jurisdictions, increasing both the prevalence of disease and the cost effectiveness of screening programmes. Other technologies such as pathogen inactivation offer potential solutions to both the 'window-period' and emerging disease problems, although again the cost effectiveness remains unclear.[34]

1.2.3 Processing

The blood supply chain includes the network of donation centres, processing centres and blood banks. In recent years, blood services such as those in Canada[35] and England[36] have undertaken projects to modernise their supply chains with capital investment directed towards new technologies and round-the-clock manufacturing. As a result of a reduction in the demand for some blood components and successful supply chain modernisation projects, these blood services have been able to close underutilised processing centres and establish large multi-model production, distribution and warehousing sites to replace them. These projects were designed to reduce the government's marginal cost of supply, highlighted by a shift from MC Supply 1 to MC Supply 2 in Figure 1.3.

After reducing their marginal cost of supply, the government is now able to supply a greater quantity of blood for the same total cost and would prefer to supply at Q_2 rather than Q*. Physicians still face a zero price at any quantity demanded so will still demand quantity Q_D. Therefore, the excess demand in the market has reduced from $Q_D - Q^*$ to $Q_2 - Q^*$ without a reduction in overall demand. As the marginal cost of supply has decreased, the government cost of supplying the excess demand has also decreased.



Q* and P* represent the equilibrium quantity and price before the shift in the marginal cost of supply
Q_2 and P_2 represent the equilibrium quantity and price after the shift in the marginal cost of supply
Q_D and P_D represent the actual quantity demanded and price faced by physicians

Figure 1.3: Marginal Cost of Supply Shift

In contrast to the publically funded blood supplies operating across most of the developed world, the US blood supply is arranged as a free market. A network of independent collection organisations compete to supply hospitals with blood products and are able to negotiate on price. Reduced demand for blood has eroded margins and resulted in cost cutting or mergers between competitors.[37] Free markets such as the US blood supply operate with an implicit profit motive, where suppliers continually strive to reduce costs as far as legally possible. Without quality incentives or regulatory requirements, new screening, sterilisation or donor-safety technologies such as red-cell genotyping and pathogen inactivation have not been implemented. The combination of market forces and a cultural reluctance to adopt a national public blood supply are threatening its security and safety.[37]

1.2.4 Storage

Fresh blood components have limited shelf lives, which vary from 5-7 days for liquid stored platelets at 20–24 °C to 12 months for fresh frozen plasma at -25 °C. The blood supply chain is designed to consistently deliver blood products to hospital blood banks within their expiry date for storage ahead of transfusion. In order to minimise wastage, hospital blood banks have traditionally operated under a first-in-first-out inventory management protocol. Currently in Australia, the assumed shelf life for RBCs refrigerated at 2-6 °C is up to 42 days.[38] However, there are structural, biochemical, and

metabolic changes that occur during storage ('the storage lesion') of RBCs, which may impact on their clinical efficacy. The 42 day expiry is based on historical in vitro data, rather than a definitive clinical difference between blood that is acceptable for transfusion and blood that is no longer acceptable.[39] Therefore, uncertainty remains over the appropriate shelf life for RBCs, which is related to how blood's clinical effectiveness changes during storage. Indeed in recent years, a body of observational evidence has emerged indicating that older RBCs may be harmful and that the clinical benefit of RBC, and therefore its therapeutic value, diminishes over time as the storage lesion develops.[40] In response, a number of 'age of blood' randomised controlled trials have been conducted comparing transfusion of RBCs of different storage duration. These trials pragmatically make use of current blood banking processes by randomising patients to either the freshest or oldest, in-date, compatible RBC unit in the inventory. The ability of these trials to detect clinical differences in outcomes such as mortality, readmissions and hospital length of stay relies on a significant difference in the age of blood transfused to each arm of the trial. One criticism of the age of blood trials is that they do not compare the freshest available blood with 'very old' blood close to expiry. This lack of comparison against very old blood was considered unethical, although it has been argued that if it is not ethical to design a study where half of the recipients will only receive blood older than 35 days, then we should not transfuse such blood in patients at all.[41]

All of the published age of blood clinical trials were in consensus with regards to finding no differences in the primary clinical endpoint of mortality between fresher and older RBCs. However, none of the published age of blood clinical trials conducted an economic evaluation that included other important outcomes such as quality of life and cost. Chapter 3 presents an economic evaluation of the standard first-in-first-out blood bank inventory protocol compared to a last-in-first-out, or freshest available, protocol in critically ill adults as part of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) trial.

Uncertainty over the appropriate shelf life of blood has potential knock-on effects for the cost of the blood supply. Reducing the shelf life without increasing the frequency of fresh blood deliveries or a compensating reduction in demand would increase the proportion of RBC units that expire. Blood that expires without being transfused is discarded as waste. Wasted blood represents a sunk cost to the healthcare system in terms of the cost of donation, screening, processing, distribution and storage for which no health benefit or value was derived. Minimising wastage maximises efficiency in the blood supply chain by obtaining the maximum health benefit from the blood donations collected. Furthermore, in countries that rely on volunteer donations to maintain their blood supply, wasted blood signifies a missed opportunity for altruistic donors that could have engaged in an alternative altruistic behaviour yielding greater societal benefit. Donors are not directly informed of the outcome

of their donation – whether their blood was transfused or wasted. Knowing that the blood and time that one donates for a good cause was wasted may negatively impact on the warm glow or alternative altruistic mechanism and reduce the likelihood of future donations.

1.2.5 Supply Chain Optimisation

The blood supply chain includes the network of individuals, organisations, infrastructure and systems that acquires blood from donors and delivers it to blood banks for storage ahead of transfusion. Since the 1970s, a detailed literature has emerged focused on optimising the blood supply chain.[42] Optimisation of the supply chain in the context of a perishable good refers to balancing the probability of shortage with the probability of wastage. Supply chain optimisation studies use regression modelling and operational research techniques to predict demand and future blood inventory stock levels. Good inventory management reduces wastage while also avoiding blood shortages. Overestimating the demand for blood will result in an increase in wastage as excess supply expires while underestimating will result in a supply shortage where patients do not receive appropriate transfusions. Blood services optimise their donor recruitment strategies to match their predictions of the demand for blood by implementing recruitment drives when the predicted demand exceeds predicted stock levels.

Over the past century, the supply side of the market for blood has seen dramatic changes with innovative technologies delivering efficiency gains to blood services. However, there are still many unanswered questions and opportunities for improvement such as those highlighted herein. As well as supply-side interventions, governments also intervene in the demand side of the market for blood, which we now discuss.

1.3 Demand

The demand side of the market for blood concerns its ability to be transfused to alleviate ill health. Blood transfusions are very common procedures, with over 630,000 units of red cells issued in Australia during 2017/18[4]. The ageing population faced by nations across the developed world at the beginning of the 21st century delivers additional demand for blood. Blood and blood product use increases with age largely due to the positive correlation between age and general healthcare consumption, including invasive procedures such as cardiac and orthopaedic surgery. Indeed, over 45% of RBC transfusions occur in patients aged 70 and over.[43] Moreover, given that most nations have an upper age bound on donor eligibility, an ageing population reduces the proportion of the population eligible to donate.

1.3.1 Therapeutic Value

Generally, RBC transfusions are indicated for one of two reasons - either a patient is actively bleeding and needs to replace the lost volume of blood (e.g., trauma, surgery) or they are unable to produce sufficient or functional blood cells (e.g., cancer, renal disease). From the 1980s, demand for RBC transfusions for both indications increased as surgical techniques became more complex and the treatment of malignancies more advanced and aggressive.[44] Transfusion of RBCs increases the recipient's haemoglobin levels and thus the supply of oxygen around the body. While RBCs account for approximately a quarter of Australia's blood product expenditure,[4] they are not the only therapeutic product that can be generated from a whole blood donation. The fractionation process separates whole blood into its component parts: red blood cells, plasma and platelets. Plasma contains blood coagulation factors and is indicated in patients who are actively bleeding or to reverse the effects of anticoagulants. Platelets are clotting agents that are indicated in patients who have thrombocytopenia to prevent haemorrhage. Cryoprecipitate is manufactured by collecting the insoluble precipitate from thawed fresh frozen plasma. It contains high concentrations of clotting factors including fibrinogen and is most commonly used in patients needing a massive transfusion.[45]

As a legacy treatment that pre-dates the evidence-based medicine movement of the 1970s, blood transfusions were not held to the high evidence standards in place today. For most of the 20th century, transfusions were viewed as having obvious clinical benefit in maintaining normovolaemia, replacing blood volume lost from haemorrhage.[46] Loss of blood volume can result in shock and eventual death, and while there are substitute fluids that can be introduced into the bloodstream to boost fluid volume, there are no substitutes that provide blood's other therapeutic characteristic – improving oxygenation through increasing the number of blood cells. To prevent anaemia, the supply of oxygen to the tissues via blood cells must remain sufficient to ensure aerobic cell respiration. Therefore, while increasing the blood cell count is related to maintaining normovolaemia, anaemia can also be a separate indication for a transfusion. For example, transfusions are indicated in leukaemia patients whose compromised bone marrow is unable to produce enough functional blood cells.

However, blood transfusions are not without risks. The most well-known risk is that of transmitting a blood-borne infection from donor to recipient. After considerable attention was paid to reducing the risk of transfusion-transmissible infections following the HIV crisis of the 1980s, the medical community appeared to be reassured of the safety of transfusions. However, while the risk of transfusion-transmitted infections has decreased dramatically, little progress has been made in avoiding non-infectious transfusion-related complications such as acute haemolytic and non-haemolytic reactions, acute lung injury, fever and allergic reactions. A transfusion recipient is currently

1,000 times more likely to experience a non-infectious complication compared to an infectious one.[47] Indeed, over the last twenty years a body of literature has emerged indicating transfusion complications are actually harming transfusion recipients.[48] A systematic literature review of RBC transfusion in the critically ill found that transfusions were associated with increased morbidity and mortality.[46] Another review concluded we have witnessed a "dramatic paradigm shift" whereby RBC transfusions, once regarded as "one of the great advances in modern medicine," are now considered harmful in some clinical situations.[49] Infectious and non-infectious transfusion-related complications both create demand for additional healthcare resources such as physician time and extended hospital stay. While the absolute risk may be low, transfusion-related complications reduce the therapeutic value of blood, especially for less morbid patients who are likely to recover without a transfusion. It follows that the therapeutic value of blood depends on the indication for the transfusion with patients in greater need placing greater value on receiving blood, creating a downward sloping societal demand curve. An optimal allocation of a scarce resource will provide in order of those who place the highest value on the product. However, as discussed earlier, modern blood supply chains are designed to ensure reliability to the point that blood may no longer be considered a scarce resource by physicians. Moreover, there are reasons to believe that physicians do not accurately perceive the correct therapeutic value or societal demand curve of blood.

A number of open-label, randomised clinical trials of restrictive versus liberal transfusion strategies have been conducted to determine whether patients can safely tolerate lower haemoglobin levels before receiving a transfusion. In these trials, patients were usually randomised to receive transfusions only when their haemoglobin levels fell below a pre-defined threshold e.g., 9 g/dL in the liberal arm versus 7 g/dL in the restrictive arm. In 2015, Holst et al. performed a systematic review and meta-analysis of restrictive versus liberal transfusion strategies for RBC transfusions.[50] The authors included 31 trials in their study from settings including critical care, surgery and trauma. The meta-analysis confirmed that a restrictive transfusion strategy was associated with a significant reduction in the proportion of patients receiving RBC transfusion and in the number of RBC units transfused. In the support of patients' ability to tolerate a lower haemoglobin threshold before receiving an RBC transfusion, there were no differences in mortality, overall morbidity or myocardial infarction between the two strategies. However, another trial of restrictive versus liberal transfusion strategies specifically in cardiac surgery patients found a higher frequency of death in the restrictive arm. The authors note that death was a secondary outcome of the study and that relatively few deaths occurred in the trial population.[51]

These clinical trial results illustrate that physicians may have historically perceived the therapeutic value of transfusions to be greater than the actual value with some patients receiving transfusions

who would have recovered without them. Observed variability in transfusion rates across physicians after adjusting for patient case-mix indicates that physicians perceive different values of blood for equivalent patients.[52] Physicians will have their own prevailing opinions about the effectiveness of blood, which is likely to vary across different indications, creating patterns of unnecessary transfusions unique to each physician. Unnecessary transfusions represent a waste of blood and unnecessarily expose patients to the risk of transfusion-related complications and society to the associated costs. The socially optimal demand for blood is underpinned by an understanding of when the clinical benefit and cost of transfusion is greater than the potential clinical risks and their associated costs. Therefore, while blood transfusions may be live-saving in settings such as critical bleeding, in other settings the direction of clinical practice is towards only transfusing patients who cannot be treated by other means.

1.3.2 Appropriate Use

Appropriate transfusions are all of those for which the marginal benefit to society is above or equal to the marginal cost, including the risk and costs of potential complications. Promoting the appropriate use of blood is a difficult task for national blood services and healthcare providers given that physicians are shielded from the price of blood by governments and perceive the benefits of transfusion to be higher than reality. Furthermore, transfusion prescriptions are driven by the concern that the patient has sufficient oxygen debt that would either create significant morbidity or not recover on its own. This creates a dynamic where the risk profile of the physician becomes a factor in the transfusion decision process. Risk averse physicians who may prefer to be actively providing care rather than waiting will have a higher tendency to prescribe transfusions, with a higher likelihood that some are unnecessary. A 2001 audit of ten major urban hospitals in Sydney found that 35% of RBC transfusions were deemed unnecessary by criteria based on a systematic literature review.[53] Other European studies published in 2011 and 2016 have found 25% and 41% of RBC transfusions in orthopaedic surgery[54] and emergency department[55] respectively to be unnecessary, and there is older evidence from 2000 of unnecessary prescriptions of platelets, plasma and cryoprecipitate in Australia.[56]

Traditionally, RBC transfusion decisions were guided by haemoglobin concentration thresholds. However, recent clinical guidelines have discouraged the use of single value haemoglobin triggers and instead encourage decisions based on the patient's intravascular volume status, evidence of shock, duration and extent of anaemia and cardiopulmonary physiologic parameters.[57] This wider assessment of physiological characteristics is designed to ensure transfusions are only prescribed to those patients with a high therapeutic value for blood. In order to facilitate the use of other blood management techniques, the transfusion community developed an evidence-based, patient-focused

approach to optimising the care of patients who might need a transfusion – patient blood management (PBM). The three pillars of PBM are optimising red blood cell mass, minimising blood loss and managing anaemia. Conceptually, PBM involves applying the best-available evidence to clinical circumstances in order to avoid the need for a transfusion. Recommendations go beyond applying a lower haemoglobin threshold to circumstances, including substitutes such as preoperative iron therapy, intraoperative cell salvage and avoiding autologous donations. As it has developed, PBM has expanded to separate recommendations for specific high blood use disciplines such as surgical or trauma patients. There is evidence of the success of single-centre PBM programmes at reducing transfusions in the US[58, 59] and Australia.[60] Following a call to action from a 2011 WHO Global Forum on Blood Safety, national blood services around the world have been developing their own patient blood management guidelines designed to reduce unnecessary transfusions. In Australia, the National Blood Authority (NBA) has published six guideline modules covering different medical disciplines including massive transfusion, obstetrics and critical care. Chapter 4 presents an assessment of the impact of the NBA's PBM guidelines for perioperative care on blood transfusions and patient outcomes in cardiac surgery. Analysing the effect of the PBM guidelines on cardiac surgery is particularly relevant given that cardiac surgery has the third highest RBC consumption in Australia behind haematology and gastroenterology[61]. Additionally, preoperative anaemia is common among these patients, which is often an indication for a RBC transfusion[59]. The introduction of the NBA's PBM guidelines coincides with a decrease in demand for RBCs in Australia as shown in Figure 1.4 – a 22% reduction between 2012 and 2017.[4]

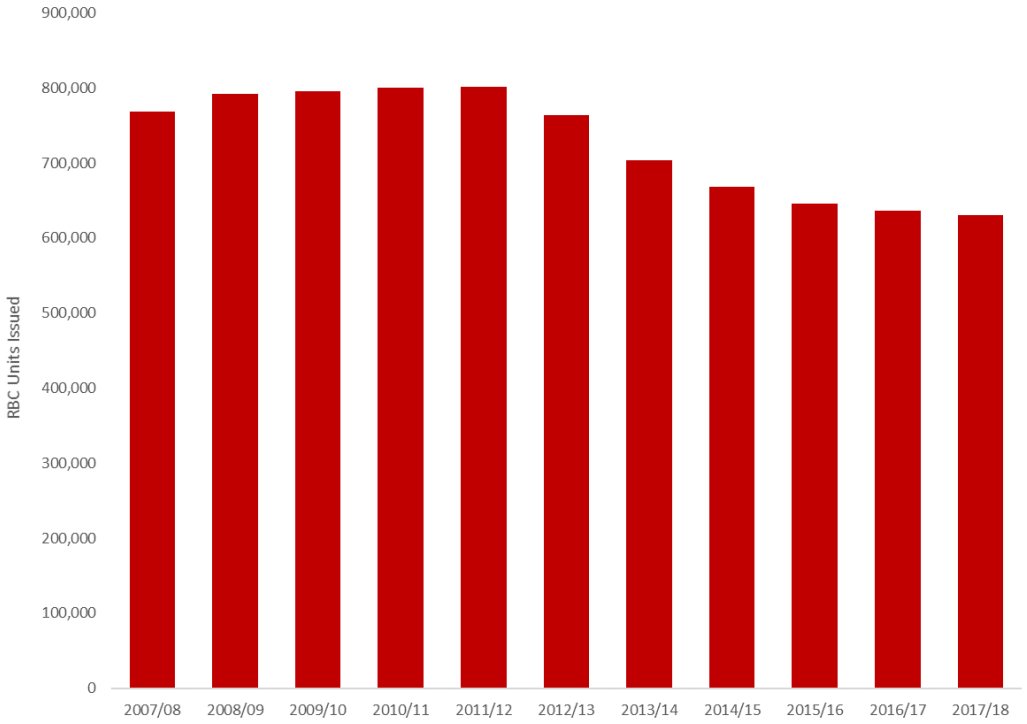
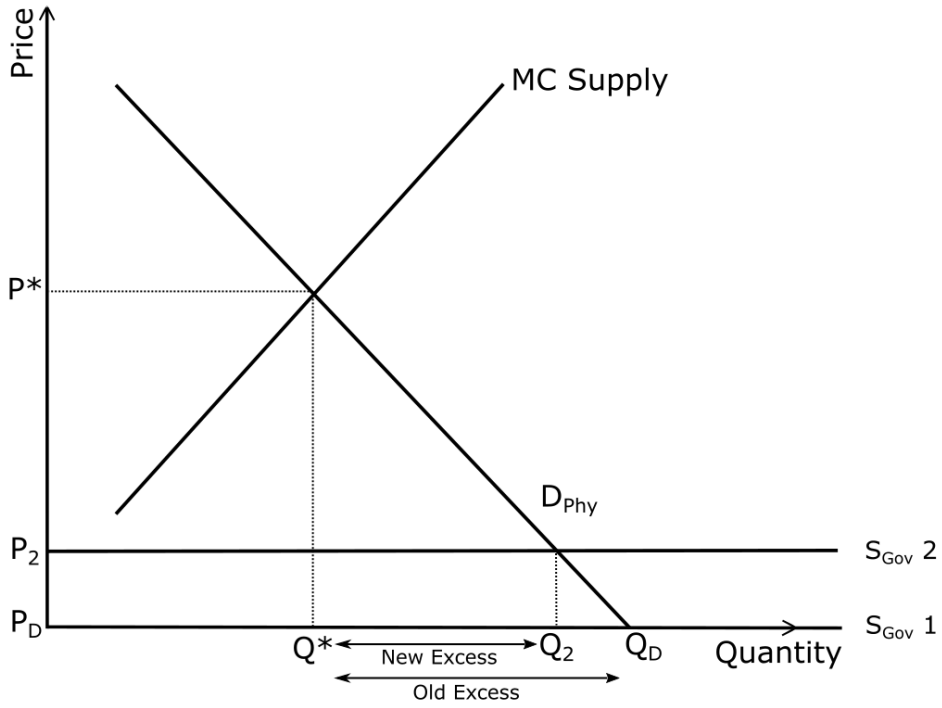


Figure 1.4: Demand for RBCs in Australia

1.3.3 Price Signals

A potential mechanism through which unnecessary blood transfusion has been able to flourish is that physicians have been removed from the cost and budgetary considerations of blood when prescribing a transfusion. In addition to clinical initiatives, such as the patient blood management guidelines, price signals have been introduced into the market for blood. Price signals can convey information on both the supply side to producers and demand side to consumers. Exposing physicians to a price signal for blood reveals the government's marginal cost of supply and promotes optimal decision-making by allowing physicians to accurately weigh up marginal benefit and marginal cost. Correctly-set price signals encourage resource users to value the scarce resource while incorrect or absent price signals permit resource users to undervalue the resource and waste it without direct consequences. In the context of the market for blood, the upstream supply chain relates to the blood donation, screening, processing, and distribution. The downstream supply chain relates to the blood utilisation in hospitals. Overall, the introduction of downstream price signals into the market is an attempt to reveal the government's marginal cost of supply to physicians via an upward shift from S_{Gov} 1 to S_{Gov} 2 in Figure 1.5. If successful, the price signal will reduce the quantity of blood demanded by physicians down from Q_D to Q_2, reducing the excess demand from $Q_D - Q^*$ down to $Q_2 - Q^*$.



Q* and P* represent the equilibrium quantity and price before the shift in the marginal cost of supply
Q_D and P_D represent the original quantity demanded and price faced by physicians
Q_2 and P_2 represent the equilibrium quantity and price signal revealing the government's supply curve

Figure 1.5: Introduction of a Price Signal

Aside from the remuneration of blood donors, prices are generally applied across the upstream supply chain. The NBA provides a budget to the ARCBS to collect donations and negotiates prices with suppliers of fractionated products which are borne by the federal, state, and territory governments. However, as blood and blood products were traditionally provided at no charge to hospitals by states and territories, there were no downstream price signals. In 2013, as part of a waste reduction initiative, the ARCBS introduced a downstream price signal by including a cost indicator on blood bag labels. These figures were not prices, as blood was still provided free of charge to hospitals, but represented the government's cost involved for collecting, screening, processing and distributing the product. The aim of the initiative was to increase physician awareness of the marginal cost associated with blood and encourage this cost to be considered in prescription decisions rather than the price.

Before the introduction of the NBA in 2003, each Australian state and territory negotiated individually with companies providing blood and blood products. Upon the signing of the National Blood Agreement in 2003, the newly formed NBA was tasked with managing the supply of blood to the states and territories on behalf of the federal government. Each state and territory was allocated a budget for blood, of which 63% is provided by the federal government and 37% is provided by the state or territory. The recent decisions by the states of New South Wales, Tasmania, Queensland, and Victoria to devolve their blood budgets down to the Area Health Services also represents a downstream price signal. Price signalling has been adopted in the market for blood around the world in places such as

England & Wales, the US, and Austria. Using England & Wales as an example, the UK National Blood Service bills each hospital monthly for the blood and blood products they order and hospitals provide annual forecasts that form the basis of the Blood Service's collection targets.[62] While economic theory supports the use of price signals, there is no quantitative evidence of their effectiveness in this context. A 2007 survey of physicians in New South Wales found that most admitted that they were unsure of the price per unit of blood, but that they were aware it was not free. Moreover, physicians revealed that the price of blood was unlikely to factor in their prescribing decision, with the health and wellbeing of the patient being the priority, rather than the cost.[63] Chapter 4 presents an analysis assessing whether budget devolution in Australia influenced the impact of the NBA's PBM guidelines on blood transfusions and patient outcomes in cardiac surgery.

In this context, price signals are designed to substitute explicit market prices for blood. Where markets exist without explicit prices, economists refer to the monetary equivalent of the good's price as the shadow price. The shadow price for blood represents the intersection between the marginal cost and marginal benefit curves. Given the uncertainty surrounding the marginal benefit of blood, there is similar uncertainty around the shadow price. Therefore, it is by no means clear at what level a price signal should be set in order to convey the correct cost to physicians. Ultimately, the effectiveness of price signals in the market for blood will be determined by whether they are set appropriately and whether the decision makers are exposed to the signal. Little change in clinical practice will arise if prescribing physicians are not directly exposed to the price signal.

1.3.4 Non-price Signals

Change in clinical practice such as reducing unnecessary blood transfusions ultimately arises from modifying physician decision-making at the point of care. Prices allow economic agents that face them to evaluate the trade-off between the benefits and costs of alternative course of action and can be effective at influencing such decisions. However, physicians are often shielded from the price of their decisions with the costs borne either by the hospital or government in a public setting, or the patients or their insurer in the private setting. Thankfully, appropriately implemented non-price mechanisms can also influence physician decision-making including reducing clinical uncertainty, changing the social norms in the institutional environment or professional benchmarking. As in other behavioural settings, engaging multiple mechanisms will likely produce superior results to a single mechanism strategy.

In healthcare, policies designed to change clinical practice target improving patient care, reducing costs, or both. While hospital ownership will play a role in determining the relative mix of factors that influence the desire to change behaviour, the general concepts will be common to both publically and

privately owned operators. Primarily, hospitals will attempt to change their behaviour in response to competition from other hospitals, to reduce costs or to attract physicians or patients. They are concerned with quality of care only to the extent that is observed by stakeholders such as the government or patients. A degree of altruism or professionalism may be incorporated into any decision that should improve patient care; however, as economic agents, maintaining their source of funding in the case of public hospitals or profitability in the case of private hospitals is a primary concern. Indeed, there is evidence to suggest that, as complex healthcare delivery organisations with an entrenched culture, hospitals experience a significant degree of inertia even when faced with solvable problems that would improve patient care.[64]

Broadly speaking, a physician's desire to change their decision-making could be the result of autonomous action or the result of a change of culture in their institutional environment. Institutional culture can be passive – "it's just the way things are done around here" – or active, in the form of hospital managers explicitly encouraging more or less use of a particular resource. From comparison of the variation between hospitals to the variation between surgeons within hospitals, there is evidence that physicians adapt their practice to that of their colleagues.[65] While evidence to suggest that peer effects can create an influencing social norm, there is no consensus on how information is disseminated through networks.[65] It is established that individuals prefer to interact with others who have similar characteristics, such as gender, age or seniority – which will influence the structure of networks within the workplace.[66] This implies that there may be social barriers between professional groups such as doctors and nurses, or between senior and junior staff members within a speciality. In the case of unnecessary blood transfusions, the most appealing incentive to hospitals is potentially that valuable resources that could be saved. Given the scale of unnecessary transfusions, suppliers of blood such as governments will also be highly motivated by the economic incentive. Physicians and other altruistic operators may be motivated by the opportunity to reduce patient morbidity.

Given acknowledgement of the problem (unnecessary transfusions), the incentive for change (economic or altruistic), and the evidence base for solution (patient blood management), the next question concerns the most appropriate method to change practice and alleviate the problem. One of the most popular strategies for bridging the gap between evidence and practice is the development and dissemination of clinical guidelines - a set of evidence-based recommendations for a course of action given a particular set of clinical circumstances, usually developed by expert groups through a systematic review of the relevant literature. Clinical guidelines have been developed by national public health bodies, professional bodies or clinical bodies and are often developed for specific health conditions, such as obesity, smoking cessation or stroke. In response to the evidence of the deleterious effects of blood transfusions, the NBA published a series of PBM clinical guidelines covering disciplines

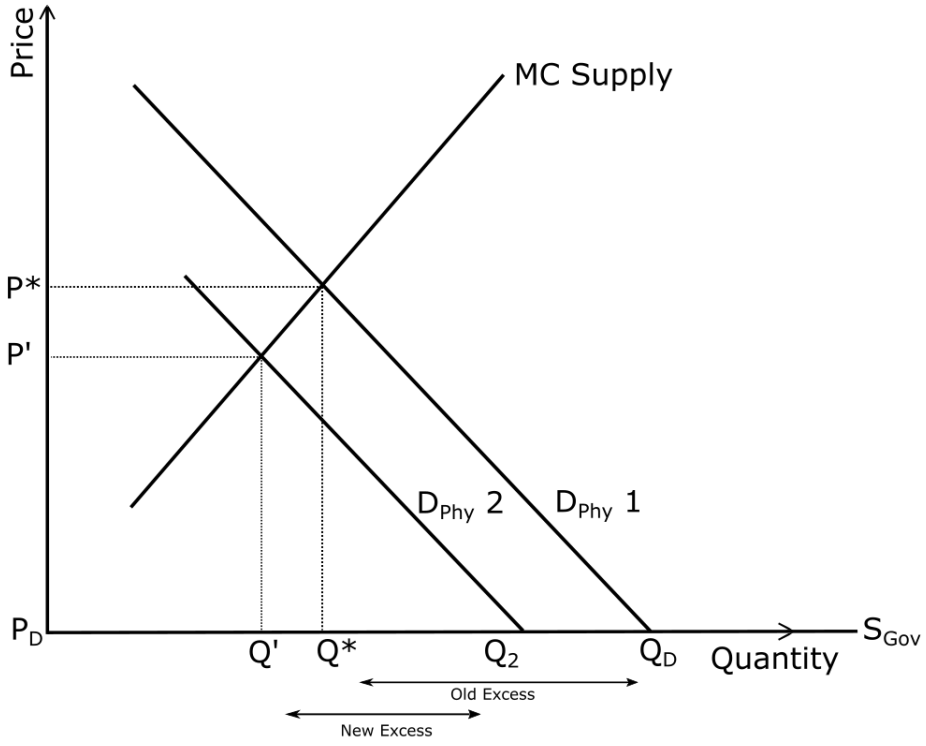
such as obstetrics, critical bleeding and paediatrics between 2011 and 2016. These guidelines were designed to encourage the appropriate use of blood and blood products in Australia by reducing the gap between evidence and practice.

Best practice clinical guidelines development involves an appraisal of the economic as well as clinical evidence. Focusing on clinical evidence alone can lead to recommendations which do not meet cost-effectiveness standards. Optimal care is not only the most effective care, but also that which appropriately balances resource availability to cost-efficiently maximise the health of the population under a fixed budget constraint.[67] Public health bodies in England and the Netherlands already explicitly consider the evidence relating to costs, quality of life and cost-effectiveness such as the economic evaluation presented Chapter 3 when formulating evidence-based recommendations, and the practice is likely to become more widespread as healthcare budgets become more constrained. The NBA considered economic issues when establishing their PBM recommendations expecting to derive savings in terms of resource use, hospital costs and laboratory costs. By incorporating cost considerations into their recommendations, the NBA are revealing the shadow price of blood to physicians and implicitly encouraging them to incorporate it into their decision making.

Clinical guidelines are designed to condense the latest advances in healthcare knowledge down to manageable recommendations that are simple to execute. Appropriate clinical guidelines alleviate the need for physicians to perform their own time-consuming appraisal of the original evidence, which many physicians are not inclined to perform of their own volition.[68] However, there are many barriers to instigating change in established patterns of care. Chief among these is the simplicity of the research findings, and of understanding when to implement the recommendations and how to implement the recommendations. A change from a simple care pathway to a more complex one, or one that requires collaboration between disciplines, will be met with more resistance than an alternative simple pathway.[69] Indeed there are potential barriers at each stage of the healthcare delivery model – the patient, the physician, the clinical team, the hospital and the wider culture.

By providing credible recommendations based on clinical evidence that reduce the perceived value of a transfusion, the physician's perceived demand curve will shift from D_{Phy} 1 to D_{Phy} 2. Physicians would now consider the marginal benefit of some of the previously prescribed transfusions to be below the zero price and the quantity of blood demanded will fall to from Q_D to Q_2. Given the shift in the physician's perceived demand curve, the equilibrium price and quantity (considering the true marginal cost of supply) have also shifted down from P* to P' and Q* to Q' respectively. The excess demand in the market has also fallen, from Q_D – Q* to Q_2 – Q'. Incorporate additional economic concerns into

recommendations such as cost attempts to further reduce excess supply by explicitly discouraging these low-value transfusions.



Q* and P* represent the original equilibrium quantity and price before the shift in the marginal cost of supply
Q_D and P_D represent the original quantity demanded and actual price faced by physicians
Q* and P* represent the new equilibrium quantity and price after the shift in the physician's perceived demand curve
Q_2 represents the actual quantity demanded after the shift in the physician's perceived demand curve

Figure 1.6: Shift in Physician Demand

Unfortunately, adherence to clinical guidelines recommendations is not guaranteed. Over the last 20 years, extensive work on the causes of non-compliance has been published by Grol and colleagues, developing theories and solutions from the behavioural science literature.[69] Cognitive theories align with those from the economics literature regarding uncertainty: deviations from the optimal course of action are a result of insufficient information. Other learning theories suggest that agents need to experience a problem first-hand before they will be amenable to adapting their behaviour towards a solution. Alternative behavioural theories suggest that changing established behaviour requires external stimuli such as feedback or incentives. Finally, social theories suggest that behaviour flows through an organisation from the top down and cultural shifts in practice will occur when senior agents within an organisation adjust the social norms. As an intervention for changing the behaviour of physicians, clinical guidelines align with the cognitive theory of behavioural change regarding reducing uncertainty through providing credible information. Good practice clinical guideline development includes providing a grade for each recommendation based on the strength of the underpinning evidence.[70] Recommendations awarded higher grades, based on stronger evidence, will reduce clinical

uncertainty more than recommendations awarded lower grades. Therefore, we expect more to find more consistent healthcare delivery for those recommendations based on stronger evidence.

While effective at synthesising the existing evidence, recommendations from clinical guidelines are generally broad so as to encompass the majority of patients. Recommendations from guidelines do not encompass every possible set of clinical circumstances, meaning that physicians must still use their own judgment under those circumstances not discussed in clinical guidelines.[71] Furthermore, medical practice encompasses a large grey area of clinical discretion, such that substantial variations may still exist even when appropriate guidelines are considered.[72] As a result, publishing clinical guidelines does not necessarily guarantee consistency of care across the population.

1.3.5 Variation in Care

Variability in the average blood transfusion rate is widely documented across hospitals in settings such as intensive care[73], cardiac,[74] and orthopaedic surgery[75] and across physicians in cardiac[52] and gastrointestinal surgery.[76] A major contributing factor to this observed variation is that physicians face inconsistent perceived demand curves for blood due to prevailing opinions about its effectiveness. This leads to a disparity where some patients are judged to have high need for a transfusion by some physicians but not others.

Beyond blood transfusions, a body of literature has been devoted to studying variation in healthcare utilisation since seminal work on this topic was published by Glover in 1938 highlighting large regional differences in paediatric tonsillectomy rates across the UK.[77] Since then, research has been published documenting an array of patient, physician and hospital characteristics across which significant variations in healthcare utilisation have been observed. Patient demographics linked to significant variations include gender[78], income[79] and ethnicity.[80] However, is it difficult to disentangle variations in practice across economic indicators that exist due to genuine need, which is understood to be positively correlated with lower socioeconomic status.[81] At the physician level, Wennberg popularised the practice style theory that attributes unexplained variations across physicians to fixed physician preferences and beliefs – such as opinions about blood.[82] Other potential objective determinants of variation across physicians are speciality,[83] place of education,[84] experience[85] and workload.[86] Hospital characteristics such as size,[85] location,[86] type[87] and capacity[88] have all been linked to variations in rates of diagnosis, treatment and health outcomes.

Variations in cost-effective care, where evidence has determined that the benefits outweigh the risks and associated costs, generally represent an underuse of rouses and avoidable loss of health. However, the appropriate intervention is clearer for some conditions, e.g. hip fracture, than is it for others, e.g.

depression. Variations among preference-sensitive care, where there are multiple treatment options and informed patient choice should be a factor in decision making, are largely due to differences in professional opinion and fall prey to supplier-induced demand. In this instance, patient preferences may lead to a degree of observed variation that is warranted. Variation in supply-sensitive care, such as the capacity of the healthcare system (e.g. hospital beds, physicians) is usually considered a result of overuse and a waste of valuable resources. Unwarranted variation was defined by Wennberg & Gittlesohnin 1973 as variation in care that cannot be explained by illness or patient preferences.[89] Reducing unwarranted variation represents an opportunity to save resources, improve health, or both.

Under this framework, blood transfusions would be classified as effective care for which there is documented overuse, although it is not clear for whom blood transfusions are effective, creating a misalignment between physicians' perceived demand curve and the actual demand curve. Without objective, authoritative standards that can be followed to guide decision making, physicians' preference, bias and risk aversion take precedence. The documented variability in blood transfusions across hospitals and physicians is therefore not surprising given the historical lack of evidence-based standards.

The NBA's PBM guidelines were an intervention designed to alleviate clinical uncertainty and physician bias by providing evidence-based recommendations that reduce the need for a blood transfusion. Through the wide diffusion of credible information to guide practice, the guidelines should improve the consistency of care across the population. However, the impact of the guidelines may not be homogeneous across the healthcare system. At the physician level, clinical guidelines are likely to be more effective when physicians are already aware that new evidence has been developed that may improve the quality of their care, when they are more familiar with the condition described and when they agree with the recommendations.[90] At the hospital level, the institutional implementation strategy is likely to influence adherence to the guidelines. Potential initiatives include distributing educational materials, training sessions, audit and feedback mechanisms, or full system redesigns, with the literature suggesting that multiple-initiative strategies may outperform single-initiative strategies.[90]

The distribution of responses to the PBM guidelines across hospitals and across physicians will determine the impact of the guidelines on pre-existing variations in care. If those hospitals and physicians who were already using blood sparingly before the guidelines were published experience stronger responses to the guidelines than more liberal users of blood, then variation in care will increase. However, those hospitals and physicians using more blood before the publication of the guidelines will have more unnecessary transfusions to alleviate through adhering to PBM techniques.

To determine the impact of the NBA's PBM guidelines on variation in care, Chapter 5 presents an examination into heterogeneity in the response to the guidelines.

1.3.6 Summary

The demand side of the market for blood involves its transfusion as a therapeutic product. As a legacy treatment, the effectiveness and safety of blood transfusions may have been assumed for some time with the societal cost excluded from prescription decisions. The current movement towards patient blood management could be considered an attempt to bring transfusion policy in line with wider healthcare policies, where treatments are assessed on the basis of evidence of their clinical benefit and cost. However, compared with a new therapy for which no standard practice has been developed, there are significant difficulties in modifying physician prescribing patterns to achieve consistent and cost-effective blood transfusion practices more aligned with a socially optimal allocation.

1.4 Research

In summary, the market for blood is characterised by a unique combination of features including its creation through donation, the necessity for screening to ensure safety, its perishable nature, the significant uncertainty in its therapeutic value and the wide variability in its use. The work presented herein addresses a number of gaps in the literature. Chapter 2 presents a systematic literature review on incentive and non-incentive based interventions for increasing the supply of blood. Chapter 3 presents an economic analysis of an age of blood intervention within an international, multi-centre, randomised, double-blind clinical trial. Chapter 4 presents an assessment of the impact of national PBM guidelines for perioperative care on blood transfusions and patient outcomes. Chapter 5 examines heterogeneity in the response to these guidelines and the subsequent impact on variation in the RBC transfusion rate across hospitals and surgeons. Finally, Chapter 6 summaries the contribution of this thesis and outlines what this evidence implies about policies and future research related to the use of blood and blood products.

2 A Systematic Review and Network Meta-analysis of Incentive and Non-remunerated Interventions for Increasing Blood Donations

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Vox Sanguinis

Background and Objectives Blood services are tasked with efficiently maintaining a reliable blood supply, and there has been much debate over the use of incentives to motivate prosocial activities. Thus, it is important to understand the relative effectiveness of interventions for increasing donations.

Materials and Methods This systematic review used a broad search strategy to identify randomized controlled trials comparing interventions for increasing blood donations. After full-text review, 28 trials from 25 published articles were included. Sufficient data for meta-analysis were available from 27 trials. Monetary incentives were assumed to be equivalent regardless of value, and non-monetary incentives were assumed to be equivalent regardless of type. Non-incentive-based interventions identified included existing practice, letters, telephone calls, questionnaires, and the combination of a letter & telephone call. A network meta-analysis was used to pool the results from identified trials. A subgroup analysis was performed in populations of donors and non-donors as sensitivity analyses.

Results The best performing interventions were letter & telephone call and telephone call-only with odds ratios of 3·08 (95% CI: 1·99, 4·75) and 1·99 (95% CI: 1·47, 2·69) compared to existing practice, respectively. With considerable uncertainty around the pooled effect, we found no evidence that monetary incentives were effective at increasing donations compared to existing practice. Non-monetary incentives were only effective in the donor subgroup.

Conclusion When pooling across modes of interventions, letter & telephone call and telephone call-only are effective at increasing blood donations. The effectiveness of incentives remains unclear with limited, disparate evidence identified.

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Key words: blood collection, donor motivation, donor recruitment, donors.

Introduction

Worldwide, more than 112 million people will donate blood in a typical year; however, many countries experience chronic or seasonal shortfalls in their blood supply [1]. Blood services are responsible for maintaining a reliable supply of blood by recruiting and retaining donors. In order to do this efficiently, it is important to understand the relative effectiveness of interventions to increase blood donations.

Since Titmuss' seminal work in the 1970s, there has been much debate on the relative importance of intrinsic

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and extrinsic motivation for donating blood [2,3]. Intrinsically motivated donors acquire personal satisfaction from donating, whereas extrinsically motivated donors require an external reward before they will donate. While altruism, an individual's degree of selflessness, is likely to play a significant role in determining who will donate under what circumstances, other factors including conforming to social norms, prestige and respect may also be involved [4].

In a pure altruism model, donors gain utility solely through providing a valuable public good. The greater the value of the public good, the greater we might expect the level of donor utility. However, contrary to this hypothesis, one study showed that those with highly valuable O-negative blood were no more willing to donate than those with less valuable blood [5]. The impure altruism model implies that there is some additional utility gained through the act of giving itself, this could take the form of a sense of civic duty associated with social expectations or a 'warm glow' [4]. This duty might in turn legitimize the expectation that the individual has reciprocal rights should they find themselves in need [6]. Indeed, reciprocal altruism was reported as the most important motive for donating blood by 45·5% of subjects in a recent survey [7].

The concern that intrinsic motivation may not be sufficient to ensure an adequate supply has led some blood services to consider offering incentives to donors. Incentives provide extrinsic motivation for the relevant behaviour and were hypothesized to be effective at increasing donations by early researchers [3]. The popular counterargument suggested by Titmuss was that incentives may erode the sense of civic duty associated with providing a public good and crowd out donors with high intrinsic motivation [2]. If Titmuss' hypothesis is correct, incentives that are insufficient in magnitude to compensate for the loss of intrinsic motivation may reduce donations [2,8,9]. Incentivizing donations with extrinsic rewards may also compromise the safety of the blood supply by encouraging individuals to respond deceptively to screening questions in order to avoid deferral and receive the reward [10].

Incentives can be monetary (e.g. cash payments) or non-monetary (e.g. goods or services) operating similarly by increasing extrinsic motivation to donate. While monetary and some non-monetary incentives may be demotivating to those with a high intrinsic motivation, other non-monetary incentives such as a reward for achieving a donation threshold may provide a recognizable signal that reinforces intrinsic motivation [11,12]. It has also been suggested that the safety concerns regarding monetary incentives may not extend to non-monetary incentives [13]. Non-incentive-based interventions are information, cues or prompts designed to increase the salience of donating blood. Non-incentive-based interventions reinforce intrinsic motivation only and include personal approaches such as telephone calls, and impersonal interventions such as letters or questionnaires [14].

Obtaining comparable treatment and control groups in observational studies of incentives is problematic given the potential impact on the composition of the donor pool. For this reason, we focus on randomized controlled trials (RCTs) to obtain comparable treatment and control groups and that minimize the risk of selection bias.

The primary aim of this study was to compare incentive- and non-incentive-based interventions for increasing blood donation utilizing data from all identified trials simultaneously in a network meta-analysis. The secondary aim was to determine whether the level of intrinsic versus extrinsic motivation affects treatment [15]. As standard donation practice in all identified studies did not involve incentives, we considered previous donors to be intrinsically motivated and non-donors to be extrinsically motivated. To assess the impact of intrinsic versus extrinsic motivation, the network meta-analysis was separately analysed on donor and non-donor subgroups.

The topic of motivating blood donations has been explored in a number of previously published systematic reviews. Godin [16] adopted broad inclusion criteria and through calculating pooled effect sizes concluded that motivational or reminder-based interventions were most effective. Without distinguishing between monetary and non-monetary incentives, Goette [17] conducted a narrative review of crowding out in blood donation concluding that incentives were effective when donors could maintain anonymity. Niza [18] conducted a systematic review and meta-analysis of incentives concluding that they did not increase donations. In a systematic review of interventions for retaining first-time donors, Bagot [19] concluded that personal approaches such as a motivational interview were most effective. Finally, in another systematic review of incentives, Chell [20] concluded that the evidence is limited and inconsistent with weak support for the effectiveness of non-monetary incentives.

However, these previous reviews of interventions to increase blood donations have either not quantitatively synthesized all identified evidence simultaneously or only summarized the available evidence with respect to one of the categories of intervention considered in the present review [16–20]. By adopting stricter inclusion criteria and pooling across modes of interventions, we are able to perform a network meta-analysis. Network meta-analyses make best use of available data by providing a global estimate of treatment effect for the complete set of interventions under evaluation and are especially useful in this case where there are direct comparisons between interventions that can be pooled to facilitate robust

comparisons between interventions with inadequate or absent direct comparisons [21].

Materials and methods

This review was developed from a broader protocol for a Cochrane review [14]. After full-text screening, it became apparent that it was infeasible to quantitatively synthesize the Cochrane protocol due to two factors:

- Including both attitudes towards donation and actual donations as outcomes.
- Including studies comparing variants of interventions (e.g. two types of letters).

To permit quantitative synthesis of the identified evidence, the Cochrane protocol was withdrawn and the review continued after incorporating additional inclusion criteria only trials with donation as the only outcome, and that compare two types of interventions. Therefore, this review represents a subset of the original Cochrane review, maintaining the systematic nature of the research.

Search strategy

The search strategy provided in the Appendix S1was initially developed for MEDLINE and modified for other databases [14]. The following bibliographic and citation databases were searched from their inception to 28/08/2018:

- MEDLINE (Ovid SP)
- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
- EMBASE (Ovid SP)
- EconoLit (EBSCOhost)
- Current Contents (ISI)
- PsycINFO (Ovid SP)
- ProQuest Dissertations and Theses database.

The following trial registers were also searched on 28/08/2018:

- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)
- ClinicalTrials.gov.

Forward citations of all included studies were searched using Google Scholar. Backward citations were searched by hand-searching reference lists of included studies and reviews.

Inclusion criteria

This review included RCTs of any two or more interventions for increasing blood donor recruitment or retention in current and potential donors of whole blood, excluding observational evidence identified by previous reviews [16,17]. Trials of interventions for plasmapheresis donation were excluded to ensure the comparability of identified studies.

Data collection

After removal of duplicates, two authors (AI & DM) independently screened titles and abstracts. Full-text copies were also double screened against the same inclusion criteria documenting reason for exclusion. Authors were not blind to publication date, authors' name, affiliation or journal.

A data extraction form was developed to capture information on participants, methods, intervention design and delivery, and results. Two authors independently completed the data extraction form for each trial (AI & AH). Differences of opinion were resolved by consensus, and data entry errors were resolved by reference to the full text. Numerical data were entered into Microsoft Excel for data management and imported into STATA version 15 [22] for the network meta-analysis.

Two authors (AI & ZM) independently applied the Cochrane Collaboration's revised tool for assessing risk of bias [23] to all included trials. This tool provides criteria for grading RCTs either at high, low or unclear risk of bias across six domains of research selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Discrepancies between the two authors were resolved by consensus. A risk of bias summary figure was generated using RevMan 5·3 [24].

Data synthesis

The outcome of interest was whole blood donation, or an attempt to donate. These were considered to be equivalent as to not exclude donors deferred for medical reasons. Treatment effects were expressed as odds ratios (ORs). Treatment effects for continuous data were transformed into ORs, based on the assumption that the underlying continuous measurements in each intervention group follow a logistic distribution [25].

Studies were grouped by type of intervention (monetary, non-monetary and non-incentive). Non-incentive-based interventions were further split by mode of delivery regardless of content. We make no distinction between monetary incentives that differed in dollar-value or between non-monetary incentives that differed in type. Therefore, results reflect average treatment effects for groups of 'like' but not identical interventions. A similar approach was taken in previous reviews comparing infection rates from paid versus unpaid donations; [10]

recognizing the distinct effects of incentives on the composition of the donor pool.

If a study reported donation rates at more than one time point, the results for the longest follow-up period were used in the meta-analysis. A number of studies were identified that included comparisons between interventions with the same mode of delivery but that delivered different messages designed to increase blood donations, for example a reminder letter highlighting seasonal shortages versus one that stressed the benefits of prosocial activity. As the aim of the review was to compare different types of interventions, the two reminder letters in the above example were pooled into a single intervention type for the purposes of the meta-analysis. Two attempts were made to contact corresponding authors when additional data were required.

In order to pool the results, a network diagram was generated based on the pairwise direct comparisons evaluated in the identified trials. The network was analysed using a frequentist random-effects meta-analysis in STATA version 15 [22] using the mvmeta package [26].

Subgroup analysis

To determine whether the level of intrinsic versus extrinsic motivation affects treatment, trials were split into donor and non-donor populations based on the enrolled participants. Donors were those who had previously donated or taken steps towards their first donation. Non-donors were individuals with no prior donation history or evidence of an intent to donate. Studies that drew from population-level samples were assumed to be non-donors. The network meta-analysis was repeated separately for these two subgroups.

Sensitivity analysis

As attitudes towards donation are likely to be influenced by social norms regarding offering incentives and many low-income countries still remunerate donors, [27] a sensitivity analysis was performed on trials performed in developed economies only as defined by the United Nations [28]. From our sample, this was studies performed in Europe, North America, Australia or New Zealand. The sensitivity of the findings to trials judged to have a high risk of bias across one or more domains was also assessed by repeating the primary analysis without these studies.

Results

Figure 1 presents the PRISMA diagram [29]. The computerized database search identified a total of 18 147 studies. Forward and backward hand-searching identified another 76 eligible studies. After excluding duplicates, 14 612 titles and abstracts were screened for eligibility and full-text review was performed on 277 studies. Twenty-five studies, comprising 28 separate trials, were included in the review. The necessary data required for inclusion in the network meta-analysis were not available from one of the trials [15]. Two unsuccessful attempts were made to contact the authors to acquire the necessary missing data before the trial was removed from the network.

Characteristics of included studies

Nine trials were identified that included comparisons involving incentives three of which included monetary incentives [9,30,31] and eight of which included non-monetary incentives [15,30,32–35]. Monetary incentives were valued from US$5 to US$23 [9,30,31]. The most common non-monetary incentive was a T-shirt, while others included a supermarket voucher, cholesterol test, anti-theft credit card sleeve, cinema tickets or a mention in the local newspaper. Non-incentive-based interventions included letters (n = 14, including emails, SMS and brochures), telephone calls (n = 13), questionnaires (n = 10) or the combination of a letter & telephone call (n = 4). Eighteen of the 27 included trials included an intervention herein described as 'existing practice'. Existing practice represents the placebo control group. This was not calling donors, not sending a questionnaire or letter, or not providing the incentive or message that was being provided to the interventional arm of the trial. We describe this group as existing practice because participants remained exposed to the blood services' regular promotional campaigns in terms of blanket television, radio or print media promotions. Table A2 in the Appendix S1 provides additional details on interventions designated existing practice for the purpose of the meta-analysis.

Table 1 presents a summary of the 56 pairwise comparisons evaluated in the 27 included trials. A more detailed summary of the studies including a full list of interventions, results and individual study forest plot is presented in the Appendix S1.

One trial contained two overlapping comparisons [33]. Some participants were offered a T-shirt upon their next donation with 50% receiving their invitations to donate via email and 50% via telephone. Including both of these comparisons non-monetary incentive versus existing practice and letter versus telephone call, double counts participants who will have correlated outcomes. This is a limitation but without information on which participants were within the incentive/no-incentive groups that received emails versus telephone calls it was decided that this was preferred to including only one of the comparisons.

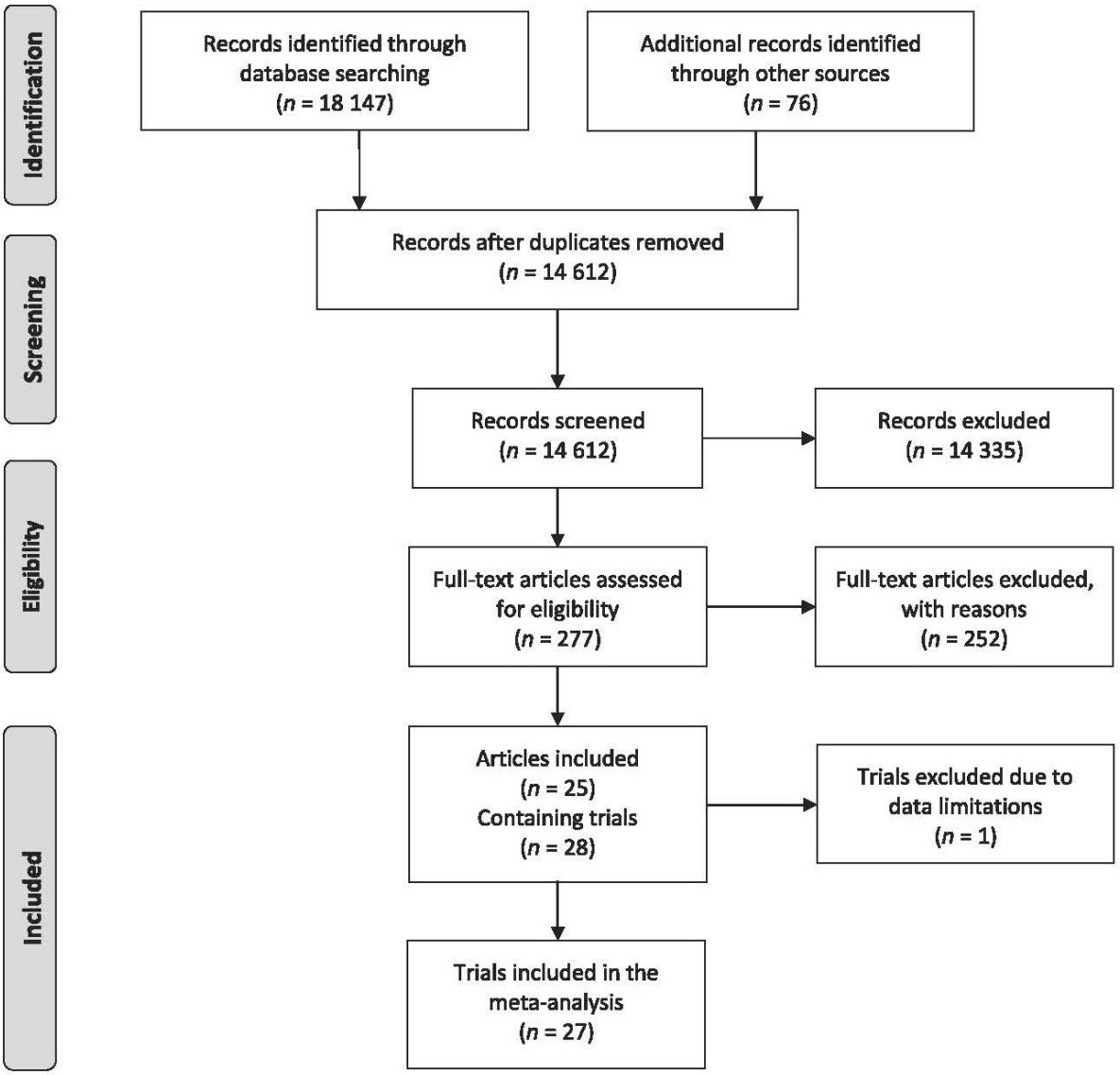


Fig. 1 PRISMA diagram.

Comparison of interventions

Figure 2 presents the network diagram and forest plot from the network meta-analysis with existing practice as the reference treatment. Each node in the network diagram represents an intervention, and lines between nodes represent a direct comparison between interventions. The thickness of the lines connecting the nodes of the network diagram indicates the relative number of direct comparisons between the interventions. Odds ratios and 95% confidence intervals for each intervention compared to existing practice are included on the forest plot with the x-axis on the log scale. The matrix beneath the forest plots presents the pairwise comparisons between all interventions calculated from the network meta-analysis.

The results indicate that letter & telephone call or telephone call-only are the most effective interventions with odds ratios of 3·08 (95% CI: 1·99, 4·75) and 1·99 (95% CI: 1·47, 2·69) compared to existing practice, respectively. There is no evidence that monetary incentives, non-monetary incentives, letters or questionnaires are effective at increasing blood donations compared with existing practice. The confidence interval around the pooled estimate for monetary incentives is particularly wide, indicating significant heterogeneity in the results of the limited evidence identified.

Table 1 Summary of pairwise comparisons

Study	Country	Prior donation history	Sample (*N*) ITT	Age (years): Mean (SD)	Female	Delivery/follow-up details
Monetary vs. non-monetary						
Iajya 2010	Argentina	NR	18 500	32·0 (NR)	41%	3 weeks of donation behaviour follow up
Monetary vs. letter						
Iajya 2010	Argentina	NR	18 500	32·0 (NR)	41%	3 weeks of donation behaviour follow up
Monetary vs. telephone call						
Upton 1973	USA	Repeat donors (half lapsed)	1261	NR	NR	Telephone recruitment
Monetary vs. existing practice						
Mellström 2008	Sweden	Novice donors	381	NR	58·0%	Incentive to undertake preliminary health examination
Non-monetary vs. letter						
Goette 2009 S1	Switzerland	Non-donors	2824	NR (NR)	48·7%	3 weeks prior to blood drive
Goette 2009 S2	Switzerland	Repeat donors	8269	44·6 (NR)	38·8%	3 weeks prior to blood drive
Iajya 2010	Argentina	NR	18 500	32·0 (NR)	41%	3 weeks donation behaviour follow up
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	Letters: 3 months after initial donation, T shirt: after first donation
Reich 2006	USA	Novice donors	6919	NR	48·6%	Open invitation with 12 months of donation behaviour follow up
Royse 1999	USA	Novice donors	1003	NR	54%	Post donation with 14 months of donation behaviour follow up
Sun 2016	China	Repeat donors	80 000	31·3	32·8%	15 day field experiment using mobile collection vehicles
Non-monetary vs. telephone call						
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	Telephone: 3 months after initial donation, T shirt: after first donation
Reich 2006	USA	Novice donors	6919	NR	48·6%	12 months of donation behaviour follow up
Non-monetary vs. questionnaire						
Myhal 2017	Canada	Novice and repeat donors	7399	38·9 (16·2)	51·7%	Post donation with 6 months of donation behaviour follow up
Non-monetary vs. existing practice						
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	T shirt: after first donation
Myhal 2017	Canada	Novice and repeat donors	7399	38·9 (16·2)	51·7%	Post donation with 6 months of donation behaviour follow up
Sun 2016	China	Repeat donors	80 000	31·3	32·8%	15 day field experiment using mobile collection vehicles
Letter vs. telephone call						
Germain 2016	Canada	Repeat donors	3553	41·8 (14·3)	51·5%	4 days prior to blood drive
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	Letter & telephone: 3 months after first donation
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, telephone: 5 6 days prior to blood drive
Mines 2000	New Zealand	Lapsed one-time donors	325	25·0 (9·9)	62·8%	6 days prior to blood drive
Ou-Yang 2017	China	Lapsed donors	1188	NR	NR	7 months of donation behaviour follow up
Reich 2006	USA	Novice donors	6919	NR	48·6%	12 months of donation behaviour follow up

Table 1 (Continued)

Study	Country	Prior donation history	Sample (*N*) ITT	Age (years): Mean (SD)	Female	Delivery/follow-up details
Letter vs. letter & telephone call						
Germain 2016	Canada	Repeat donors	3553	41·8 (14·3)	51·5%	4 days prior to blood drive
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, telephone: 5 6 days prior to blood drive
Letter vs. questionnaire						
Mines 2000	New Zealand	Lapsed one-time donors	325	25·0 (9·9)	62·8%	6 days prior to blood drive
Wevers 2015	The Netherlands	Novice donors	937	NR	70·5%	2 weeks of donation behaviour follow up
Letter vs. existing practice						
Cioffi 1998	USA	NR	1121	NR	NR	6 days prior to blood drive
Gimble 1994	USA	4·7-6·6% novice donors	65 865	NR	47-53%	1 2 weeks prior to blood drive
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	Letter: 3 months after first donation
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, telephone: 5 6 days prior to blood drive
Ou-Yang 2017	China	Lapsed donors	1188	NR	NR	7 months of donation behaviour follow up
Sun 2016	China	Repeat donors	80 000	31·3	32·8%	15 day field experiment using mobile collection vehicles
Wevers 2015	The Netherlands	Novice donors	937	NR	70·5%	2 weeks of donation behaviour follow up
Telephone vs. letter & telephone call						
Germain 2016	Canada	Repeat donors	3553	41·8 (14·3)	51·5%	4 days prior to blood drive
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, Telephone: 5 6 days prior to blood drive
Telephone call vs. questionnaire						
Sinclair 2010	USA	Novice and repeat donors	427	31·1 (13·5)	59·1%	1 month after donation with 12 months of donation behaviour follow up
Sinclair-Miracle 2018	USA	Repeat donors	195	37·2 (13·5)	27·2%	1 month after donation with 12 months of donation behaviour follow up
Mines 2000	New Zealand	Lapsed novice donors	325	25·0 (9·9)	62·8%	6 days prior to blood drive
Telephone call vs. existing practice						
Ferrari 1985	USA	NR	78	NR	NR	2 days prior to blood drive
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, telephone: 5 6 days prior to blood drive
Maghsudlu 2017	Iran	Novice donors	1356	NR	10·4%	Telephone: 3 months after first donation

Table 1 (Continued)

Study	Country	Prior donation history	Sample (*N*) ITT	Age (years): Mean (SD)	Female	Delivery/follow-up details
Ou-Yang 2017	China	Lapsed donors	1188	NR	NR	7 months of donation behaviour follow up
Weisenthal 1989	Canada	Novice donors	209	NR	NR	1 week after index donation
Letter & telephone call vs. existing practice						
LaTour 1989 S1	USA	NR	800	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
LaTour 1989 S2	USA	NR	1200	NR	NR	Letter: 3 4 weeks, telephone: 1 2 weeks prior to blood drive
Masser 2016	Australia	Novice donors	3646	32·0 (12·3)	65·2%	Brochure/email: 1 week, telephone: 5 6 days prior to blood drive
Questionnaire vs. existing practice						
Godin 2008	Canada	Repeat donors	4672	NR	38·4%	1 month after donation
Godin 2010	Canada	Novice donors	5000	30·4 (12·9)	53·0%	3 weeks prior to becoming eligible to donate again
Godin 2014	Canada	Lapsed donors	7000	38·2 (13·8)	50·2%	Any time after being classified as lapsed donor
Myhal 2017	Canada	Novice and repeat donors	7399	38·9 (16·2)	51·7%	Post donation with 6 months of donation behaviour follow up
Wevers 2015	The Netherlands	Novice donors	937	NR	70·5%	2 weeks of donation behaviour follow up
van Dongen 2013 S1	The Netherlands	Novice donors	7008	33·4 (12·1)	66·6%	10 days before first appointment, 6 months of donation behaviour follow up
van Dongen 2013 S2	The Netherlands	Repeat donors	11 789	44·8 (13·0)	51·1%	6 months of donation behaviour follow up

Risk of bias

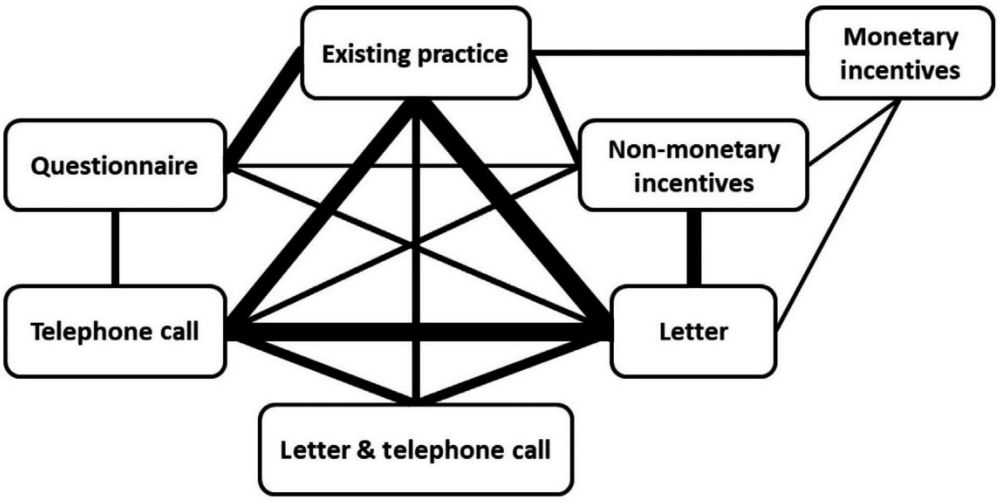
The risk of bias summary for each included trial rated on six domains of potential bias is presented in Fig. 3. Domains rated low, unclear and high risk are highlighted green, yellow and red, respectively. Selection bias was the chief concern with the majority of trials poorly reporting how they generated their random sequence and whether allocation was adequately concealed to researchers and participants. Performance, detection, attrition and reporting bias were generally low across the pool of identified trials. Six trials received a high-risk rating for one or more of the domains, where the rigour of the methods risked introducing substantial bias into the results.

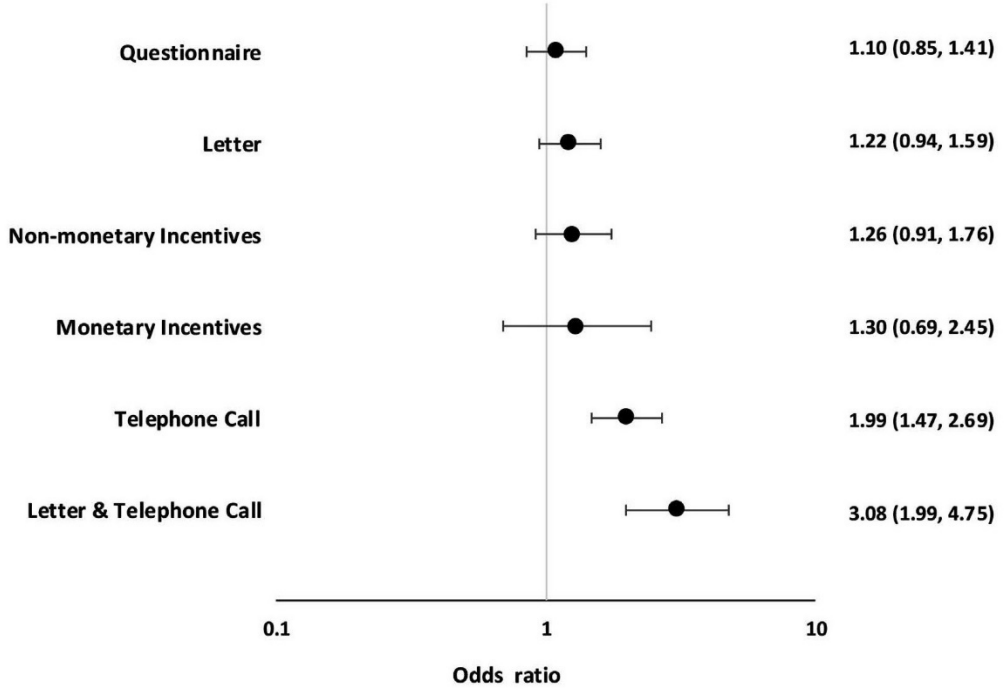
Subgroup analysis

Six trials were conducted in a population considered to be non-donors. These trials used general population samples, voters, students or employees as participants. Twenty-one trials were conducted in individuals who had donated or previously made steps towards donating.

Figure 4 presents the results of the subgroup analysis. In the non-donor subgroup, while only based on one study, [30] monetary incentives outperformed all other interventions. However, there is considerable uncertainty in this result, which is also undermined by the high risk of bias in this study. Non-monetary incentives and letters do not significantly outperform existing practice among non-donors. As with the primary analysis, the best performing non-incentive-based interventions were letter & telephone call and telephone call-only with odds ratios of 8·17 (95% CI: 4·03, 16·60) and 2·82 (95% CI: 1·29, 6·13) compared to existing practice, respectively.

In the donor subgroup analysis, monetary incentives, questionnaires and letters do not significantly outperform existing practice. Compared to the ineffective finding for the non-donor subgroup, non-monetary incentives are more effective at recruiting donors than existing practice with odds ratios of 1·30 (95% CI: 1·05, 1·61). The best performing interventions were telephone call-only and letter & telephone call with odds ratios of 1·72 (95% CI: 1·39, 2·13) and 1·68 (95% CI: 1·24, 2·28) compared to existing practice, respectively.



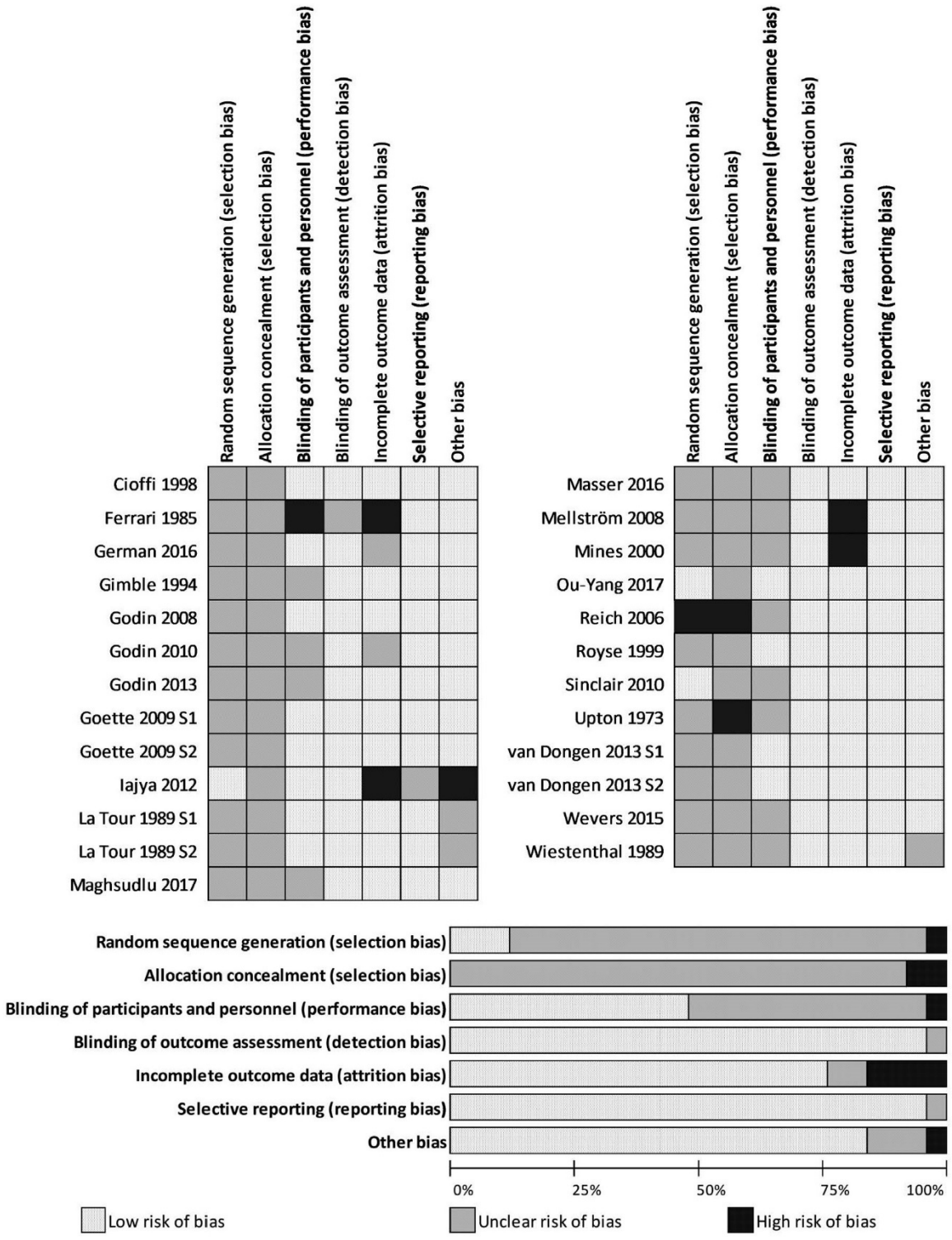


Questionnaire	1.10 (0.85, 1.41)					
Letter	1.22 (0.94, 1.59)	1.12 (0.81, 1.53)				
Non-monetary Incentives	1.26 (0.91, 1.76)	1.15 (0.79, 1.67)	1.03 (1.75, 1.42)			
Monetary Incentives	1.30 (0.69, 2.45)	1.19 (0.61, 2.30)	1.06 (0.56, 2.01)	1.03 (0.52. 2.04)		
Telephone Call	1.99 (1.47, 2.69)	1.82 (1.29, 2.56)	1.64 (1.22, 2.17)	1.58 (1.09, 2.28)	1.53 (0.84, 2.79)	
Letter & Telephone Call	3.08 (1.99, 4.75)	2.81 (1.75, 4.50)	2.52 (1.68, 3.77)	2.44 (1.49, 3.99)	2.37 (1.21, 4.64)	1.55 (1.05, 2.28)
Reference treatment ->	Existing Practice	Questionnaire	Letter	Non-monetary	Monetary	Telephone Call

Fig. 2 Network diagram and forest plot. Nodes in the network diagram represent interventions, lines between nodes represent trials directly comparing connected interventions with the thickness of the lines indicating the number of trials. All odds ratios in the forest plot are compared to existing practice. 95% confidence intervals are provided in parentheses. The matrix provides odds ratios for all possible comparisons in the network.

Sensitivity analysis

Forest plots for the sensitivity analyses are presented in the Appendix S1. The conclusion regarding the effectiveness of letter & telephone call as well as telephone call-only at increasing blood donations remains robust in both scenarios. The sensitivity analyses also highlight the uncertainty regarding monetary incentives.


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Cioffi 1998
Ferrari 1985
German 2016
Gimble 1994
Godin 2008
Godin 2010
Godin 2013
Goette 2009 S1
Goette 2009 S2
Iajya 2012
La Tour 1989 S1
La Tour 1989 S2
Maghsudlu 2017
Masser 2016
Mellström 2008
Mines 2000
Ou-Yang 2017
Reich 2006
Royse 1999
Sinclair 2010
Upton 1973
van Dongen 2013 S1
van Dongen 2013 S2
Wevers 2015
Wiestenthal 1989
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

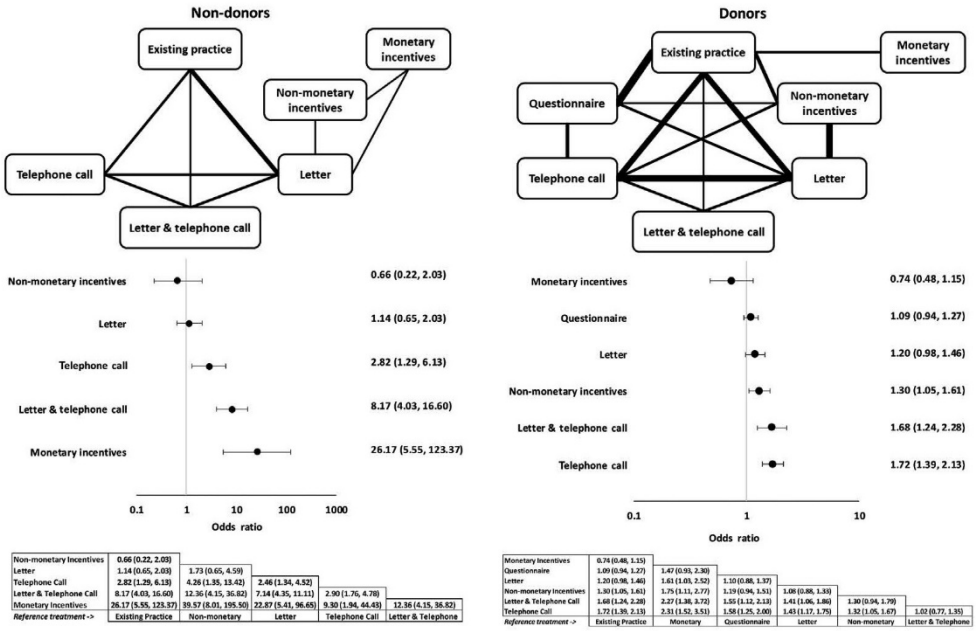


Fig. 4 Subgroup analysis. Nodes in the network diagram represent interventions, lines between nodes represent trials directly comparing connected interventions with the thickness of the lines indicating the number of trials. All odds ratios in the forest plot are compared to existing practice. 95% confidence intervals are provided in parentheses. The matrix provides odds ratios for all possible comparisons in the network.

All three monetary incentive studies had a high risk of bias – removing this intervention completely from that scenario. After removing studies performed outside of developed economies, monetary incentives perform significantly worse than in the primary analysis.

Discussion

In this systematic review of RCTs of interventions for increasing blood donations, a network meta-analysis of 27 trials from 25 studies found that the combination of a letter & telephone call or a telephone call-only was the most effective. Our findings were consistent when considering our pre-specified subgroups of donors and non-donors and when we repeated the analysis excluding trials at high risk of bias in at least one domain or trials performed outside of developed economies.

Only three trials were identified that included a comparison with monetary incentives. These trials were disparate in a number of ways, one was conducted in Argentina with high-value supermarket vouchers, [30] one was conducted in the 1970s in the United States [31] when remunerated blood donation was still commonplace and the other used hypothetical incentives [9]. Unfortunately, this precludes being able to draw strong conclusions about the effectiveness of monetary incentives. That only a few trials were identified assessing monetary incentives is an interesting finding in itself, given we know they are still used in low-income countries [1]. The majority of identified trials were conducted in the developed world where blood supplies are largely based on volunteer non-remunerated donations. The evidence base for non-monetary incentives was considerably broader and comparable. The results from the primary analysis indicated that non-monetary incentives do not significantly outperform existing practice; however, there was evidence to suggest non-monetary incentives may be effective in the donor subgroup supporting the theory that gifts or tokens of low monetary value may not crowd out those with high intrinsic motivation [11].

This review builds on previously published systematic reviews in this area. Our findings are in concordance with Godin [16] and Bagot [19] supporting interventions with personal contact such as telephone calls. We find similar results to Godin, [16] Niza [18] and Chell [20] with regard to the weak and ineffective evidence base for incentives. As we synthesized identified interventions simultaneously using a network meta-analysis, our study is able to draw broader conclusions. We directly compare incentive- and non-incentive-based interventions concluding that incentives are outperformed by a telephone call-only and the combination of a letter & telephone call.

The results from the subgroup analysis allow us to draw tentative conclusions regarding the impact of motivational crowding out for different groups of donors. For the one study in non-donors, monetary incentives significantly increased the odds of donation suggesting that extrinsic motivation from monetary incentives outweighed any loss of intrinsic motivation. For the two studies in donors, the monetary incentives on offer may have provided insufficient external motivation to outweigh the loss of intrinsic motivation. However, given the small evidence base identified, this is not conclusive. Non-monetary incentives were only effective in the donor subgroup suggesting that they may not provide sufficient extrinsic motivation to low intrinsically motivated individuals. This conclusion supports the theory that rather than crowd out intrinsically motivated individuals, non-monetary incentives may actually reinforce intrinsic motivation [11,12].

Our review has a number of limitations. The primary concern is the generalizability of the pooled results from our network meta-analysis. The pooled estimates from a network meta-analyses reflect a weighted average of included trials but there may be considerable heterogeneity in the effects in terms of population, design, interventions and effect modifiers [21]. We used subgroup and sensitivity analyses to explore the robustness of the results to selecting subsets of similar trials; however, a degree of heterogeneity persists. To address the gap in the literature, quantitatively synthesizing the available data was a primary aim of this research. Given the limited nature of the evidence identified, this was only possible when pooling the results across trials. Additionally, our meta-analysis used odds ratios as the measure of treatment effect. While previously used in this setting, [16] odds ratios can be misleading when donation rates are low, such as for the non-donor subgroup analysis. A small increase in donations results in a large increase in the odds ratio.

Our review did not assess the cost to blood services of identified interventions. Given our conclusion regarding personal approaches such a telephone calls which are resource intensive by definition, this is an important area for future research. It was also assumed that all monetary incentives were in equivalent in value and all non-monetary incentives were equivalent in type. This simplifying assumption was a necessity given the limited number of trials identified that incorporated incentives. Furthermore, our review included only RCTs, as they represent the highest level of evidence. Widening the inclusion criteria to observational or non-randomized studies would have generated more evidence related to incentive-based interventions but at the expense of potential bias. For example, non-randomized trials have found that non-monetary incentives are effective at increasing donations without increasing deferrals with larger effects reported for incentives of greater value [36,37]. However, the authors also report a displacement effect with reductions in donations reported at neighbouring blood drives that were not offering the incentives. Although the wider and long-term effects of universally offering such incentives remain unclear, the positive conclusions from these non-randomized studies support further research in this area. Finally, our review focused on increasing blood donations and does not add to the body of literature that links incentives with the safety of donated blood. This is an important concern for blood services with observational evidence suggesting paid donations are at higher risk of infections [10].

Given the limited evidence identified, future trials to determine the safety and effectiveness of incentives are warranted. While our subgroup analysis assessed how donation history affected the effectiveness of interventions, one may also expect differential effectiveness across other characteristics such as age. Better evidence for mediating characteristics would allow interventions to be accurately targeted at appropriate donor segments.

To our knowledge, this is the first review on the topic to group interventions by delivery method, providing a framework for data synthesis across a wide range of interventions through a network meta-analysis. The results from the primary analysis suggest that blood services should focus on interventions with a personal approach such as telephone calls.

Conclusion

When pooling across all identified trials, the combination of a letter & telephone call or telephone call-only is the best performing interventions. While non-monetary incentives are only effective in the donor subgroup, the effectiveness of monetary incentives remains unclear with limited, disparate evidence identified.

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Conflicts of interest

The authors declare no conflict of interests.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Search Strategy
Table A1 Summary of Included Studies
Table A2 Existing Practice
Figure A1 Forest Plot of Included Studies by Comparison
Figure A2 Sensitivity Analysis Developed Economies
Figure A3 Sensitivity Analysis Risk of Bias

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3 Fresh Red Cells for Transfusion in Critically Ill Adults: An Economic Evaluation of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) Clinical Trial

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The full list of board members of the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) Investigators is provided in the **Supplementary Appendix** (Supplemental Digital Content 1, http://links.lww.com/CCM/E540).

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Objectives: Trials comparing the effects of transfusing RBC units of different storage durations have considered mortality or morbidity as outcomes. We perform the first economic evaluation alongside a full age of blood clinical trial with a large population assessing the impact of RBC storage duration on quality-of-life and costs in critically ill adults.

Design: Quality-of-life was measured at 6 months post randomization using the EuroQol 5-dimension 3-level instrument. The economic evaluation considers quality-adjusted life year and cost implications from randomization to 6 months. A generalized linear model was used to estimate incremental costs (2016 U.S. dollars) and quality-adjusted life years, respectively while adjusting for baseline characteristics.

Setting: Fifty-nine ICUs in five countries.

Patients: Adults with an anticipated ICU stay of at least 24 hours when the decision had been made to transfuse at least one RBC unit.

Interventions: Patients were randomized to receive either the freshest or oldest available compatible RBC units (standard practice) in the hospital transfusion service.

Measurements and Main Results: EuroQol 5-dimension 3-level utility scores were similar at 6 months–0.65 in the short-term and 0.63 in the long-term storage group (difference, 0.02; 95% CI, −0.00 to

0.04; $p = 0.10$). There were no significant differences in resource use between the two groups apart from 3.0 fewer hospital readmission days (95% CI, −5.3 to −0.8; $p = 0.01$) during follow-up in the short-term storage group. There were no significant differences in adjusted total costs or quality-adjusted life years between the short- and long-term storage groups (incremental costs, −$2,358; 95% CI, −$5,586 to $711) and incremental quality-adjusted life years: 0.003 quality-adjusted life years (95% CI, −0.003 to 0.008).
Conclusions: Without considering the additional supply cost of implementing a freshest available RBC strategy for critical care patients, there is no evidence to suggest that the policy improves quality-of-life or reduces other costs compared with standard transfusion practice. (*Crit Care Med* 2019; XX:00–00)
Key Words: blood transfusion; cost-effectiveness analysis; critical care; economic evaluation; quality of life; red blood cells

RBC transfusion is a potentially life-saving treatment in many clinical situations (1). However, in recent years RBC transfusions have also been associated with an increased risk of morbidity and mortality in critically ill patients (1). Attention has focused on the possible adverse impact of transfusing RBCs stored for a prolonged duration, as there is known to be an accumulation of structural, biochemical, and metabolic changes in RBC units during storage (2). Depending on national regulations, RBC units can be stored for up to 42 days, and in order to minimize wastage, usual practice is for hospitals to issue the oldest, in-date, compatible RBCs (3, 4).

A number of randomized controlled trials (RCTs) comparing transfusion of RBCs of different storage duration have found no differences in mortality (5, 6). The Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) was the largest RCT (n = 4,994) comparing RBCs of different storage duration and concluded that the age of red cells did not affect 90-day mortality among critically ill adults (7). A recently published meta-analysis of ICU patients concluded that older blood was not associated with an increased risk of death, adverse events, or posttransfusion infections (8).

Economic evaluations estimate the impact on quality-of-life and cost—and are important even when no significant difference in clinical outcomes has been detected. Relative to underlying illness and other treatments, the effect of the duration of storage of RBCs may be better reflected in changes in quality-of-life and compensating treatments. Thus, there is a need to consider not only mortality implications of a freshest available RBC strategy, but also changes in quality-of-life, and the cost of other healthcare resources used.

Economic evaluations of RCTs are becoming routine in the field of healthcare decision-making; however, the only published age of blood economic evaluation to date is on a small subsample of the Age of Blood Evaluation (ABLE) trial (9). The work presented here is an economic evaluation alongside TRANSFUSE using within trial data on quality-of-life, survival, and patient resource use to estimate whether short-term RBC storage is cost-effective compared with long-term storage among critically ill adults.

MATERIALS AND METHODS

TRANSFUSE Trial

The methodology, statistical analysis plan, and main results of TRANSFUSE have been published elsewhere (2, 7). In brief, TRANSFUSE was conducted in 59 participating hospital sites across five countries—Australia, New Zealand, Ireland, Finland, and Saudi Arabia. Eligible participants were adults with an anticipated ICU stay of greater than or equal to 24 hours when the decision had been made to transfuse at least one RBC unit. In total, TRANSFUSE randomized 4,994 ICU patients in a 1:1 ratio stratified by center to receive either the freshest, compatible RBC unit (short-term storage group) or the oldest, compatible RBC unit (long-term storage group). TRANSFUSE was double-blinded with study group allocation concealed from treating medical and nursing staff as well as from research personnel (2). Ethics approval for the trial was provided by committees at Monash University and each participating site. Waivers, opt-out, or deferred consent procedures were used depending on local legislation.

Quality-of-life was assessed using the EuroQol 5-dimension 3-level (EQ-5D-3L) which assesses five domains of health—mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. At 6 months post randomization site research staff contacted patients by telephone to administer the questionnaire. Proxies were used where the patient was not available.

The economic evaluation took a within-trial time horizon considering the implications for costs and quality-adjusted life years (QALYs) from randomization to 6 months. Using EQ-5D-3L data collected at 6-month follow-up, the incremental cost per QALY gained from short-term storage compared with long-term storage was calculated as the ratio of the estimated between group mean difference in the cost of healthcare resources used and the estimated between group mean difference in QALYs gained.

Outcomes

For patients who did not die during the trial, QALYs were calculated as the area under the curve up to EQ-5D-3L utility score at 6 months. Given critically ill adults are often ventilated and heavily sedated in ICU, a utility score of zero was applied from randomization until final discharge from ICU (10) and a linear improvement to the EQ-5D-3L utility score at 6-month follow-up was assumed. A sensitivity analysis was performed assuming a linear improvement from randomization rather than final discharge from ICU, as has been done in other economic evaluations in critical care (9, 11, 12). A utility of zero was applied for patients who died at any point during the trial. The EQ-5D-3L was valued using the widely adopted U.K. time trade-off tariffs with Australian time trade-off tariffs explored in the sensitivity analysis (13, 14).

Even though the 6-month follow-up date did not always occur exactly at 180 days post randomization, in the base-case analysis it was assumed that this was the EQ-5D-3L utility score at 180 days post randomization. A sensitivity analysis was conducted using linear extrapolation to predict the EQ-5D-3L

utility score at 180 days for patients whose follow-up telephone survey occurred before or after 180 days.

Resource Use

Resource use was collected during the ICU stay, at discharge from the index hospitalization, and at 6-month follow-up. During the ICU stay, as well as capturing information on RBC use, data on the number of mechanical ventilation hours, renal replacement therapy (RRT) days, and extracorporeal membrane oxygenation (ECMO) hours were also collected. Days on inpatient hospital wards were calculated as the difference between hospital and ICU length of stay. A simple model, described in the Supplementary Appendix (Supplemental Digital Content 2, http://links.lww.com/CCM/E541), determined discharge destination length of stay and any secondary discharge destinations.

At 6-month follow-up, as well as hospital readmission days, the use of post-discharge RRT, mechanical ventilation, and ECMO was also collected. No information on end-of-life resource use was captured for participants who died after discharge from hospital.

We did not account for the implementation costs in providing critically ill adults with fresher blood than usual, only the potential downstream costs implications related to changes in resource use were considered.

Unit Costs

Australian prices were adopted for the trial-wide population as 79% of patients were recruited in Australia. The unit costs used in the analysis were collated from Australian national sources and are presented in **Table A1** (Supplemental Digital Content 2, http://links.lww.com/CCM/E541). Where necessary, unit costs were inflated to 2016 levels using the consumer price index published by the Australian Bureau of Statistics (15) before converting to 2016 U.S. dollars using purchasing power parities (16).

Missing Data

There was only a small amount of missing data. A complete case analysis was performed for the base case with patients missing any information required for the calculation of total costs or QALYs being dropped in the estimation of that outcome only. A sensitivity analysis was performed using multiple imputations on total costs and total QALYs stratified by treatment.

Statistical Analysis

Data are presented as numbers with proportions or means and standard deviations as appropriate. EQ-5D-3L data are the proportion of patients reporting problems within each domain. A 5% level of statistical significance was adopted for all analyses. Continuous data were compared using *t* tests. Binary and categorical data were compared using Fisher exact tests (17). As the time horizon of the economic evaluation was only 6 months, costs, and QALYs were not discounted (18).

Incremental costs were estimated using the method of recycled predictions from a generalized linear model (GLM). Following the adjustment in the clinical evaluation, and to potentially improve the statistical power of the estimated treatment effect, the GLM included terms for treatment group, Acute Physiology and Chronic Health Evaluation (APACHE) III risk of death score, hemoglobin at randomization, blood group, age, and fixed effects for hospital site (7). The Modified Park, Pearson Correlation, Pregibon Link, and Modified Hosmer-Lemeshow tests were used to determine GLM family and link functions (19).

Incremental QALYs were also estimated using the method of recycled predictions but from a linear regression on treatment group, APACHE III risk of death score, hemoglobin at randomization, blood group, age, and fixed effects for hospital site. Unadjusted cost and QALY differences between treatment groups are also reported for completeness.

Bootstrapped SEs and 95% CIs were calculated for 1,000 iterations using the bootstrap acceptability method stratified by treatment group (19). To explore the robustness of the

TABLE 1. Baseline Characteristics of Trial Participants

Characteristics	Short-Term Storage		Long-Term Storage	
	Missing	*n* = 2,457	Missing	*n* = 2,462
Age, yr, mean ± SD	0 (0.0%)	62.5 ± 16.8	0 (0.0%)	61.4 ± 17.3
Male, *n* (%)	0 (0.0%)	1,311 (53.4)	0 (0.0%)	1,258 (51.1)
Acute Physiology and Chronic Health Evaluation III score[a], mean ± SD	2 (0.1%)	72.6 ± 29.2	0 (0.0%)	73.2 ± 29.6
Hemoglobin, g/L, mean ± SD	0 (0.0%)	77.4 ± 12.8	0 (0.0%)	77.3 ± 13.0
Mechanical ventilation at randomization, *n* (%)	0 (0.0%)	1,219 (49.6)	0 (0.0%)	1,267 (51.5)
Renal replacement therapy at randomization, *n* (%)	0 (0.0%)	342 (13.9)	0 (0.0%)	360 (14.6)
Extracorporeal membrane oxygenation at randomization, *n* (%)	1 (0.0%)	34 (1.4)	0 (0.0%)	33 (1.3)

[a]Acute Physiology and Chronic Health Evaluation III scores range from 0 to 299, with higher scores indicating a high probability of death.

conclusions, probabilistic results are presented on the cost-effectiveness plane and acceptability curve (20).

Adjusted cost-effectiveness estimates were also generated for the same three predefined population subgroups as for the clinical evaluation—blood type (group O vs nongroup O), APACHE III score at baseline (< median vs ≥ median), and Sequential Organ Failure Assessment score at baseline (≤ median vs > median) (2). All analyses were conducted in Stata 15 (StataCorp, College Station, TX).

RESULTS

TRANSFUSE randomized 4,994 patients to either the short-term or long-term storage groups. Baseline characteristics at randomization of the 4,919 TRANSFUSE patients who did not withdraw consent and were not lost to follow-up at 90 days are presented in **Table 1**. With the exception of age, patient characteristics were not significantly different between the groups. The imbalance in mean age was small (difference, 1.2 yr; 95% CI, 0.2–2.1) and was included as a covariate in the modeled adjustment of total costs and QALYs. As expected for a population of critically ill adults in need of a RBC transfusion, mean APACHE III risk of death scores are high—72.6 and 73.2 in the short-term and long-term storage groups, respectively.

Mortality and Quality-of-Life Outcomes

There were no significant differences in survival at 6 months with 28.0% and 27.5% mortality in the short-term and long-term storage groups, respectively (difference, 0.4%; 95% CI, –2.1% to 3.0%; $p = 0.75$).

TABLE 2. Quality-of-Life at 6 Months

	Short-Term Storage		Long-Term Storage			
Item	Missing	*n* = 2,457	Missing	*n* = 2,462	Difference (95% CI)	*p*
Day of follow-up, mean ± SD	50 (2.0%)	194.4 ± 42.8	49 (2.0%)	193.7 ± 38.0	0.6% (−1.6 to 2.9)	0.580
EQ-5D-3L scores, mean ± SD	213 (8.7%)		202 (8.2%)			
All		0.45 ± 0.41		0.44 ± 0.41	0.01% (−0.01 to 0.03)	0.421
Alive at 6 mo		0.65 ± 0.33		0.63 ± 0.34	0.02% (−0.00 to 0.04)	0.101
EQ-5D-3L profiles						
Mobility, *n* (%)	211 (8.5%)		199 (8.1%)			0.556
No problems		798 (51.2)		796 (50.2)	1.0% (−2.5 to 4.5)	
Some problems		687 (44.1)		702 (44.2)	−0.2% (−3.7 to 3.3)	
Unable		74 (4.8)		88 (5.6)	−0.8% (−2.3 to 0.7)	
Self-care, *n* (%)	211 (8.5%)		199 (8.1%)			0.066
No problems		1,129 (72.4)		1,088 (68.6)	3.8% (0.6–7.0)	
Some problems		338 (21.7)		388 (24.5)	−2.8% (−5.8 to 0.1)	
Unable		92 (5.9)		109 (6.9)	−1.0% (−2.7 to 0.7)	
Usual activities, *n* (%)	211 (8.5%)		199 (8.1%)			0.088
No problems		666 (42.7)		634 (40.0)	2.7% (−0.7 to 6.2)	
Some problems		691 (44.3)		707 (44.5)	−0.3% (−3.7 to 3.2)	
Unable		202 (13.0)		245 (15.5)	−2.5% (−4.9 to 0.1)	
Pain/discomfort, *n* (%)	212 (8.6%)		199 (8.1%)			0.271
No problems		761 (48.8)		730 (46.1)	2.8% (−0.7 to 6.3)	
Moderate problems		697 (44.7)		743 (46.8)	−2.1% (−5.6 to 1.4)	
Extreme problems		100 (6.4)		113 (7.1)	−0.7% (−2.5 to 1.0)	
Anxiety/depression, *n* (%)	212 (8.6%)		202 (8.2%)			0.629
No problems		916 (58.8)		926 (58.5)	0.2% (−3.2 to 3.7)	
Moderate problems		544 (34.9)		568 (35.9)	−0.9% (−4.3 to 2.4)	
Extreme problems		98 (6.3)		88 (5.6)	0.7% (−0.9 to 2.3)	

EQ-5D-3L = EuroQol 5-dimension 3-level.

TABLE 3. Index Hospitalization and Post-Discharge Resource Use

Item	Short-Term Storage		Long-Term Storage		Difference (95% CI)	*p*
	Missing	*n* = 2,457	Missing	*n* = 2,462		
Index hospitalization						
RBCs, mean units ± SD	0 (0.0%)	4.0 ± 5.9	0 (0.0%)	3.9 ± 6.2	0.1% (−0.3 to 0.4)	0.688
Fresh frozen plasma, mean units ± SD	1 (0.0%)	1.0 ± 6.9	0 (0.0%)	0.8 ± 8.0	0.2% (−0.2 to 0.6)	0.355
Platelets, mean units ± SD	1 (0.0%)	0.3 ± 1.5	0 (0.0%)	0.3 ± 2.2	0.0% (−0.1 to 0.1)	0.819
Cryoprecipitate, mean units ± SD	1 (0.0%)	0.6 ± 4.6	0 (0.0%)	0.5 ± 5.3	0.1% (−0.2 to 0.4)	0.369
ICU stay, mean days ± SD	0 (0.0%)	8.0 ± 11.0	0 (0.0%)	8.4 ± 13.6	−0.5% (−1.1 to 0.2)	0.198
Ward stay, mean days ± SD	0 (0.0%)	14.1 ± 20.2	0 (0.0%)	15.0 ± 21.6	−0.9% (−2.1 to 0.3)	0.134
ECMO	2 (0.1%)		4 (0.2%)			
Received, *n* (%)		36 (1.5)		41 (1.7)	−0.2% (−0.9 to 0.5)	0.574
Mean hours ± SD		230.9 ± 165.5		176.9 ± 124.7	54.0% (−12.1 to 120.0)	0.108
Discharge destination, *n* (%)	3 (0.1%)		2 (0.1%)			
Other acute hospital		356 (18.1)		372 (18.7)	−0.6% (−3.0 to 1.8)	0.640
Rehabilitation		506 (25.7)		483 (24.3)	1.4% (−1.3 to 4.1)	0.299
Long-term care		69 (3.5)		83 (4.2)	−0.7% (−1.9 to 0.5)	0.281
Home		1,034 (52.7)		1,051 (52.8)	−0.2% (−3.3 to 2.9)	0.903
Post-discharge						
Length of stay, mean days ± SD						
Ward (index and secondary)		14.4 ± 19.1		15.4 ± 20.5	−1.0 d (−2.1 to 0.9)	0.071
Rehabilitation		6.4 ± 11.4		6.3 ± 11.3	0.1 d (−0.5 to 0.8)	0.706
Long-term care		19.4 ± 46.2		19.0 ± 45.6	0.4 d (−2.2 to 3.0)	0.767
Home		140.7 ± 36.6		140.2 ± 36.8	0.4 d (−2.2 to 3.1)	0.739
Hospital readmission						
Readmitted, *n* (% of alive)	38 (1.5%)	636 (36.9)	36 (1.5%)	592 (34.1)	2.9% (−0.3 to 6.2)	0.077
Mean days ± SD	10 (0.4%)	14.5 ± 18.6	6 (0.2%)	17.6 ± 21.2	−3.0 d (−5.3 to −0.8)	0.008
Mechanical ventilation	7 (0.3%)		7 (0.3%)			
Received, *n* (% of readmitted)		30 (4.7)		40 (6.8)	−2.1% (−4.7 to 0.6)	0.062
Mean hours on readmission ± SD		2.8 ± 19.8		4.5 ± 37.2	−1.7 hr (−5.1 to 1.6)	0.302
Renal replacement therapy	7 (0.3%)		5 (0.2%)			
Received, *n* (% of readmitted)		19 (3.0)		17 (2.9)	0.1% (−1.8 to 2.0)	0.894
Mean days on readmission ± SD		1.4 ± 9.8		0.9 ± 7.3	0.5 d (−0.4 to 1.5)	0.284
ECMO	8 (0.3%)		4 (0.2%)			
Received, *n* (% of readmitted)		0 (0.0)		1 (0.2)	0.2% (−0.5 to 0.2)	0.302
Mean days on readmission ± SD		0.0		0.0 ± 0.4	0.0 d (−0.0 to 0.0)	0.302

ECMO = extracorporeal membrane oxygenation.
Resource use on readmission estimated for patients readmitted to hospital only.

Table 2 presents 6-month quality-of-life as measured by the EQ-5D-3L. Mean utility scores of those alive at 6 months were not significantly different; 0.65 in the short-term and 0.63 in the long-term storage group (difference, 0.02; 95% CI, –0.00 to 0.04; $p = 0.10$).

Resource Use

Table 3 summarizes resource use during the trial and follow-up. Patients in the short-term storage group received a mean of 4.0 RBC units compared with 3.9 U in the long-term

TABLE 4. Costs and Quality-Adjusted Life Years at 6 Months

Outcome	Short-Term Storage Estimate (95% CI)	Long-Term Storage Estimate (95% CI)	Incremental Estimate (95% CI)
Unadjusted			
Costs (2016 USD)	$61,195 ($58,983–$63,551)	$64,395 ($62,008–$64,369)	−$3,200 (−$6,411 to $68)
QALYs	0.107 (0.103–0.111)	0.104 (0.101–0.109)	0.002 (−0.003 to 0.008)
ICER			Dominant
Adjusted			
Costs (2016 USD)	$61,703 ($59,409–$64,023)	$64,061 ($61,755–$66,472)	−$2,358 (−$5,586 to $711)
QALYs	0.107 (0.103–0.111)	0.104 (0.101–0.109)	0.003 (−0.003 to 0.008)
ICER			Dominant

ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year, USD = U.S. dollars.
Estimates calculated using method of recycled predictions from a generalized linear model (costs) and multiple linear regression (QALYs) adjusted for Acute Physiology and Chronic Health Evaluation III risk of death, hemoglobin at baseline, blood group, age, and including fixed effects for hospital site.
95% CIs based on bootstrap procedure involving 1,000 replications, stratified by treatment.

storage group (difference 0.1 U; 95% CI, –0.3 to 0.4; $p = 0.69$). As reported in the clinical evaluation, the mean age of RBCs was 11.8 days in the short-term and 22.4 days in the long-term storage group with a mean difference of 10.6 days (95% CI, 10.3–11.0; $p < 0.001$) (7).

There were no significant differences in ICU or ward length of stay between the groups (–0.5 ICU days; 95% CI, –1.1 to 0.2; $p = 0.20$ and –0.9 ward days; 95% CI, –2.1 to 0.3; $p = 0.13$). The proportion of patients discharged to each destination was similar between the two groups ($p = 0.55$). There was a significant difference in the number of hospital readmission days with 3.0 fewer days reported in the short-term storage group (95% CI, –5.3 to –0.8; $p = 0.008$). There were no significant differences in other post-discharge resource use (Table 2).

Costs and QALYs

Table 4 presents the unadjusted and adjusted total costs and QALYs. When considering the unadjusted point estimates, short-term storage is the dominant strategy; however, both the estimated cost savings of $3,200 (95% CI, –$6,411 to $68) and increase in QALYS of 0.002 (95% CI, –0.003 to 0.008) fail to reach statistical significance. The cost savings for short-term storage are largely attributed to the significant reduction in hospital readmission days. In the absence of any significant difference in survival at 6 months, the small improvement in EQ-5D-3L utility score reported in Table 3 accounts for the small incremental QALY gain for short-term storage.

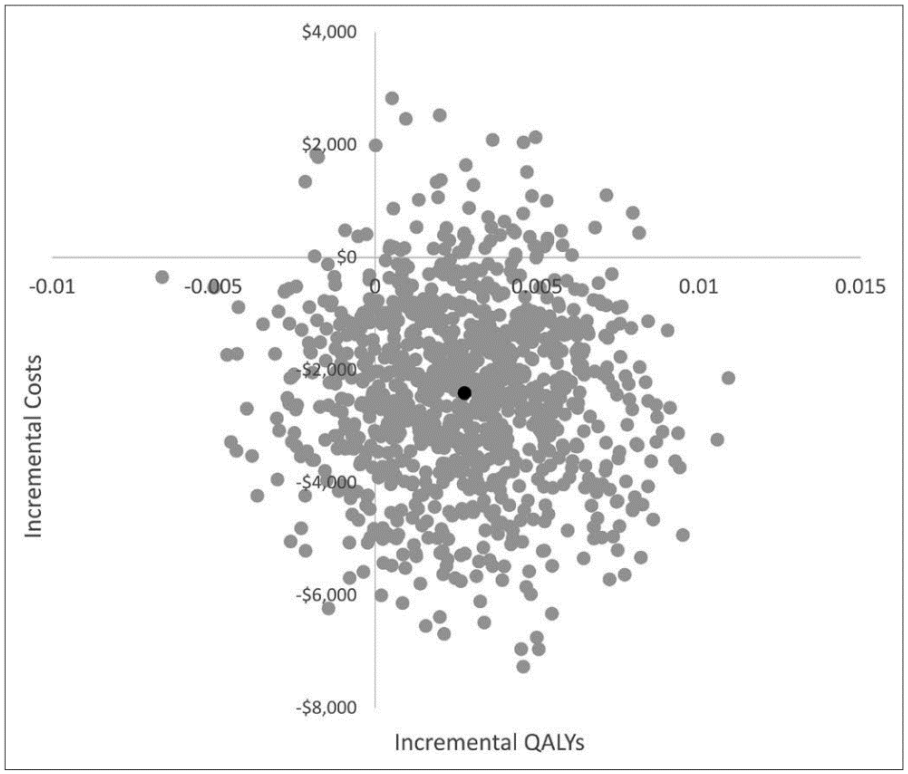

Figure 1. Cost-effectiveness plane of short-term versus long-term storage at 6 months. QALY = quality-adjusted life year.

After adjusting for patient characteristics at randomization, the estimated cost savings for short-term storage falls to $2,358 (95% CI, –$5,586 to $711), whereas incremental QALYs increase slightly to 0.003 (95% CI, –0.003 to 0.008). Short-term storage remains dominant; however, the incremental effects are small, and the bootstrapped 95% CIs for both outcomes span zero implying a statistically insignificant difference.

Figure 1 presents the cost-effectiveness plane for short-term versus long-term storage at 6 months. Each gray point represents the incremental costs and QALYs for one of the 1,000 bootstrapped samples, and the black point represents the mean adjusted incremental cost-effectiveness ratio. The cost-effectiveness acceptability curve is presented in **Figure A1** (Supplemental Digital Content 3, http://links.lww.com/CCM/E542; **legend**, Supplemental Digital Content 1, http://links.lww.com/CCM/E540).

Sensitivity and Subgroup Analysis

The results of the subgroup and sensitivity analyses are presented in **Table A2** (Supplemental Digital Content 4, http://links.lww.com/CCM/E543) and **Table A3** (Supplemental Digital Content 5, http://links.lww.com/CCM/E544). The sensitivity analysis demonstrates that the conclusions remain robust to alternative modeling assumptions, with statistically insignificant incremental cost savings and QALY gains for short-term storage. From the subgroup analysis, there is evidence of a quality-of-life improvement for the less morbid APACHE III subgroup with a small but significant improvement of 0.010 QALYs in the short-term storage group (95% CI, 0.003–0.018).

DISCUSSION

The clinical evaluation of TRANSFUSE reported that transfusion with freshest available RBCs did not affect 90-day mortality among critically ill adults (7). The 6-month quality-of-life data measured by the EQ-5D-3L revealed no significant differences between the storage groups. Furthermore, the economic evaluation of TRANSFUSE found no significant difference in terms of costs or QALYs. The results from both the clinical and economic evaluations of TRANSFUSE are in-line with the previously published age of blood clinical trial literature providing strong evidence that the current transfusion policy is appropriate (5, 6, 9).

To date, there have only been two published studies on the effect of age of blood on quality-of-life. One study analyzed 20 *n*-of-1 trials and concluded that there were no significant difference in quality-of-life between fresh and standard aged blood (21). The other study was a small subsample ($n = 357$) of the ABLE study, an RCT comparing transfusion of fresh (≤ 7 d) with standard issue RBCs in critically ill patients, and found similar results with regards to quality-of-life (9). This study is also the only other published age of blood economic evaluation. The authors also concluded that there was no evidence of a difference between fresh and standard issue blood in terms of costs or QALYs. However, there was still considerable uncertainty in the estimates of incremental costs and QALYs—£231 (95% CI, –£4,786 to £4,415) and –0.010 (95% CI, –0.078 to 0.057), respectively. Given the larger sample size in TRANSFUSE ($n = 4,994$) our results are considerably more precise—after converting into 2016 U.S. dollars, the 95% CIs for incremental costs and QALYs are two and 14 times smaller than those reported from the ABLE study, respectively. This additional precision allows for more confidence in our conclusions.

Our economic evaluation ignores any implementation costs in adopting a freshest available RBC strategy for critically ill adults; only potential downstream costs differences related to resource use are considered. In reality, such a policy may require modifications to the blood supply chain such as holding reduced stock or more frequent deliveries in order to maintain appropriate stocks of fresh blood. National blood organizations have already implemented efficiency improvements in order to reduce the average age of transfused blood. For instance, the English blood service has consolidated its blood processing operations by closing a number of smaller centers and increasing capacity at larger centers (22).

A stock-and-flow simulation model of the U.S. blood supply suggested that implementing a freshest available strategy for ICU patients would not increase the number of expired RBCs; however, conclusions were highly dependent on the duration threshold for "fresh" blood (23). Furthermore, a number of jurisdictions have reduced their shelf life for RBCs from 42- to 35-days after studies demonstrated the robustness of blood supplies to the policy change (24–26). Based on our results, it appears that these efforts are unlikely to have improved quality-of-life or decreased downstream direct healthcare costs.

This is the first evaluation of the effect of age of transfused RBCs on quality-of-life in critically ill adults and the first economic evaluation of a full RCT with a large patient population. The trial was pragmatically designed to make best use of the available inventory in each of the 59 sites and minimized bias through allocation concealment and the blinding of patients, clinical staff, and outcome assessors. However, our study has some limitations. Chiefly, we did not take into account the hospital and blood supply chain costs of implementing a freshest available RBC strategy for critically ill adults. Implementing such a policy within the current system may increase delivery and wastage costs for hospital blood banks, reducing the cost effectiveness of the policy.

CONCLUSIONS

Using quality-of-life, survival, and resource use information captured in the trial's 6-month follow-up period, this economic evaluation of TRANSFUSE found no evidence to suggest that short-term storage either improves quality-of-life or reduces costs compared with long-term storage. The results of this study should assure the transfusion community that the current practice of issuing the oldest available RBCs to critically ill adults remains appropriate.

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4 Impact of patient blood management guidelines on blood transfusions and patient outcomes during cardiac surgery

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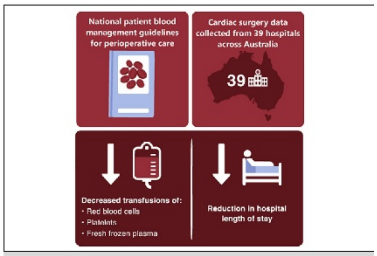
ABSTRACT

Objective: In March 2012, Australia's National Blood Authority published national patient blood-management guidelines for perioperative care developed by a systematic review and clinical expert opinion. This study assesses how blood transfusions and patient outcomes in cardiac surgery changed after the guidelines were published.

Methods: Blood transfusions and patient outcomes in cardiac surgery were compared before and after implementation of the guidelines using an interrupted time series analysis. The evaluation included red blood cells, platelets, cryoprecipitate, fresh-frozen plasma, 30-day mortality, 30-day readmissions, and hospital and intensive care length of stay. Patient characteristics were controlled for along with hospital characteristics using fixed effects. Different responses across institutional settings were assessed with an expanded difference-in-differences model.

Results: After the guidelines were published, our model found a significant reduction in red blood cell, platelet, and fresh-frozen plasma transfusions. There was also a significant reduction in hospital length of stay but no significant impact on cryoprecipitate, 30-day mortality, 30-day readmissions, or intensive care unit length of stay. The subgroup analyses found no differences with regards to institutional settings.

Conclusions: Following the publication of the guidelines, there was a measurable reduction in perioperative blood transfusions in cardiac surgery with an associated reduction in hospital length of stay but no detectable differences in other patient outcomes. (J Thorac Cardiovasc Surg 2019;■:1-9)



Are clinical guidelines effective in changing behavior?

Central Message

National patient blood management guidelines were associated with a reduction in blood transfusions and hospital length of stay for cardiac surgery patients in Australia.

Perspective

Patient blood-management initiatives have been implemented in response to growing evidence that reducing unnecessary blood transfusions alleviates morbidity and mortality. The work presented herein is the first quantitative assessment of the impact of Australia's national patient blood management guidelines for perioperative care using routinely collected individual cardiac surgery data.

See Commentary on page XXX.

Clinical guidelines can be effective at influencing practice.[1] However, many factors mediate their success, including the discipline, development, dissemination, and implementation. Assessing the impact of published guidelines is important for future guideline development as well as assuring policymakers that they are an appropriate tool for enacting change.

Given the highly invasive nature of the procedure, blood transfusions during cardiac surgery are very common despite recent changes in practice, including lowering the

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Abbreviations and Acronyms

ANZSCTS = Australian & New Zealand Society of Cardiac & Thoracic Surgeons
CI = confidence interval
FFP = Fresh-frozen plasma
ICU = intensive care unit
ITS = interrupted time series
LOS = length of stay
NBA = National Blood Authority
PBM = patient blood management
RBC = red blood cell

hemoglobin threshold trigger or the routine use of antifibrinolytic drugs and postoperative cell salvage.[2-5] However, observational evidence has emerged indicating that blood transfusions may be associated with increased morbidity and mortality[6,7] and a risk factor for increased hospital and intensive care (ICU) length of stay (LOS)[8-10] in patients undergoing cardiac surgery. Possible mechanisms include acute hemolytic and nonhemolytic reactions, viral or bacterial disease transmission, immunomodulation, transfusion-related acute lung injury, and transfusion-associated circulatory overload.[8] In response, the World Health Organization convened a Global Forum for Blood Safety in 2011 to highlight the importance of patient blood management (PBM), an evidence-based and systematic approach to optimize the management of patients and transfusion of blood products.[11]

A recent meta-analysis of 13 clinical trials in cardiac surgery found no evidence that restrictive red blood cell (RBC) transfusion strategies, defined by lower hemoglobin thresholds, are clinically inferior to liberal strategies, with similar rates of mortality, myocardial infarction, renal failure, and infection.[12] PBM recommendations expand beyond lower hemoglobin thresholds to cover anemia, hemostasis management, blood-conservation strategies, and appropriate transfusion practices.[13] However, the most effective method for implementing PBM in routine surgical settings remains unclear. Although there is evidence of successful implementation of PBM programs in single cardiac centers,[14,15] no studies have quantitatively evaluated the impact of national PBM guidelines on blood transfusions or patient outcomes in cardiac surgery.

Australia's National Blood Authority (NBA), which coordinates the supply of blood in Australia,[16] developed a series of comprehensive, evidence-based PBM guidelines, which included recommendations specific to cardiac surgery. The primary aim of this study was to assess the impact of these national PBM guidelines on blood transfusions and patient outcomes in cardiac surgery. Although the PBM guidelines are primarily designed to reduce RBC transfusions, they also specifically recommend against prophylactic use of platelets or fresh-frozen plasma (FFP). Therefore, we hypothesize that after the publication of the guidelines, transfusions for these blood products will decrease. Improvements in patient outcomes may also be detected if sufficient inappropriate transfusions are avoided to reduce transfusions-related complications.

The secondary aim was to assess whether the institutional setting influenced the impact of the guidelines. In Australia, private hospitals offer similar elective cardiac surgery options to the public system. This facilitates an analysis comparing the impact of the guidelines in public versus private hospitals. Unobserved differences in the type of staff (eg, financially motivated), funding structure, or institutional culture could all influence previous behavior and adherence to the guidelines. A second subgroup analysis was performed on the subset of public hospitals to determine whether economic incentives might affect the impact of the guidelines. In Australia, 4 of the 8 states and territories (New South Wales, Tasmania, Queensland, and Victoria) have devolved their budgets for blood products from the government health department down to the local public hospital. At the end of each year, these public hospitals receive an incentive payment if their blood budget is in surplus.[17] Budget devolution promotes transparency of costs and shifts the price signal towards the decision makers. We hypothesize that physicians in devolved public hospitals will pay greater attention to the guidelines and experience greater reductions in transfusions.

MATERIALS AND METHODS

Patient Blood Management Guidelines

PBM revolves around 3 pillars: optimizing RBC mass, minimizing blood loss, and managing anemia. There are considerations for each pillar in the preoperative, intraoperative, and postoperative phases of the surgical separation.[18] PBM principles can be applied in the management of any hematologic disorder to reduce transfusion-associated risk.[19] Published in March 2012, *Patient Blood Management Guidelines: Module 2—Perioperative* was the second in a series of 6 guidelines developed by systematic review on behalf of the NBA.[19] Where sufficient evidence was identified, 22 recommendations were established and graded based on the strength of the evidence. The general and cardiac surgery–specific recommendations are listed in Tables E1 and E2.

Data Sources

We performed a retrospective analysis of surgery-level data routinely collected by the Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS) Database. The ANZSCTS Database began collecting data in 2001, with an initial enrollment of 6 hospitals. Our sample included 23 public and 16 private hospitals across Australia; a timeline of hospital enrolment into the database is presented in Figure E1. The database captures preoperative, intraoperative, and postoperative information for each cardiac surgery patient treated at an enrolled hospital through standardized data collection forms. As well as detailed patient and surgery characteristics, the database contains information on blood product use and patient outcomes. As many PBM

recommendations involve managing the preoperative surgical phase, the sample was restricted to patients undergoing elective surgery only.

Outcomes

The blood products under evaluation were RBCs, platelets, cryoprecipitate, and FFP. Although a reduction in transfusions demonstrates a specific resource saving, of particular interest to physicians and policymakers is whether the guidelines also resulted in an improvement in patient outcomes. Our study assessed the impact on 30-day mortality, 30-day readmissions, and hospital and ICU LOS. The regression model for ICU LOS was restricted to 2008 onwards as data were incomplete before this time. Ethics approval for the study was provided by Monash University (Project ID 9097).

Statistical Analysis

We performed an interrupted time series (ITS) analysis modeled using a linear regression to compare blood transfusions and patient outcomes between the preguideline period (March 2005 to February 2012) and the postguideline period (March 2012 to December 2017). This quasiexperimental design is effective for analyzing natural experiments in real-world settings, when randomized controlled data are not available.[20]

Unadjusted differences in patient characteristics and outcomes were assessed to determine the similarity of the patients across the periods. Relying on the large sample size and the central limit theorem, we did not exclude outliers and tested all continuous data regardless of normality using t tests, medians using the Mann–Whitney U test, and rates using the Fisher exact test. These patient characteristics formed the vector of control variables for all of our regressions and were the same as a previous predictive model of RBC transfusions in cardiac surgery.[21] In addition, hospital fixed effects were included to account for unobserved differences between hospitals. The regression equation was as follows:

$$y_{ijt} = \alpha + \beta X_{it} + \sigma G_t + \varphi M1_t + \gamma(M2_t.G_t) + h_j + \varepsilon_{ijt}$$

Where y_{ijt} is the outcome for individual i in hospital j month t, X_{it} is the vector of control variables, G_t is an indicator for surgeries that occurred after the guidelines were published, $M1_t$ is the overall monthly trend starting in March 2005, $M2_t$ is postguideline monthly trend, which takes zero before the guidelines and increases after March 2012, h_j represents the hospital fixed effects, and ε_{ijt} is the error term.

The same regression equation was used to assess changes in blood transfusions and patient outcomes. Our model is flexible in that it allows for a contemporaneous shift in the outcome when the guidelines were published (represented by σ) and for a change in the monthly trend (represented by γ).[20] To better understand the impact on both the decision to transfuse and then on how many units to transfuse, as well as total units, models were fit on the number of units conditional on a transfusion occurring. To assess their impact on the results, blood product regressions were also run without hospital fixed effects.

Subgroup Analysis

Two subgroup analyses were performed by expanding the model to include an indicator for hospital status (private/devolved) interacted with the guideline indicator, the overall trend, and the change in trend. This "difference-in-differences" model provides an estimate of the difference between the 2 hospital groups in these coefficients. A third subgroup analysis was performed on the subset of isolated coronary artery bypass patients to confirm comparability.

Sensitivity Analysis

As the data were largely complete, a complete case analysis was adopted as the base case. To explore potential bias related to missing data, multiple imputation using chained regressions was implemented on all control variables to create 10 imputed datasets on which identical regressions were performed and compared.[22]

To support the notion that the guidelines were responsible for the changes in outcomes rather than an alternative change in policy, a threshold analysis was performed by estimating the RBC regressions with "placebo" guideline splits at all months before and after March 2012. Model fit in terms of R^2 was then plotted against the guideline split month to determine if model fit was maximized close to the true publication month. Additional falsification tests were conducted by replacing the dependent variable with 3 therapies that would not be expected to be affected by the PBM guidelines—inotropes, intravenous nitrates, and steroids. Finally, the appropriateness of our linear model was assessed by comparison with models including quadratic and cubic terms for the trends.

RESULTS

Between March 2005 and December 2017, there were 78,179 elective cardiac surgery procedures recorded in the ANZSCTS Database and included in the analysis. The patient characteristics of our sample are presented in Table 1. Patients were predominantly male (72.3%), with a mean age of 66.2 years. The majority (63.8%) underwent coronary artery bypass grafting, 46.6% underwent valve surgery, 14.0% underwent both, and 19.6% had undergone previous cardiac surgery. Tests for differences in patient characteristics between the periods revealed some small but statistically significant differences. All patient characteristics in Table 1 were included as control variables in all regressions.

Raw blood transfusion and patient outcomes not adjusted for patient characteristics or trends are presented in Table 2. The mean number of RBC, platelet, and FFP units transfused per patient all fell significantly from 1.5 ± 3.5 to 1.1 ± 2.8 units (difference –0.5 units, 95% confidence interval [CI], –0.5, –0.4; $P < .001$), 0.6 ± 3.6 to 0.5 ± 2.0 (difference –0.1 units, 95% CI, –0.2, –0.1; $P < .001$) and 0.9 ± 2.7 to 0.5 ± 2.3 (difference –0.4 units, 95% CI, –0.4, 0.3; $P < .001$) respectively. Transfusion rates for RBCs, platelets, and FFP experienced similar reductions of 39.9% to 31.0% (difference –8.9%, 95% CI, –9.5, –8.2%; $P < .001$), 20.0% to 18.1% (difference –1.9%, 95% CI, –2.5, –1.3; $P < .001$), and 19.8% to 13.4% (difference –6.5%, 95% CI, –7.0, –5.9; $P < .001$), respectively. There was an increase in the use of cryoprecipitate with mean units increasing from 0.7 ± 3.8 to 0.8 ± 7.3 (difference 0.1 units, 95% CI, 0.0-0.2; $P < .014$) and the transfusion rate increasing from 7.7% to 8.8% (difference 1.1%, 95% CI, 0.7-1.5; $P < .001$).

Mean ICU LOS increased significantly from 61.3 to 66.5 hours (difference 5.2 hours; 95% CI, 3.6-3.7; $P < .001$) whereas hospital LOS fell from 12.0 to 11.8 days (difference –0.2 days; 95% CI, –0.4, –0.0; $P = .025$). Thirty-day readmissions increased marginally from 9.6% to 9.9% (difference 0.3%; 95% CI, –0.1, 0.7; $P = .126$) whereas 30-day mortality fell significantly from 2.0% to 1.6% (difference –0.4%; 95% CI, –0.6, –0.2%; $P < .001$).

TABLE 1. Patient characteristics

Characteristic	Preguideline		Postguideline		*P* value
	Missing	N = 29,584	Missing	N = 48,595	
Age, y	<0.1%		<0.1%		
Mean ± SD		66.2 ± 12.9		66.1 ± 12.9	.392
Median (IQR)		68 (59, 76)		68 (59, 75)	.353
Male, n (%)	<0.1%	21,151 (71.5%)	<0.1%	35,378 (72.8%)	<.001
BMI, kg/m^2	0.3%		0.2%		
Mean ± SD		28.3 ± 5.3		28.8 ± 5.6	<.001
Median (IQR)		27.8 (24.8, 31.2)		28.1 (24.9, 31.7)	<.001
Cardiac catheterization, n (%)	0.4%	26,671 (90.5%)	0.1%	44,569 (91.8%)	<.001
Cardiogenic shock, n (%)	0.2%	123 (0.4%)	0.1%	200 (0.4%)	.954
Congestive heart failure, n (%)	0.3%	6593 (22.4%)	<0.1%	9,634 (19.8%)	<.001
Cerebrovascular disease, n (%)	0.2%	3396 (11.5%)	0.1%	4871 (10.0%)	<.001
Diabetes, n (%)	0.2%	8160 (27.6%)	0.1%	14,054 (28.9%)	<.001
eGFR, mL/min/1.73 m^2	0.8%		0.1%		
Mean ± SD		73.5 ± 33.6		82.5 ± 35.1	<.001
Median (IQR)		69.1 (50.1, 92.1)		78.2 (58.1, 101.9)	<.001
Infective endocarditis, n (%)	0.2%	413 (1.4%)	0.1%	898 (1.8%)	<.001
Myocardial infarction, n (%)	0.2%	8812 (29.9%)	<0.1%	12,745 (26.2%)	<.001
Peripheral vascular disease, n (%)	0.2%	2877 (9.7%)	0.1%	3809 (7.8%)	<.001
Respiratory disease, n (%)	0.2%	3833 (13.0%)	0.1%	6368 (13.1%)	.584
Dialysis, n (%)	0.1%	391 (1.3%)	0.1%	618 (1.3%)	.557
Intra-aortic balloon pump, n (%)	0.3%	611 (2.1%)	<0.1%	907 (1.9%)	.048
Previous cardiac surgery, n (%)	0.1%	5702 (19.3%)	0.1%	9614 (19.8%)	.093
Angina—CCS classification, n (%)	0.9%		0.2%		<.001
0		11,573 (39.5%)		23,039 (47.5%)	
1		3377 (11.5%)		5514 (11.4%)	
2		8231 (28.1%)		11,694 (24.1%)	
3		4622 (15.8%)		5754 (11.9%)	
4		1529 (5.2%)		2500 (5.2%)	
Ejection fraction, n (%)	<0.1%		<0.1%		<.001
Normal >60%		18,732 (63.3%)		31,810 (65.5%)	
Mild 46%-60%		6985 (23.6%)		11,241 (23.1%)	
Moderate 30%-45%		2962 (10.0%)		4248 (8.7%)	
Severe <30%		905 (3.1%)		1296 (2.7%)	
Coronary artery bypass, n (%)	<0.1%	20,084 (67.9%)	<0.1%	29,752 (61.2%)	<.001
Valve surgery, n (%)	0.1%	12,955 (43.8%)	<0.1%	23,430 (48.2%)	<.001

SD, Standard deviation; *IQR*, interquartile range; *BMI*, body mass index; *eGFR*, estimated glomerular filtration rate; *CCS*, Canadian Cardiovascular Society.

Box plots including outliers and a graph illustrating how the distribution of transfused units changed for all blood products are presented in Figures E2 and E3. The largest change is the significant increase in patients receiving zero units of RBCs, FFP, and platelets with a general shift in the distribution toward transfusions of fewer units. However, significant outliers persist across all blood products. Box plots and histograms for LOS outcomes are also presented in Figures E4 and E5. These graphs do not capture change in trends and, as such, the distributions appear to be roughly equivalent between the 2 periods.

Modeled estimates controlling for patient characteristics and trends for blood transfusions and patient outcomes are presented in Tables 3 and 4, respectively, with monthly trends from the model scaled up to yearly. Using the RBC transfusion rate regression without hospital fixed effects as an example, the guideline shift coefficient of –0.039 can be interpreted as a contemporaneous 3.9% reduction in the transfusion rate when the guidelines were published. The overall yearly trend coefficient of 0.008 represents an increasing trend of 0.8%/year in the preguideline transfusion rate and the change in yearly trend coefficient

TABLE 2. Unadjusted outcomes

Outcome	Preguideline		Postguideline		Difference (95% CI)	*P* value
	Missing	N = 29,584	Missing	N = 48,595		
Red blood cells	<0.1%		0.2%			
Total units, mean ± SD		1.5 ± 3.5		1.1 ± 2.8	−0.5 (−0.5, −0.4)	<.001
Transfused, n (%)		11,787 (39.9%)		15,034 (31.0%)	−8.9% (−9.5, −8.2)	<.001
Units conditional on transfusion, median (IQR)		2 (2, 4)		2 (1, 4)	0 (N/A)	<.001
Platelets	0.1%		<0.1%			
Total units, mean ± SD		0.6 ± 3.6		0.5 ± 2.0	−0.1 (−0.2, −0.1)	<.001
Transfused, n (%)		5916 (20.0%)		8797 (18.1%)	−1.9% (−2.5, −1.3)	<.001
Units conditional on transfusion, median (IQR)		2 (1, 4)		2 (1, 3)	0 (N/A)	<.001
Cryoprecipitate	0.2%		<0.1%			
Total units, mean ± SD		0.7 ± 3.8		0.8 ± 7.3	0.1 (0.0-0.2)	.014
Transfused, n (%)		2273 (7.7%)		4278 (8.8%)	1.1% (0.7, 1.5)	<.001
Units conditional on transfusion, median (IQR)		8 (5, 10)		8 (5, 10)	0 (N/A)	.021
Fresh-frozen plasma	0.1%		1.5%			
Total units, mean ± SD		0.9 ± 2.7		0.5 ± 2.3	−0.4 (−0.4, 0.3)	<.001
Transfused, n (%)		5866 (19.8%)		6489 (13.4%)	−6.5% (−7.0, −5.9)	<.001
Units conditional on transfusion, median (IQR)		4 (2, 5)		2 (2, 4)	−2 (N/A)	<.001
ICU length of stay, h	10.2%		3.3%			
Mean ± SD		61.3 ± 90.3		66.5 ± 92.3	5.2 (3.6, 6.7)	<.001
Median (IQR)		43 (23, 69)		46 (25, 73)	3 (N/A)	<.001
Hospital length of stay, d	0.1%		0.1%			
Mean ± SD		12.0 ± 14.2		11.8 ± 10.8	−0.2 (−0.4, −0.0)	.025
Median (IQR)		9 (7, 13)		9 (7, 13)	0 (N/A)	<.001
30-d readmissions, n (%)	2.2%	2768 (9.6%)	1.4%	4747 (9.9%)	0.3% (−0.1, 0.7)	.126
30-d mortality, n (%)	<0.1%	604 (2.0%)	<0.1%	795 (1.6%)	−0.4% (−0.6, −0.2)	<.001

CI, Confidence interval; *SD*, standard deviation; *IQR*, interquartile range; *N/A*, not applicable; *ICU*, intensive care unit.

of –0.019 indicates that this trend was reduced by 1.9%/year after the guidelines were published (ie, switching from a positive to a negative trend). The models find significant coefficients for RBCs, platelets, and FFP regressions in both the specifications with and without hospital fixed effects. However, after we controlled for unobserved differences between hospitals, coefficients in the cryoprecipitate regressions fail to reach significance. Therefore, our study design indicates significant decreases in RBC, platelet, and FFP transfusions at the time of the guidelines, but not significant increase in cryoprecipitate. Figure 1 presents the adjusted mean monthly transfusion rate for all blood products alongside their regression models. Figures for total and conditional blood product units are presented in Figures E6 to E13.

Our regressions found no significant coefficients for mortality, readmissions, or ICU LOS. This is contrary to the significant differences in unadjusted ICU LOS and mortality, highlighting the importance of adjusting for patient characteristics and trends before drawing conclusions. Significant coefficients of interest were found for hospital LOS, presented in Figure 2. The upward hospital LOS trend in the preguideline period dissipated after the publication of the guidelines. Corresponding figures for the remaining patient outcomes are presented in Figures E14 to E16.

Regression results and graphs for all subgroup analyses, robustness checks, falsification tests, and the threshold analyses are presented in Figures E17 to E22. The results of the subgroup analyses indicate that the impact of the guidelines was statistically similar across public and private hospitals and across devolved and nondevolved public hospitals. Results for isolated coronary artery bypass patients were also similar to the full population. Our results remained consistent when imputing missing data or expanding the model to including quadratic and cubic terms. Providing some support to the internal validity of our model, neither of the coefficients of interest reach statistical significance for inotropes, intravenous nitrates or steroids, which are unrelated to PBM. The threshold analyses reveal a clear peak in model fit for RBC units when the guideline split is set 2 months after the true publication date. At the same time point, there is a similar peak in model fit for the RBC transfusion rate, although the picture is less clear with another peak 16 months after the true publication date. Overall, these checks support the results of the main model and the conclusions regarding the impact of the guidelines.

TABLE 3. Blood product regressions

Term	Total red blood cell units						Red blood cell transfusion rate						Conditional red blood cell units					
	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value
Guideline shift	−0.324	0.044	<.001	−0.346	0.097	<.001	−0.039	0.006	<.001	−0.044	0.018	.015	−0.473	0.102	<.001	−0.507	0.161	.002
Overall yearly trend	0.040	0.011	<.001	0.051	0.038	.173	0.008	0.001	<.001	0.008	0.006	.142	0.015	0.023	.496	0.060	0.051	.240
Change in yearly trend	−0.069	0.013	<.001	−0.077	0.038	.044	−0.019	0.002	<.001	−0.017	0.007	.009	−0.004	0.031	.884	−0.055	0.054	.309
Hospital fixed effects	✗			✓			✗			✓			✗			✓		
N	77,122			77,122			77,214			77,214			26,504			26,504		
R^2	0.0969			0.1153			0.1519			0.1870			0.0605			0.0758		
	Total platelet units						**Platelet transfusion rate**						**Conditional platelet units**					
Guideline shift	−0.090	0.053	.087	−0.056	0.070	.421	−0.009	0.006	.101	−0.014	0.015	.360	−0.285	0.233	.221	−0.085	0.290	.770
Overall yearly trend	0.011	0.012	.391	0.024	0.026	.344	0.010	0.001	<.001	0.010	0.004	.009	−0.096	0.054	.075	−0.045	0.097	.646
Change in yearly trend	−0.022	0.014	.103	−0.042	0.037	.255	−0.018	0.002	<.001	−0.017	0.004	<.001	0.153	0.059	.009	0.046	0.149	.756
Hospital fixed effects	✗			✓			✗			✓			✗			✓		
N	77,322			77,322			77,322			77,322			14,560			14,560		
R^2	0.0199			0.0358			0.0520			0.0732			0.0124			0.0945		
	Total cryoprecipitate units						**Cryoprecipitate transfusion rate**						**Conditional cryoprecipitate units**					
Guideline shift	0.086	0.077	.269	0.065	0.123	.596	0.011	0.004	.007	0.007	0.013	.587	−0.267	0.793	.736	−0.044	0.729	.952
Overall yearly trend	0.032	0.014	.022	0.036	0.033	.270	0.001	0.001	.513	0.001	0.003	.700	0.350	0.150	.019	0.221	0.172	.198
Change in yearly trend	−0.050	0.017	.004	−0.050	0.042	.237	0.000	0.001	.891	−0.001	0.004	.860	−0.564	0.167	.001	−0.291	0.238	.222
Hospital fixed effects	✗			✓			✗			✓			✗			✓		
N	77,322			77,322			77,322			77,322			6,493			6,493		
R^2	0.0070			0.0136			0.0329			0.0674			0.0046			0.0272		
	Total fresh-frozen plasma units						**Fresh-frozen plasma transfusion rate**						**Conditional fresh-frozen plasma units**					
Guideline shift	−0.110	0.036	.002	−0.111	0.076	.143	−0.009	0.005	.089	−0.010	0.014	.459	−0.297	0.149	.047	−0.283	0.250	.258
Overall yearly trend	0.014	0.009	.117	0.009	0.028	.743	0.007	0.001	<.001	0.005	0.005	.234	−0.080	0.038	0.034	−0.057	0.068	.404
Change in yearly trend	−0.108	0.011	<.001	−0.080	0.034	.020	−0.027	0.002	<.001	−0.022	0.006	<.001	0.000	0.048	.999	−0.002	0.080	.982
Hospital fixed effects	✗			✓			✗			✓			✗			✓		
N	77,322			77,322			77,322			77,322			12,205			12,205		
R^2	0.0391			0.0640			0.0589			0.0948			0.0280			0.0561		

Full regression output provided in Table E4 to E7; monthly trend scaled up to yearly. *Coef*, Coefficient; *SE*, standard error; *P* value, *P* value highlighting whether the coefficient is significantly different from zero.

DISCUSSION

We used a large national dataset to perform an ITS analysis assessing the change in blood transfusion and patient outcomes during cardiac surgery after the publication of national PBM guidelines. We found significant reductions in RBC, platelet, and FFP transfusions and in hospital LOS. In our subgroup analysis, we did not find any evidence to suggest that private hospital status or budget responsibility influenced the impact of the guidelines. This is the first quantitative study to assess the impact of any national PBM guidelines on outcomes in cardiac surgery, highlighting that resources have been saved without a loss of health.

Similar PBM guidelines in cardiac surgery have been implemented in the United States in 2007[23] and Europe in 2017.[24] The only published assessment of their impact is a survey of American anesthesiologists and perfusionists conducted 2 years after the publication of their guidelines. The authors concluded that while they had been widely distributed, little change in clinical practice could be

TABLE 4. Patient outcome regressions

Term	ICU length of stay, h			Hospital length of stay, d			30-d readmissions/1000 patients			30-d mortality/1000 patients		
	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value	Coef.	SE	*P* value
Guideline shift	−1.635	2.075	.431	−0.941	0.324	.004	−5.850	7.716	.448	−0.782	2.023	.699
Overall yearly trend	2.941	1.171	.012	0.411	0.103	<.001	-0.505	2.215	.819	0.425	0.521	.415
Change in yearly trend	−2.014	1.356	.138	−0.334	0.117	.004	2.203	2.845	.439	−0.388	0.588	.509
Hospital fixed effects	✓			✓			✓			✓		
N	66,684			77,258			76,240			77,322		
R^2	0.1074			0.088			0.0186			0.0410		

Full regression output provided in Table E8. Monthly trend scaled up to yearly. *ICU*, Intensive care unit; *Coef.* coefficient; *SE*, standard error; *P* value, *P* value highlighting whether the coefficient is significantly different from zero.

attributed to the guidelines.[25] Despite the lack of evidence for the effectiveness of national PBM guidelines, the success of PBM initiatives in single cardiac surgery units is well established, with 2 separate hospitals in the United States reporting reductions in their RBC transfusion rates from 39% to 21% over 6 years[15] and from 43% to 18% over 4 years.[14] We find a smaller reduction from 36% to 27% over 5 years using data from 39 hospitals, supporting the existing literature on the effectiveness of PBM at reducing blood transfusions in cardiac surgery.

In line with previously published research in adults undergoing cardiac surgery,[7,8,10,14] a significant reduction in hospital LOS was observed that coincided with the reduction in blood transfusions. However, the previously published link between blood transfusions and mortality or ICU LOS was not corroborated.[6,7] Two open-label, randomized controlled trials in cardiac surgery patients have found restrictive transfusion strategies resulted in noninferior rates of combined 30-day mortality and severe morbidity[26] and noninferior rates of a composite outcome of death, myocardial infarction, stroke, or renal failure.[27] These trial results provide strong evidence of the clinical safety of implementing lower hemoglobin transfusion triggers in cardiac surgery. In our observational study, we found no evidence that PBM initiatives, which included lower hemoglobin triggers, increased ICU LOS, readmissions, or mortality.

The subgroup analysis found no differences in the impact of the guidelines with regards to private hospital status or

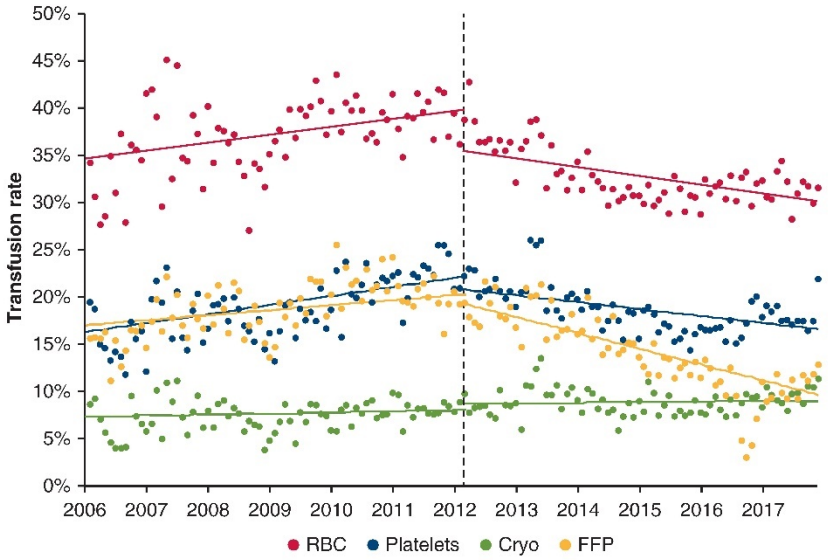

FIGURE 1. Transfusion rate. Each *dot* represents the adjusted mean monthly blood product transfusion rate, the *vertical dashed line* represents the publication of the guidelines, and the *solid lines* represent the regression model. *RBC*, Red blood cells; *FFP*, fresh-frozen plasma.

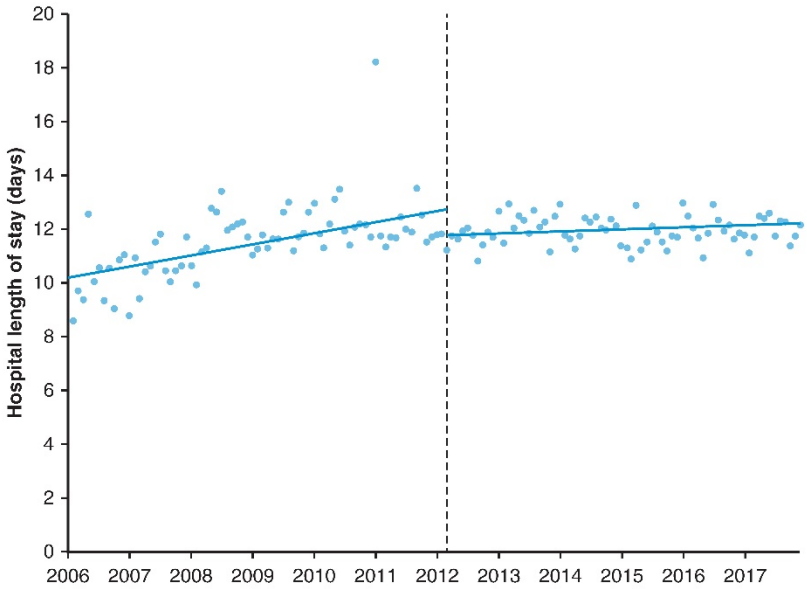

FIGURE 2. Hospital length of stay. Each *dot* represents the adjusted mean monthly hospital length of stay in days, the *vertical dashed line* represents the publication of the guidelines, and the *solid lines* represent the regression model.

budgetary arrangements in public hospitals. Surgeons and anesthesiologists in Australia often operate across both public and private sectors, likely taking their personal operating characteristics and propensity to prescribe blood into both settings, and thus reducing the power to detect a difference.[28] Also, the operating team in devolved public hospitals may not have been exposed to the price signal or were already under pressure to manage costs, something we are not able to observe.

We performed a back-of-the-envelope calculation of the resources saved over 5 years from March 2012 to March 2017 presented in Table E9. Assuming the preguideline trend would have continued in absence of the guidelines would have likely overestimated the resource savings given the global movement toward PBM highlighted by the World Health Organization Global Forum.[29] Instead, to remain conservative, our resource saving estimates assumed a zero trend for the counterfactual from March 2012 onwards. Unit costs were taken from Australian national sources and converted into US dollars. Across the 48,595 patients in the database from March 2012 to March 2017, the reductions in blood transfusions and hospital LOS saved approximately $31M, or $647 per patient.

The main limitation of this study is the lack of a suitable control group. As the guidelines were implemented nationally at the same time, it is not possible to create a relevant control group from surgeries performed in Australia. Therefore, although we are unaware of any other relevant changes in policy that were implemented at a similar time, without a control group we cannot exclude the possibility that the observed changes were determined by factors other than guidelines. Diligent physicians may have already been aware of PBM recommendations published elsewhere and incorporated them into their care. We also do not know the degree to which the guidelines were read by surgeons or specifics regarding implementation initiatives. Furthermore, an assumption of ITS analyses is that the preintervention trend would have perpetuated in the absence of the intervention.[20] We cannot be confident that a reduction in blood transfusions would not have eventuated without the guidelines, given the global movement toward PBM. Finally, all of the models have low R^2 values, suggesting that much of the variation in blood transfusions is related to variation in unobserved clinical and patient characteristics. Each surgery is inherently unique and presents physicians with a series of decisions that influence the likelihood of a transfusion. Although the overall objective of PBM is to reduce transfusions, the recommendations are linked to managing a patient's own blood in each phase of the surgery rather than a strict set of rules for when transfusions are appropriate.

The strengths of this study include assessing the impact of national guidelines using a large dataset with a wide timeframe. Using these data, we were able to adjust for a range of patient characteristics that predict blood transfusions and unobserved differences between hospitals using fixed effects. We were also able to evaluate changes in patient outcomes.

Many of PBM recommendations are based on evidence from observational studies. High-quality research providing

stronger evidence of the effects of implementing these recommendations is warranted. Moreover, determining the contribution of individual PBM recommendations to the observed reductions in blood transfusions and hospital LOS would help guide future guideline development and implementation strategies. Also, assessing the relationship between anemia and transfusions under a PBM program would be particularly interesting, given anemia's historical use as a benchmark for transfusions.

CONCLUSIONS

After the publication of the NBA's PBM guidelines for perioperative care in March 2012, there was a significant reduction in RBC, platelet, and FFP transfusions in patients undergoing elective cardiac surgery. We also found an associated significant reduction in hospital LOS. Assuming that the changes identified are a result of the guidelines, resources have been saved without negatively affecting health.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: patient blood management, cardiac surgery

5 Assessing Heterogeneity in the Response to Clinical Guidelines and Subsequent Changes in Variation in Care – the Case of Blood Transfusions during Cardiac Surgery

5.1 Introduction

Variations in care are widespread, having been observed across many medical disciplines.[91] Clinical guidelines are a widely used intervention for providing hospitals and physicians with the most up-to-date evidence regarding treatment efficacy. It is hoped that providing credible information will reduce uncertainty regarding best practice, dispel intrinsic biases and subsequently reduce variations in care.[92] However, the extent to which hospitals and physicians respond to guidelines is likely to differ. If adherence is concentrated in hospitals or physicians who were already performing well, then guidelines may increase variation in care. While studies assessing the overall adherence to clinical guidelines are common, their direct impact on variation in care is rarely appraised. The objective of this study was to develop and apply methods to assess heterogeneity in the response to a set of clinical guidelines across surgeons and hospitals and the subsequent impact on variation in care.

Healthcare utilisation is underpinned by three factors – incidence of ill health, the information and technology available to treat the ill health, and patient preferences.[93] Due to information asymmetry, where physicians have superior information regarding the diagnosis, treatment and prognosis of ill health, patients usually delegate treatment decisions to their physician, who makes their recommendations based on their knowledge of the available treatment options.[93] Therefore, if equivalent treatments were available regardless of location, and if all physicians were abreast of the latest knowledge regarding treatment choices, we would expect similar patients to receive consistent care across different regions. However, since Glover's seminal 1938 study into tonsillectomy rates across school districts in the UK,[77] an expansive literature has emerged highlighting variations in care across an array of patient, physician, hospital and health system characteristics. Unwarranted variations are disparities that cannot be explained by illness or patient preferences.[89] They represent an opportunity to increase efficiency either through improving health outcomes, reducing unnecessary resource use, or both.

Over the last half century, following important work highlighting that physician decision-making was motivated by intrinsic bias of assumed effectiveness rather than evidence, medicine has transitioned towards an evidence-based approach.[94, 95] Driven by regulatory requirements and professional bodies,

modern medicine has seen dramatic growth in high quality evidence, and society experiences an opportunity cost in terms of providing the best possible care until this latest evidence is universally acknowledge and utilised. However, the diffusion of the latest evidence down to the appropriate healthcare workers is not guaranteed. Assimilation of the latest evidence requires significant skills and resources including defining the evidence gap, searching for the evidence, critically appraising the evidence identified and developing a strategy for revising practice. Clinical guidelines are a tool for distributing the latest evidence and, when prepared to high standards, can efficiently relieve the costly burden of independent evidence assessment from healthcare workers. Clinical guidelines are evidence-based statements recommending a specific course of action given a specific set of clinical circumstances. They are usually developed by systematic review along with input from clinical experts and are designed to improve the quality and consistency of care by providing healthcare workers with the best-available evidence to inform diagnostic or treatment decisions.[96]

While clinical guidelines can be effective at changing practice,[97] their impact may not be homogenous across the healthcare system. At the physician level, clinical guidelines are likely to be more effective when physicians are already aware that new evidence has been developed that may improve the quality of their care, when they are more familiar with the condition described and when they agree with the recommendations. There is also evidence to suggest that young cohorts are more likely to adhere to guidelines than older, more experienced physicians.[90] At the hospital level, the institutional implementation strategy is likely to influence adherence to the guidelines. Potential initiatives include distributing educational materials, training sessions, audit and feedback mechanisms or full system redesigns with the literature suggesting that multiple-initiative strategies may outperform single-initiative strategies.

While the literature has established the presence of significant variation in care across a broad range of disciplines, little work has assessed how variation responds to policies or interventions.[71] Studies assessing the impact of clinical guidelines generally focus on the degree of adherence, rather than changes in variation. Clinical guidelines will only reduce variation in care if the previously worst performing physicians or hospitals on average experience greater adherence than the best performing. After controlling for differences in patient preferences and case-mix over which observed variation may be warranted, one method for assessing changes in variation would be to compare the variance in predicted healthcare utilisation rates across units (physicians or hospitals) before and after the intervention. However, estimates of the variance of predicted utilisation rates will be in general biased upwards due to sampling error in each prediction.[98]. Although it is not common for variation studies to adjust the estimated variance across units for sampling error, we propose a method herein using

established statistical techniques from the meta-analysis literature and compare the results against the unadjusted variance.[99]

In this study, we use the setting of red blood cell (RBC) transfusions during cardiac surgery to examine heterogeneity in response to clinical guidelines and the subsequent impact on variation in care. The evidence regarding variations in RBC transfusions during cardiac surgery is well established across hospitals in the USA,[100-105] Australia[74] and internationally,[106] and across surgeons in the USA[107] and Canada.[52] The guidelines under evaluation were published in March 2012 by Australia's single blood provider, the National Blood Authority, and were specifically designed to reduce unnecessary RBC transfusions during surgical separations by following patient blood management (PBM) techniques.[108] The focal point of the guidelines was a set of recommendations and practice points for alternative care pathways that should reduce the need for an RBC transfusion, which are very common during cardiac surgery due to significant perioperative blood loss from the invasive nature of the procedure.[109] We quantify the change in variation in the RBC transfusion rate during cardiac surgery across hospitals and surgeons in Australia following the publication of the national PBM guidelines. We assume that unobserved hospital- and surgeon-level factors will influence adherence to the guidelines, such as institutional culture, cost consciousness and prevailing opinions regarding the effectiveness of RBC transfusions. We hypothesise that we will observe a reduction in variation brought about by those hospitals and surgeons with high pre-guideline transfusion rates on average experiencing larger responses to the guidelines than hospitals and surgeons with low pre-guideline transfusion rates. We measure the extent to which this is true, and therefore the contribution of the guidelines to reducing variation in care.

5.2 Materials and Methods

5.2.1 Data Source

This study used surgery-level data routinely collected by the Australian & New Zealand Society of Cardiac & Thoracic Surgeons (ANZSCTS). Hospitals participating in the ANZSCTS Cardiac Surgery Database submit pre-defined data on all cardiac surgeries performed. The database includes patient demographics and risk factors, surgical history, pre- and intra-operative medication and post-operative outcome data. The database includes data on RBC transfusions during the surgical separation as well as de-identified hospital and surgeon codes.

There are currently 23 public and 17 private hospitals across Australia enrolling patients in the database; however, the sample was restricted to the 25 hospitals that were contributing data before the guidelines were published in March 2012. As many of the guideline's recommendations concern

managing the pre-operative phase of care, the sample was also restricted to patients undergoing elective surgery only. In order to improve the accuracy of the estimates, only data from the 71 surgeons who performed at least 50 elective surgeries recorded in the ANZSCTS Database in both the pre- and post-guideline period were included.

5.2.2 Outcomes

After the publication of the PBM guidelines, in line with the recommendations, there was a significant decrease in the RBC transfusion rate. In this study, variation in the RBC transfusion rate in the 5 years preceding the guidelines (March 2007 – February 2012) was compared with the variation in the 5 years following the guidelines (March 2012 – February 2017).

5.2.3 Statistical Analysis

We set out to estimate variation in the blood transfusion rate across hospitals, across all surgeons across all hospitals (hospital-surgeons) and across surgeons within each hospital. In the primary analysis, the 15 surgeons who operated across multiple hospitals were considered separate "hospital-surgeons" in each hospital. We do not distinguish between a separate surgeon effect (controlling for the hospitals they operate in) and a hospital effect (controlling for the surgeons that operate in that hospital). To separately estimate these effects across all hospitals and all surgeons we would need all hospitals to contain surgeons that operate in multiple hospitals in a fully connected network of hospitals. In our data we have multiple separate networks of connected hospitals and a number of hospitals that contain surgeons who we do not see operating elsewhere. We present further details in the Appendix outlining and exploring methods for using the differential response of surgeons who operate across multiple hospitals to identify specific hospital-level versus surgeon-level responses to the guidelines using a two-way fixed effect model. Below we instead use a one-way fixed effect approach to predict the transfusion rate for each hospital and each hospital-surgeon which we use to estimate the variance across hospitals and across hospital-surgeons.

To assess heterogeneity in the response to the guidelines, each unit's (hospital or hospital-surgeon) RBC transfusion rate was predicted from the following fixed effect regression:

$$y_{ijt} = \alpha + \beta X_{it} + \varphi M_t^0 + \gamma M_t^1 + u_j^0 + u_j^1 + \varepsilon_{ijt}$$

Where, y_{ijt} is an indicator variable representing whether patient i received a perioperative RBC transfusion in month t from unit j, X_{it} is the vector of control variables, M_t^0 is the overall monthly trend starting in March 2007 and M_t^1 is post-guideline monthly trend which takes zero before the guidelines and increases after March 2012. Separate fixed effects were estimated for the pre- and

post-guideline periods, u_j^0 and u_j^1 respectively. The patient control variables were identified from a previously published predictive model of RBC transfusions using the same ANZSCTS database.[74]

Predictions of the transfusion rate for each unit (hospital or hospital-surgeon) in the pre- and post-guideline periods including fixed effects were estimated as if they had treated all of the patients in the dataset, thus removing the variation due to each unit's patient case-mix. As the regression model included fixed effects and time trends in both periods, an adjustment was made for the contribution of the time trend for the pre-guideline prediction of post-guideline patients and vice versa by fixing the month of surgery for the predictions. For the pre-guideline predictions, all surgeries were assumed to have taken place in February 2012 - the month before the guidelines were published. For the post-guideline predictions, all surgeries were assumed to occur in in the middle month of the post-guideline window, September 2014. Therefore, these predictions not only adjust for patient characteristics but also for when patients were treated to give comparable estimates of pre- and post-guideline transfusion behaviour for each unit.

To assess the variation in care in the pre- and the post- guideline period, the variance in the estimated transfusion rates was calculated as:

$$s^2 = \frac{\sum(y_j - \bar{y}_j)^2}{n-1}$$

Where, y_j is the predicted transfusion rate for unit j, $\bar{y}_j$ is the mean of the transfusion rates across all units and n is the number of units. As the predicted transfusion rates y_j are estimates, s^2 will be biased upwards and the extent of the bias will vary given the unequal denominator of surgeries across the units and across the periods. We compare s^2 with estimates adjusted for sampling error by adopting a random error model for pooling the predicted transfusion rates and decomposing the observed variation into true heterogeneity (i.e. variation) and random (i.e. sampling) error. Our random error model for units $j = 1, \dots, J$ is defined as:

$$y_j = \mu_j + \varepsilon_j \qquad \varepsilon_j \sim N(0, \sigma_j^2) \qquad\qquad \mu_j = \mu + E_j \qquad E_j \sim N(0, \tau^2)$$

Where, y_j is still the predicted transfusion rate for unit j, μ_j is the true mean effects for unit j and, ε_j is the mutually independent, normally distributed sampling error contained in the predicted transfusion rate and σ_j^2 is the variance of this sampling error. μ is the true underlying unit mean for all units, E_j is the mutually independent, normally distributed error term which reflects the true variation from the overall unit mean and thus τ^2 is the between-unit variance. The between-unit variance τ^2 across all hospitals, across all surgeons and across surgeons within hospitals before and

after the publication of the guidelines was estimated assuming the true unit effects μ_j are normally distributed. Under the hypothesis, τ^2will decrease in all scenarios.

A common method for assessing the heterogeneity in effect sizes, the null hypothesis that τ^2 is zero, is based on the test statistic Q.[110] Q is calculated as the sum of the squared deviations of each unit's effect from the pooled overall effect, weighted by the inverse variance in that unit's effect.

$$Q = \sum_j w_j(y_j - \bar{y}_w)^2$$

Where, y_j is the predicted transfusion rate of unit j, $\bar{y}_w = \sum_j w_j y_j / \sum_j w_j$ is the weighted estimate of the transfusion rate across all units, and weight w_i is the inverse of the variance of units j. Under the null hypothesis of homogenous effect sizes ($\tau^2 = 0$), Q approximates a χ^2 distribution with $n - 1$ degrees of freedom. The popular DerSimonian-Laird method of moments technique was used to estimate τ^2.[111]

$$\hat{\tau}^2 = \frac{Q - df}{\sum w_j - \sum w_j^2 / \sum w_j}$$

The variation above what would have been expected by sampling error is quantified by the difference between Q and the degrees of freedom (*df*) and rescaled to place $\hat{\tau}^2$ on the same scale as the effect. Thus $\hat{\tau}^2$ represents an estimate of the absolute variation in the transfusion rate across units. If the observed variance between units is less than would be expected by sampling error, then $Q < n - 1$ and $\hat{\tau}^2$ will be negative. As the between-unit variance cannot be less than zero, $\hat{\tau}^2$ will be set to zero in these circumstances, such that the precision of the random error model cannot exceed that of a model that only considers sampling error. This truncation means that $\hat{\tau}^2$ will be an upward biased estimator for τ^2 when τ^2 is very low.[112]

Assessing the statistical significance of any change in the variance requires an estimate of the uncertainty in the between-unit variance, which is itself based on effect sizes measured with sampling error. As has been suggested for quantifying uncertainty in similar summary estimates from random effect meta-analyses,[99] bootstrapping with replacement across surgeries stratified by units within the pre- and post-guideline periods was performed to generate 500 estimates of $\hat{\tau}^2$ for each period, which were compared using the percentile method.

The relationship between response to the guidelines and the pre-guideline transfusion rate will determine the impact on variation in care. This was explored across hospitals and across hospital-surgeons. The relationship between change in variation and pre-guideline within-hospital variation was also analysed, expecting that hospitals containing surgeons performing similarly before the

guidelines will experience smaller reductions in within-hospital variation than those with more variation to eliminate. The relationship between response to the guidelines and the median number of surgeries performed per year at the hospital and surgeon level was also examined. Larger hospitals may be better resourced to implement new initiatives and high volume surgeons may place more value on providing the best possible care. Finally, the relationship between response to the guidelines and private hospital status was assessed, where surgeons in private hospitals may be subject to less institutional oversight.

5.3 Results

The sample was restricted to elective surgeries (66,069 of 94,567 surgeries) and then to surgeons who performed at least 50 elective surgeries in each period (48,504 of 66,069 surgeries). The final analysis sample comprised 48,048 elective cardiac surgeries performed by 88 hospital-surgeons across 25 hospitals, 20,988 in the 5-year pre-guideline period and 27,060 in the 5-year post-guideline period. A summary of the patient and surgery characteristics that comprised the vector of controls is presented in the Appendix.

The Appendix contains the results from the fixed effect regression models. After controlling for patient and surgery characteristics, the mean predicted pre-guideline transfusion rate across all hospitals was 40.3% (95% CI: 36.0%, 44.6%) with a range of 21.9% to 60.5%. After the guidelines were published the transfusion rate across hospitals fell significantly by 7.6% to 32.7% (95% CI: 29.0%, 36.4%) with a range of 17.0% to 51.9%. The predicted pre-guideline transfusion rate across hospital-surgeons was 40.1% (95% CI: 37.6%, 42.6%) with a range of 17.4% to 68.0% which also fell significantly by 7.6% to 32.5% (95% CI: 30.2%, 34.9%) with a range of 10.5% to 60.1% after the publication of the guidelines.

Figure 5.1 presents the controlled pre- and post-guideline predicted transfusion rates for each hospital and hospital-surgeon as bars and circles respectively. The red and blue bars and circles represent the pre- and post-guideline periods respectively. The hospitals are ordered by their predicted pre-guideline transfusion rate and labelled alphabetically with the best performing hospitals towards the left-hand side. Smaller bars and circles are more precise estimates.

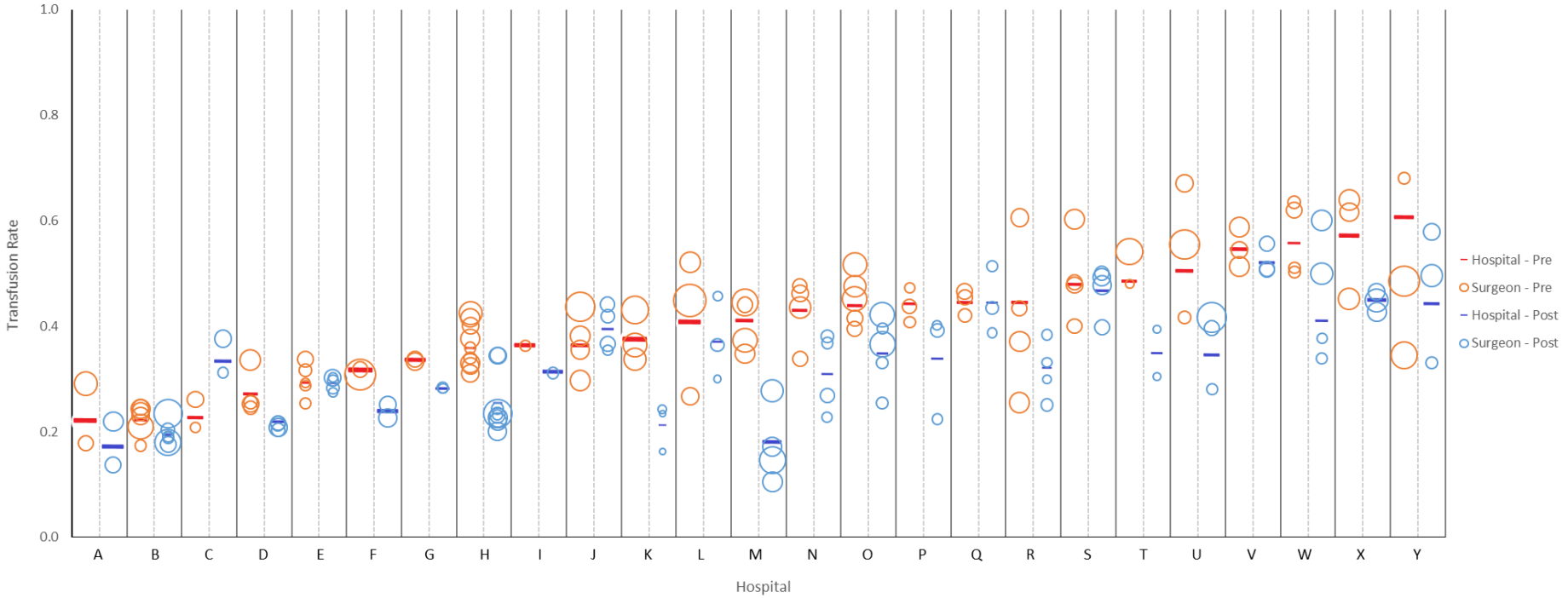

Figure 5.1: Hospital and Hospital-surgeon Change in Transfusion Rate

Those hospitals that have responded to the guidelines are those for which their post-guideline transfusion rate, represented by the blue bar, is below the associated pre-guideline rate, represented by the red bar. Larger responses were observed in hospitals with higher pre-guideline transfusion rates, shown to the right of the figure. However, response did not appear to be consistent for all hospitals with similar pre-guideline transfusion rates. Among hospitals with high pre-guideline transfusion rates, hospitals Q, S and V did not appear to respond significantly, and among the hospitals with low pre-guideline transfusion rates, hospitals C and J experienced an increase in their predicted transfusion rate.

The distribution of red and blue circles representing predicted hospital-surgeon transfusion rates within each hospital indicates the within-hospital variation. In some hospitals such as hospitals D, L and X, the circles became more clustered from pre to post guidelines, suggesting a reduction in within-hospital variation. However, the reverse is true in other hospitals such as P and W, where within-hospital variation increased.

Table 5.1 presents the change from pre- to post-guidelines in the variance across the point estimates of the predicted hospital and hospital-surgeon transfusion rates and the between-hospital and between-hospital-surgeon variance estimated from the random error model. At both the hospital and hospital-surgeon level the variation decreased significantly when moving from the pre- to the post-guideline period, with a larger reduction in $\hat{\tau}^2$ from the random error model, compared with taking the variance across the point estimates of the predicted transfusion rates.

Table 5.1: Simple Variance vs. Random Error Model

	Pre-guideline		Post-guideline		Change	
Unit	**Variance**	$\hat{\tau}^2$	**Variance**	$\hat{\tau}^2$	**Δ Variance**	**Δ** $\hat{\tau}^2$
Hospital	0.0120	0.0117	0.0091	0.0075	-0.0029	-0.0042***
Hospital-Surgeon	0.0142	0.0142	0.0125	0.0096	-0.0017	-0.0046*

*** p<0.01, ** p<0.05, * p<0.010

Table 5.2 presents the change in each hospital's predicted transfusion rate and the change in the within-hospital variation across their hospital-surgeons. There is no variation in Hospital I as it contained only one hospital-surgeon. We can see that for hospitals F and G, the estimate of the change in $\hat{\tau}^2$ is zero. Rather than no change in variation, this has occurred because the random error model has predicted that the excess variation is negative and $\Delta\hat{\tau}^2$ has been truncated to zero in both periods. This occurs when the expected variation across hospital-surgeons is less than would be expected by chance if they had the same true blood transfusion rate. This is linked to the number of hospital-surgeons operating within the hospital with both hospitals F and G containing only 2 hospital-surgeons.

Twenty-one of the twenty-five hospitals experienced a significant reduction in their predicted transfusion rate. Two hospitals with relatively low pre-guideline transfusion rates experienced significant increases in their predicted transfusion rates and two hospitals remained largely unchanged. Significant reductions in within-hospital variation were observed for only four hospitals, all of which have high pre-guideline transfusion rates and within-hospital variation. Two hospitals, Q and W, experienced a significant increase in within-hospital variation, some hospital-surgeons in these hospitals did not respond to the guidelines, or even experienced an increase in their transfusion rate compared to their within-hospital peers who did respond.

Table 5.2: Change in Hospital Transfusion Rate and Within-hospital Variation

Hospital	Δ Transfusion rate	$\Delta\hat{\tau}^2$	Hospital	Δ Transfusion rate	$\Delta\hat{\tau}^2$
A	-0.0494***	-0.0029	N	-0.1201***	0.0019
B	-0.0271***	-0.0002	O	-0.0908***	0.0029
C	0.1068***	0.0006	P	-0.1040***	0.0096***
D	-0.0521***	-0.0005	Q	0.0000	0.0040*
E	-0.0003	-0.0004	R	-0.1239***	-0.0167***
F	-0.0779***	0	S	-0.0127***	-0.0034
G	-0.0531***	0	T	-0.1357***	0.0031
H	-0.1039***	0.0012	U	-0.1598***	-0.0169**
I	-0.0500***	-	V	-0.0254***	-0.0002
J	0.0316***	-0.0001	W	-0.1470***	0.0059*
K	-0.1613***	0.0017	X	-0.1224***	-0.0086**
L	-0.0366***	-0.0143*	Y	-0.1635***	-0.0157
M	-0.2292***	0.0028			

*** p<0.01, ** p<0.05, * p<0.10

Figure 5.2 presents the relationship between the change in hospital transfusion rate and the change in within-hospital variation measured by $\Delta\hat{\tau}^2$. In this chart, bubble size represents the hospital pre-guideline transfusion rate, with smaller circles indicating lower rates, and the colour of circles represents the pre-guideline within-hospital variation. Pre-guideline variation was ≤0.001, 0.001 to 0.008 and >0.008 as measured by $\hat{\tau}^2$ in the green, orange, and red circles respectively. Hospitals towards the left-hand side of the figure, which experienced the greatest reduction in the transfusion rate, appear to have larger circles indicating higher pre-guideline transfusion rates. Similarly, those hospitals who experienced the greatest reduction in within-hospital variation towards the bottom of the graph were those with highest pre-guideline within-hospital variation depicted by the red circles. There is a positive correlation between the change in transfusion rate and change in within-hospital variation. Hospitals that experienced reductions in their transfusion rates were more likely to experience reductions in their within-hospital variation.

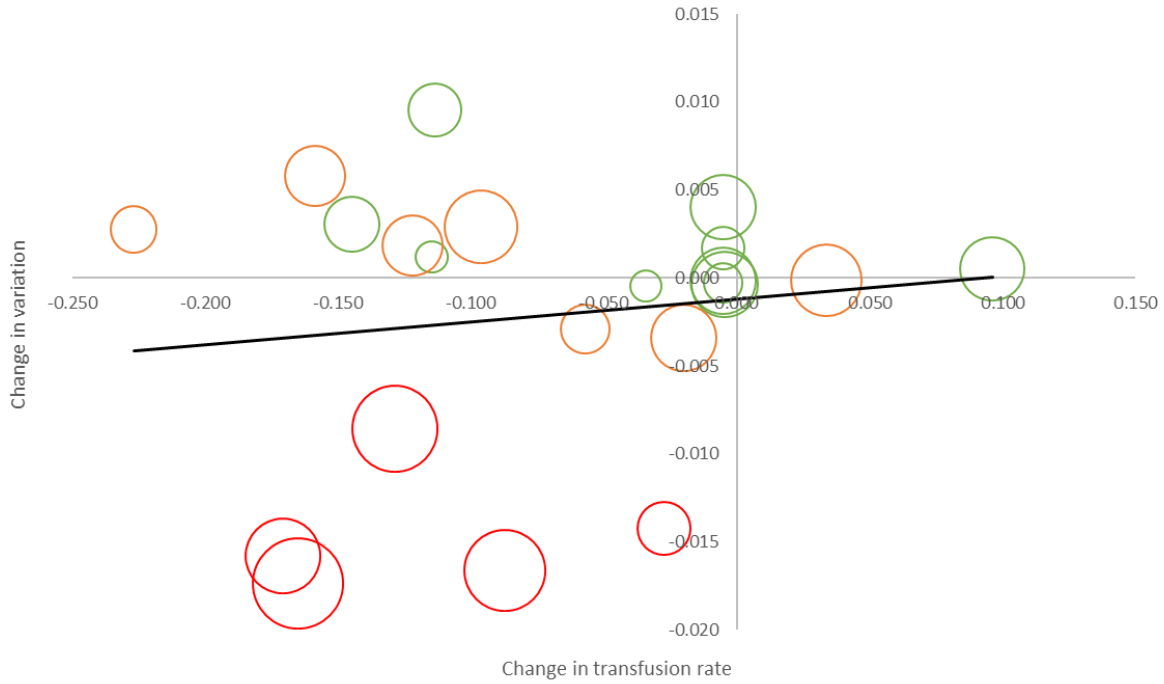

Figure 5.2: Change in Transfusion Rate vs. Change in Variation

Figure 5.3 presents the relationship between the change in transfusion rate at the hospital and hospital-surgeon level and the median annual number of surgeries. Again, bubble size represents the pre-guideline transfusion rate. At the hospital level, there appears to be a relationship between median annual number of surgeries and the change in transfusion rate, with larger reductions for hospitals that perform more surgeries. However, the relationship does not hold at the hospital-surgeon level.

Six private hospitals were included in the analysis - hospitals A, E, K, L, U and Y from Figure 5.1. There does not appear to be any systematic difference in pre-guideline transfusion rates between the public and private hospitals. However, the three hospitals with the largest pre-guideline within-hospital variation were all private hospitals (L, U and Y) suggesting weaker peer or coordination effects in private hospitals, where surgeons work more independently of each other. However, this is not a consistent finding across all private hospitals, with very low pre-guideline variation evident in hospitals E and K. The private hospitals with high pre-guideline transfusions rates all responded very strongly to the guidelines with significant reductions, and given the aforementioned high pre-guideline variation, hospitals L, U and Y all experienced reductions in their within-hospital variation.

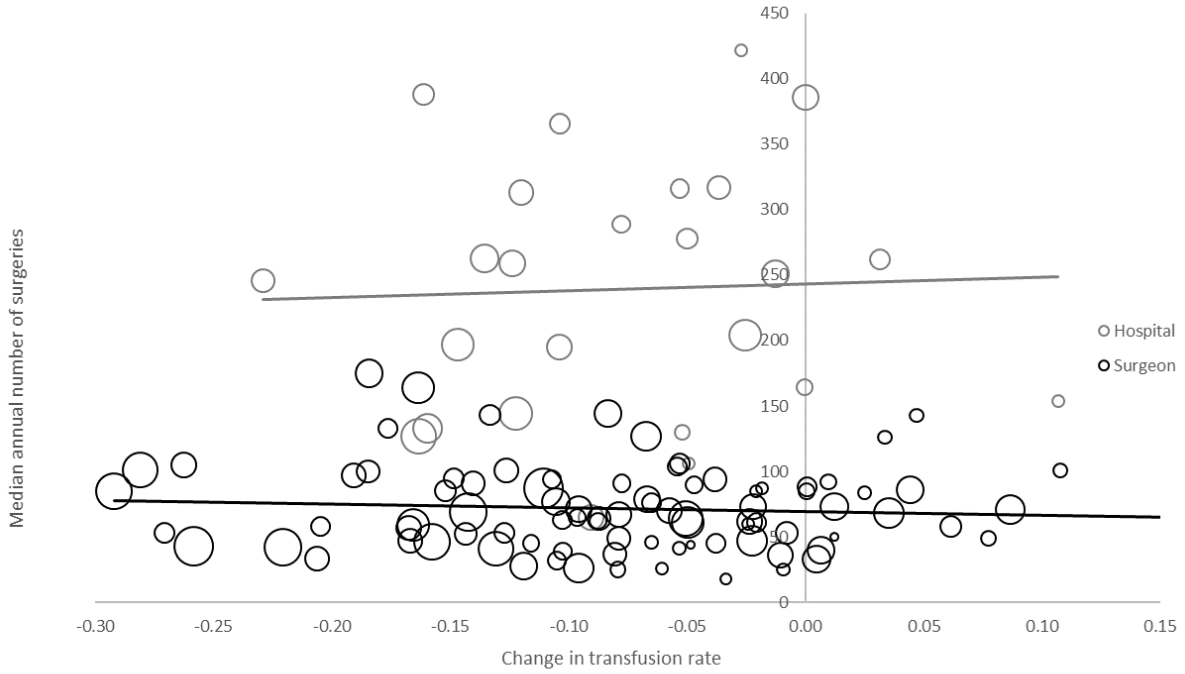

Figure 5.3: Change in Transfusion Rate vs. Median Annual Number of Surgeries

The exploratory analysis presented in the Appendix describes how a two-way fixed effect model can partition reductions in variation to hospital effects and surgeon effects but only for networks of hospitals that contain surgeons who operate in multiple hospitals. Here we see that for one network, the variation in surgeon-specific effects decreases after the guidelines with little change in the hospital-specific variation, while for another network we see a decrease in both surgeon-specific and hospital-specific variation after the guidelines.

5.4 Discussion

In this study, we assessed heterogeneity in the response to a set of national clinical guidelines promoting the appropriate use of RBC transfusions across hospitals and surgeons in Australia and the subsequent impact on variation in care. We found that the guidelines did not have a consistent effect across hospitals or hospital-surgeons. As hypothesised, higher pre-guideline transfusion rates were correlated with larger responses, leading to significant reductions in variation in care across hospitals and across hospital-surgeons. Higher pre-guideline transfusion rates are likely to be associated with more unnecessary transfusions and therefore more room for improvement from implementing guideline recommendations. When assessing within-hospital variation we found generally larger reductions in those hospitals with high pre-guideline variation. This finding is also in line with

expectations given the intrinsic link between these two outcomes - where a reduction in the transfusion rate will always reduce within-hospital variation if the worst performing hospital-surgeons experience the strongest responses. At the hospital level, we found a positive relationship between median annual number of surgeries and response to the guidelines. Larger hospitals may be better resourced, more efficient at communication and are more likely to be teaching hospitals. Private hospital status did not influence response to guidelines. Overall, the conclusions are in line with a key assumption of diffusion of information theory, that clinical uncertainty is reduced by providing high quality, reliable evidence that should standardise treatment.

Providing consistent, appropriate care across the population is a core objective of health policy around the world.[93] However, little research has assessed interventions for reducing observed variation in care.[71] Interventions that reduce the variation in care that exists after controlling for patient case-mix and preferences will likely improve population health, save resources, or both. This study assesses the impact of clinical guidelines, a non-price signal designed to alleviate information asymmetry by collating the best available evidence. Other interventions include incentives or even regulation. Further research is warranted to determine the most cost-effective method for reducing variation and how to assess changes in variation appropriately. One of this study's contribution to variation analyses is using established techniques from the meta-analysis literature to remove the sampling error in the observed variance. We considered this important in our setting where hospitals and surgeons performed different numbers of surgeries, both compared to other hospitals and surgeons and also before and after the guidelines. Therefore, we expect sampling error to be heterogeneous across hospitals and surgeons, and to bias the observed variance upwards. Our statistical approach increases the precision and reduces the bias in the conclusions.[98]

Our study is based upon the premise that a proportion of RBC transfusions during cardiac surgery are unnecessary, and that patients would have recovered from their surgery in a similar or better fashion in the absence of the transfusion. However, some transfusions are likely to be warranted, especially in circumstances of significant blood loss, to maintain normovolaemia. Therefore, necessary transfusions may also have been avoided to the detriment of the patient's health. This could be explored in an analysis assessing the impact of changes in the RBC transfusion rate on patient outcomes and variation in patient outcomes. Indications for transfusions are broad, and the degree to which surgeons remain risk-averse in their prescription of blood transfusions will determine whether patients do not receive necessary transfusions. While the optimal transfusion rate for patients undergoing cardiac surgery remains unclear, the evidence of the safety of PBM initiatives such as lower haemoglobin thresholds in cardiac surgery from clinical trials[113, 114] should assure the

transfusion community that the transfusions avoided through following PBM initiatives were rarely necessary, if at all.

In an exploratory analysis using both hospital and surgeon fixed effects, we found evidence of reductions in variation across surgeons after controlling for hospitals, as well as an increase in variation across hospitals after controlling for surgeons for one of the networks. In our data, hospitals contain a small number of surgeons, with relatively few surgeons operating across multiple hospitals. As such it is difficult to disentangle the hospital effect from a surgeon effect in the same way that labour economists have done using their firm versus worker frameworks.[115] Using a mixed model with fixed and random effects would allow surgeons to be nested within hospitals in a multiple-membership hierarchy. However, these models make strong assumptions about the distribution of treatment effects and that hospitals or surgeons do not differ in terms of the patients they treat (i.e. patient characteristics are the same).

Our study is limited by a number of factors. In order to improve the accuracy of our estimates of the transfusion rate, we restricted our data to surgeons who performed at least 50 surgeries in the pre- and post-guideline period in each hospital in which they operated. As a result, we excluded a significant proportion of surgeries, surgeons and even hospitals from our analysis. Given its binary nature, estimates of the transfusion rate based on small numbers of surgeries would return spurious results, making our restrictions a necessity. Additional hospital or surgeon characteristics are needed to further explain the heterogeneous responses to the guidelines. Institutional implementation strategies as well as location and teaching status may influence hospital response to the guidelines. Surgeon age, gender, experience and attitudes towards the guidelines may influence both practice patterns and adherence to guidelines. Understanding the peer network could also provide a valuable insight into peer effects and the spread of treatment patterns. Given our data, we attribute transfusion decisions to the operating surgeon; however, in reality these decisions are made by the operating team, including the anaesthetist. A dataset including identifiers for the supervising and operating surgeon as well as the anaesthetist would have provided additional granularity to our analysis. There is significant scope for future research in this area, incorporating implementation strategies into an assessment of the heterogeneity in response to previous editions of the guidelines could help inform the implementation strategy for future editions.

The strengths of our study include using a large national dataset to predict both hospital and surgeon response to a set of national guidelines and demonstrating techniques for reducing bias in the observed variation. In summary, we demonstrate heterogeneity across hospitals and across surgeons in response to a set of national clinical guidelines designed to reduce RBC transfusions in cardiac

surgery. As hospitals and surgeons with high pre-guideline transfusion rates generally exhibited the largest responses there was a subsequent reduction in variation in care between hospitals and surgeons. The largest reductions in within-hospital variation were experienced in hospitals with high pre-guideline within-hospital variation.

6 Concluding Remarks

6.1 Summary of Findings

This thesis examines a number of research questions relating to the market for blood. Interventions on the supply side of the market are concerned with maintaining a cost efficient, reliable and adequate supply through donation. Interventions on the demand side of the market are designed to ensure efficiency in the use of blood as a therapeutic. Here we discuss how the evidence generated in this thesis fits into the wider economics of blood literature and what it means for policy and future research. We then discuss recent trends in blood products and what we can take from the current evidence base to inform blood product policies and research moving forward.

6.1.1 Blood Donation

A number of interventions are available to blood services to recruit and retain donors, including monetary and non-monetary incentives as well as non-incentive based interventions such as letters and telephone calls. Previous reviews in this area have summarised the data with respect to one or another of these intervention groups rather than together. To address this gap in the literature, Chapter 2 presented a systematic literature review of RCTs for increasing blood donations, adopting a network meta-analysis for synthesis to compare all interventions simultaneously. We concluded that personal approaches such as telephone calls outperformed all other interventions including monetary and non-monetary incentives. Limited evidence for the effectiveness of incentive-based interventions was identified from a search strategy that focused only on randomised controlled trials that offer the highest level of evidence.

The lack of RCT evidence of incentives reflects the antipathy in many countries towards the idea of remunerated donations. Nevertheless, remuneration does occur in some countries and there is observational evidence from large non-randomised studies suggesting that non-monetary incentives may significantly increase donations.[116, 117] However, the authors also report a displacement effect with reductions in donations reported at neighbouring drives that were not offering the incentives. Therefore, it is important to consider the social spill-overs from such policies and the differences between geographically selective trials and universal policies. One potential benefit of the shift in donations observed when offering non-monetary incentives could be to reallocate donations in response to shortages – both temporally (i.e. bring future donations forward in time to address the shortage) and geographically. Considering unintended consequences on other altruistic activities of

donors would also be useful to better understand the true costs of increasing donations from altruistic donors.

There may be diminishing marginal returns to interventions for increasing blood donations with future telephone calls to the same individual having less impact. Incentive-based interventions are potentially more likely to be subject to diminishing marginal returns as non-incentive based interventions are able to draw on an individual's degree of altruism and the sense of civic duty associated with blood donation, whereas an incentive may be more aligned with a traditional consumable good, though there is very little evidence on the long-term impacts or unintended consequences of interventions and policies to increase donations. There are research techniques available for eliciting preferences from respondents which could be useful in evaluating attitudes towards blood donation instead of conducting expensive clinical trials. A recent discrete choice experiment, where respondents are presented with a series of choices between alternative hypothetical scenarios, revealed that US and German college students were willing to accept incentives such as cash or paid leave for donating blood.[118] Contingent valuation methods have also been used on the demand side of the market to estimate patient's willingness-to-pay for blood.[119]

Strong evidence regarding the long-term effectiveness, cost effectiveness and safety of offering incentives to donors would be of particular value in the developing world, where blood supplies are less reliable. However, most trials are conducted outside of these jurisdictions where funding for research is limited. As trends in blood product use change over time, potentially due to ageing populations placing additional pressure on supply through increased demand and a reduced donor pool, there may be sufficient motivation for blood services to conduct more research into this topic. Finally, the possibility of manufacturing blood, or a blood-like substitute should not be ruled out – if an economically viable substitute product were to be developed by the pharmaceutical industry or others, the current donation-based blood supply could be replaced with a traditional competitive market for a healthcare good.

6.1.2 Age of Blood

Blood services are tasked with optimising the supply chain for blood. As a product with a finite shelf life, this refers to not only minimising wastage but also maximising the therapeutic value of blood. Observational evidence emerged challenging the assumption that prior to expiry, the age of blood did not impact upon its effectiveness – leading to policies shortening the shelf life for blood in some jurisdictions. In response, a number of age of blood RCTs were commission which discredited the clinical findings from the observational studies. Chapter 3 presents an economic evaluation of one of the age of blood RCTs confirming that the current policy of transfusing the oldest, compatible, in-date

RBCs to critically ill adults appears appropriate in terms of little gain in quality of life or reduction of costs from switching to fresher blood.

However, determining the relationship between age of blood and risk is beset by a number of practical difficulties that undermine the ability of these trials to detect the effects of the storage lesion.[120] All of the published age of blood trials assessed two age distributions using alternative blood bank inventory protocols. Despite the significant difference in the mean age of blood between the two arms, there was overlap of the distributions reducing the statistical power to detect clinically meaningful differences in outcomes. Dichotomising a naturally continuous variable such as age is not a methodologically robust way to explore risk. Risk is likely to change in a smooth fashion with age but not necessarily linearly, rather than either high or low with a jump at some unknown value as the trial design assumes.[120]

Therefore, while the transfusion community appears be to assured of the safety of the current blood bank inventory protocol, the true relationship between age and risk has not been uncovered by the age of blood clinical trials. There may be additional value in performing further trials comparing blood that is 'very' fresh with blood that is near the end of its shelf life, however such trials have controversially been deemed unethical.[41] A trial requiring blood to be transfused at specific ages would be logistically challenging without modifications to the blood supply chain and potentially result in an increase in wastage. Value of information analysis is a useful tool in this setting however, the costs of acquiring more information will be significant and the expected benefit, assuming the current conclusions are incorrect, may be small. At a minimum, an individual patient data meta-analysis on the pooled data from currently published age of blood trials would provide additional statistical power to detect differences. As the only published economic evaluation on a full age of blood trial population, Chapter 2 suggested there may be a potential cost-saving associated with fresher blood which warrants further investigation.

Policymakers would be particularly interested in whether adopting a freshest available RBC strategy would require a higher frequency of donations, deliveries of fresh blood or impact on wastage. Simulation studies conducted in the US have suggested it may be possible to preferentially allocate the freshest-available RBCs to a small subset of high-risk patients without adversely impacting the reliability of the blood supply under current arrangements.[121] If future studies uncover a positive relationship between the age of blood and risk, blood services will have scope for further optimisation of the supply chain.

6.1.3 Patient Blood Management Guidelines

As a legacy treatment that pre-dates the evidence-based medicine movement of the 1970s, blood transfusions were never held up against the same safety standards as new medicines are today. An increasing body of observational evidence emerged suggesting that transfusions themselves were associated with morbidity and mortality. In response, a number of RCTs confirmed the safety of restrictive haemoglobin transfusion triggers indicating that a significant portion of historical transfusions were likely prescribed unnecessarily – where the expected benefit did not outweigh the potential risks of alternative course of action (including no therapy or delaying transfusion). However, instigating change in medical practice can be a difficult task given the complexity of the discipline and the barriers to change. Chapter 4 highlighted the success of the NBA's PBM guidelines for perioperative care at reducing blood transfusions during cardiac surgery. While assessing the impact of clinical guidelines can help shape future guideline development, dissemination and implementation strategies, an assessment of their cost effectiveness may also be prudent. The NBA has not published information on the cost of developing their suite of PBM guidelines or any associated implementation initiatives. There is an opportunity for additional data collection as NBA are currently updating their PBM guidelines to reflect the latest evidence. Pro-actively collecting information on implementation strategies across hospitals would provide valuable information on the most effective methods for ensuring adherence. Given data with sufficient granularity, an assessment could be performed to determine which recommendations are most adhered to, by whom and under what settings and which recommendations had the biggest impact on overall blood use. However, collecting data is an expensive process and the degree to which it is worthwhile rests on the value of the insights that it may bring. As blood transfusions are already falling given the current methods adopted by the NBA, there may be insufficient value to be gained from collecting additional detailed data to facilitate these analyses. However, the first wave of unnecessary transfusions eliminated will likely have been those most easily judged to be unnecessary and therefore the cheapest to eliminate. There will be diminishing marginal returns to publishing more clinical guidelines to further reduce unnecessary transfusions, with the marginal cost of eliminating the next unnecessary transfusion higher than the last.

Continually striving for fewer transfusions raises some interesting questions for policymakers. What is the appropriate transfusion rate? How close to zero transfusions should we be aiming for? The appropriate transfusion rate is all patients for whom the expected benefit (minus a zero cost in countries where governments supply blood free of charge) exceeds the potential risks. However, it is difficult to assess the expected benefit of RBC transfusion as current diagnostic technology does not permit an accurate measure of oxygen debt, the underlying physiological characteristic RBC transfusions intend to resolve. Instead, physicians have historically used haemoglobin thresholds to

guide RBC transfusions. High quality evidence from randomised clinical trials have confirmed that patients can safely tolerate lower haemoglobin thresholds.[113, 114] However, through focussing on haemoglobin thresholds physicians invariably improve haemoglobin levels but may not be transfusing patients with an underlying oxygen debt.[122] As such, to improve the efficiency in the use of blood there is a need to move beyond haemoglobin thresholds as the primary physiological characteristic driving transfusion decisions. This is true for RBC and for other blood products such as platelets, where a similar lack of appropriate diagnostic technology does not permit physicians to understand a patient's true platelet function under all circumstances. Indeed recent clinical guidelines have encouraged decisions based on the patient's intravascular volume status, evidence of shock, duration and extent of anaemia and cardiopulmonary physiologic parameters.[57] Until an accurate physiological assessment of the need for a transfusion can take place, it will remain difficult to the point of impossible to determine the appropriate transfusion rate for blood and blood products. RCTs are useful for comparing strategies in this context, but large, expensive samples are required to prove non-inferiority.

6.1.4 Changes in Variation in Care

Significant research has been dedicated to explaining variations in care across observable differences in patients, physicians, hospitals or health systems. However, the literature assessing changes in variation in care over time in response to policy or otherwise is sparse and the methodology unrefined. Chapter 5 presents an investigation into heterogeneity in response to a set of clinical guidelines and the subsequent impact on variation in care. Using the NBA's perioperative PBM guidelines and the ANZSCTS cardiac surgery database, we were able to show that responses to the guidelines were heterogeneous across hospitals and across surgeons. Given a pattern of response where the largest responses to the guidelines were in general in those hospitals and surgeons with the highest pre-guideline transfusion rates, we observed a reduction in variation in care across hospitals, across surgeons and within hospitals. Consequently, by adjusting the frequency and intensity of high use outliers in terms of hospitals and surgeons in the distribution, the guidelines reduced variation in care. Therefore, measuring the response of outliers is an alternative performance measure for assessing changes in variation in care. Some high use outliers in our analysis did not respond to the guidelines; an understanding of the causes of non-compliance could improve future intervention targeting at non-responders.

To our knowledge, the sampling bias inherent in estimates of the variance across rates with unequal denominators has not been well discussed in the context of variation in care. We suggest established statistical techniques from the meta-analysis literature to control for this bias in studies assessing

variation in care.[98] Other methodological questions concern the appropriate modelling framework for this data that often has a multilevel structure where units of the lower order (surgeons) can exist in multiple units of the higher order (hospitals). In our analysis, we conduct two separate fixed effects regressions for hospitals and for surgeons and explore the conclusions from a two-way fixed effect regression (see Appendix for Chapter 5). A random effects framework is a popular alternative where the effects are considered a random variable unrelated to patient characteristics arising from an assumed distribution with unknown variance. Random effects can be estimated for the intercept in the case of variation across higher order units, or for the slope as well, to permit additional variation by lower order units. This model is sometimes referred to as a mixed model which is a model that contains both 'fixed' and random effects. In our example, the 'fixed' part of the model relates to the control variables for patient case mix (different to fixed effects in economics), and the random effects would be estimated for hospitals and surgeons. A random effects model reduces the number of parameters to be estimated – just the spread of the effects rather than a specific effect for each hospital-surgeon. Random effects model can include time-invariant unit level characteristics such as hospital location or surgeon gender (which would be omitted under any form of fixed effects framework for being collinear) and is less likely to estimate more extreme results to units with low volume because effects are informed from the common distribution.[123, 124] However, random effects models require additional restrictive assumptions regarding the distribution of hospital and surgeon effects and that the effects are uncorrelated with the independent variables (i.e. patient and surgery characteristics). Conversely, by definition our fixed effects model allows the individual hospitals and surgeon effects to be correlated with the independent variables (e.g. different surgeons operate on different types of patients such as those at high risk of needing a transfusion). The degree to which this assumption holds true should guide the modelling framework decision.

Medical science is highly complex with many patient characteristics that contribute to decision making and a significant grey area in diagnoses and prescriptions. As a result, the complete eradication of variation in practice is potentially an ill-informed goal. However, the degree of disparities observed indicate significant improvements in the consistency of care are feasible and desirable. Whether it is possible to determine the correct rate of treatment depends on the strength of the evidence base and the definition of the indication. If high-quality evidence is available indicating that a treatment is effective for a well-defined patient population, then treating every eligible patient represents the correct rate. As the evidence grade slips, or the indication widens, it becomes increasingly more difficult to determine the correct rate of treatment. Future studies assessing changes variation in care should focus on treatments with high-quality evidence in well-defined patient populations.

6.2 The Future of the Economics of Blood

In 2020, the market for blood across the developed world is characterised by a relatively safe and stable supply of RBCs coupled with falling demand due to initiatives such as PBM which offer alternative care pathways to reduce the need for a transfusion. There is still scope for future research to optimise and improve efficiency in the supply and demand for RBCs including questions related to incentivising donations and the storage lesion. One emerging area of research is the impact of washing RBC with saline to remove potential allergen proteins and to mitigate the effect of the storage lesion. To date very few clinical trials of washed RBCs have been performed; however, early results suggest that selective washing of RBCs destined to particular patient groups (e.g. pre-term infants or acute leukemia patients) may be beneficial.[125]

Meanwhile, the dynamics of the market for blood are changing such that the demand for other innovative blood products is placing significant economic burden on publicly funded blood services. In the 15 years to 2017/18, the NBA's annual expenditure on plasma and recombinant products has increased by $389 million.[4] Here we discuss one such product, now the principal product obtained by fractionation (separation) of human plasma, is intravenous immunoglobulin (IVIg).[126] IVIg is primarily indicated is for immune deficiencies with increasing evidence of its therapeutic value in inflammatory, autoimmune and rheumatic diseases.[127] The cost of IVIg is dependent on the strength and volume of the dose, 2017/18 Australian prices provided by the NBA range from $156 for a 2.5g/25mL dose up to $1,800 for a 40g/400mL dose.[4] Figure 6.1 presents the demand for IVIg in Australia, increasing at 11% per annum.[18]

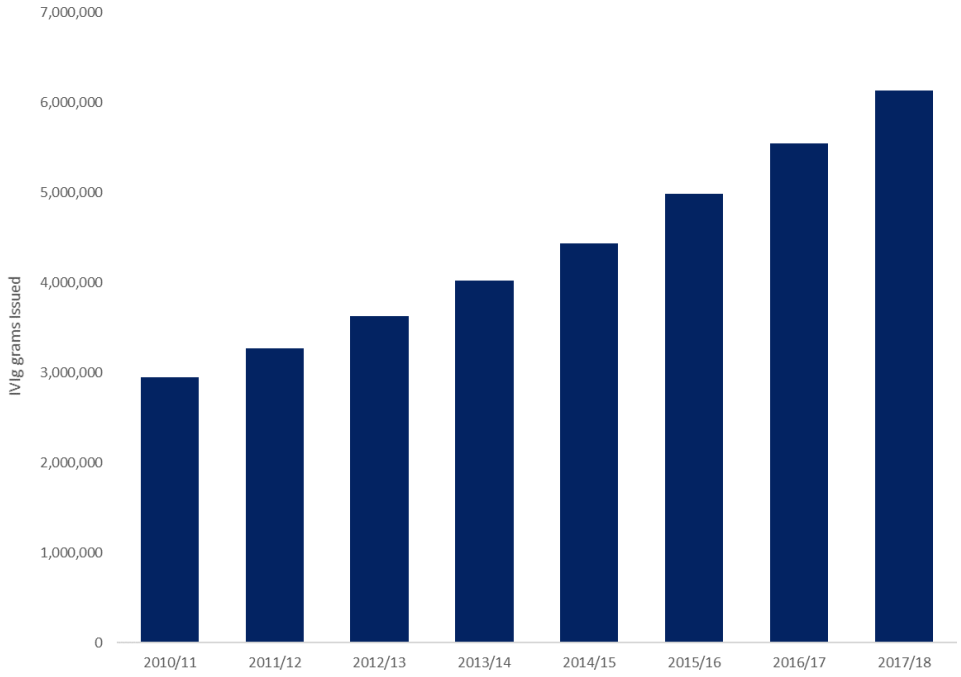

Figure 6.1: Demand for IVIg in Australia

In response to the increasing demand for IVIg, governments and research institutes have been conducting RCTs to formally evaluate its effectiveness compared to alternative therapies in the increasingly wide variety of indications that it is being used. There have been positive trial results for the use of IVIg for recurrent infections in immunocompromised patients[128] and in treating other steroid-resistant autoimmune disease[129] but negative results in recurrent miscarriage[130] and Alzheimer's disease[131]. Trials are also ongoing in other indications such as Kawasaki disease[132] and neuropathy.[133] The timely diffusion of the results of these trials to align the physicians' perceived demand curve for IVIg with the true societal demand curve will result in an efficient allocation of resources.

Unlike whole blood donation, plasma for fractionation is donated by apheresis. During an apheresis donation, blood is extracted from a donor and passed through a machine which separates out the plasma before returning the blood back to the donor. An apheresis donation can take up to 2 hours compared to 10-15 minutes for a donation of whole blood. The additional burden on donors in terms of time means that only the very highly motivated (intrinsically or extrinsically) commit to donating plasma. While the volunteer non-remunerated donation system has been able to meet the demand for whole blood, the same system has so far been unable to provide enough plasma for fractionation to meet demand. There is some evidence to suggest that volunteer plasma donors are likely to be even more altruistic than volunteer whole blood donors, placing higher value on 'a desire to help others' when surveyed.[134] Therefore, in a similar manner to the systematic review presented

in Chapter 2, future research should assess the relative effectiveness of strategies for increasing apheresis donations recognising the distinctive altruistic characteristics of the behaviour.

The only country self-sufficient in plasma is the US which has adopted a competitive, for-profit, plasma donation industy.[2] As a result, the US now exports plasma-derived products to the rest of the developed world. In 2017/18, Australia imported 47% of the IVIg prescribed from US pharmaceutical companies such as CSL.[4] This creates a dichotomy in countries that do not remunerate donors where fresh blood products are donated voluntarily by domestic donors but fractionated products may be imported from paid donations. As with fresh blood products, an obvious question emerges regarding the safety of products manufactured from remunerated donations. However, the safety of plasma-derived products is assured due to characteristics of the manufacturing process and pathogen deactivation steps not possible with whole blood donation.[135] Yet blood services around the developed world, the US aside, continue to only collect plasma from volunteer non-remunerated donors. The justification for this policy may rest on society's view of the donation process as a whole. The differences between whole blood and plasma donations may be too nuanced to explain to the general population (and donors) why it is appropriate and desirable to remunerate donors for some types of donations but not others, and risks degrading the current sense of civic duty associated with whole blood donation. However, evidence suggests that products produced from the domestic supply of plasma are more expensive than equivalent imported products, including the cost of remunerating donors.[136] The higher costs could be a result of the additional marketing spend required to recruit voluntary plasma donors versus the efficient, competitive, high-volume collection regimes in the for-profit sector. Therefore, if the supply of products manufactured from paid plasma donations was sufficient, blood services could save resources by importing all of their supply from the USA. In reality, this may not be a favourable solution as relying solely on imported product raises security concerns if the US supply chain stalled. Instead, by acknowledging the differences between whole blood and plasma donation, governments such as Australia's could adopt a similar model to the US and begin to remunerate plasma donations within a competitive market model. This would provide a boost to the economy through new business opportunities and by purchasing domestically rather than from abroad.

Future research in the market for blood will consider not only RBCs but also other blood products including IVIg. Many questions are common across blood products including maintaining a cost efficient and reliable supply as well as ensuring consistent, appropriate transfusion practices. Other questions may be specific, such as the effect of the storage lesion of RBCs, or the reliance on voluntary plasma donations for fractionation. Thankfully, data collection conducted by organisations

such as the ANZSCTS and the NBA will ensure important questions are answered to save precious resources, improve patient health, or both.

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Appendices

A.1 Appendix for Chapter 2

A.2 Search Strategy

Embase (Ovid)

1. blood donor/
2. ((blood or plasma or platelet*) adj5 (donor* or donat*)).ti,ab,kw.
3. ((give or gave or giving) adj blood).ti,ab,kw.
4. donor*.ti. and (blood or plasma or platelet*).mp.
5. or/1-4
6. randomized controlled trial/
7. controlled clinical trial/
8. single blind procedure/ or double blind procedure/
9. crossover procedure/
10. random*.tw.
11. placebo*.tw.
12. ((singl* or doubl*) adj (blind* or mask*)).tw.
13. (crossover or cross over or factorial* or latin square).tw.
14. (assign* or allocat*).tw.
15. or/6-14
16. 5 and 15

Embase

1. 'blood donor'/exp
2. (blood OR plasma OR platelet*) NEAR/5 (donor* OR donat*)
3. (give OR gave OR giving) NEAR/1 blood
4. donor*:ti AND (blood:de,ab,ti OR plasma:de,ab,ti OR platelet*:de,ab,ti)
5. 1 or 2 or 3 or 4
6. 'randomized controlled trial':de
7. 'controlled clinical trial':de
8. 'single blind procedure':de OR 'double blind procedure':de
9. 'crossover procedure':de
10. random*:ab,ti
11. placebo*:ab,ti
12. ((singl* OR doubl*) NEXT/1 (blind* OR mask*)):ab,ti
13. crossover:ab,ti OR 'cross over':ab,ti OR factorial*:ab,ti OR 'latin square':ab,ti
14. assign*:ab,ti OR allocat*:ab,ti
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
17. 5 and 15

PsycINFO (Ovid)

1. tissue donation/

2. ((blood or plasma or platelet*) and (donor* or donat*)).ti,ab,hw,id.
3. ((give or gave or giving) adj blood).ti,ab,id.
4. or/1-3
5. random*.ti,ab,hw,id.
6. trial*.ti,ab,hw,id.
7. controlled stud*.ti,ab,hw,id.
8. placebo*.ti,ab,hw,id.
9. ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id.
10. (cross over or crossover or factorial* or latin square).ti,ab,hw,id.
11. (assign* or allocat*).ti,ab,hw,id.
12. treatment effectiveness evaluation/
13. mental health program evaluation/
14. exp experimental design/
15. "2000".md.
16. or/5-15
17. 4 and 16

Current Contents (Ovid)

1. ((blood or plasma or platelet*) adj5 (donor* or donat*)).mp.
2. ((give or gave or giving) adj1 blood).mp.
3. 1 or 2
4. (random* or trial* or placebo* or assign* or allocat* or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or crossover or cross over or factorial* or latin square).mp.
5. 3 and 4

Current Contents (ISI)

1. TS=((blood or plasma or platelet*) NEAR/5 (donor* or donat*))
2. TS=((give or gave or giving) NEAR/5 blood)
3. #1 or #2
4. TS=(random* or trial* or placebo* or assign* or allocat* or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or crossover or “cross over” or factorial* or “latin square”)
5. #3 and #4

MEDLINE (Ovid)

1. blood donors/
2. ((blood or plasma or platelet*) adj5 (donor* or donat*)).tw.
3. ((give or gave or giving) adj blood).tw.
4. (tissue donors/ or donor*.ti.) and (blood or plasma or platelet*).mp.
5. or/1-4
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. random*.tw.
9. placebo.ab.
10. clinical trials as topic.sh.
11. trial.ti.

12. or/6-11
13. exp animals/ not humans.sh.
14. 12 not 13
15. 5 and 14

WHO ICTRP

blood dono* OR blood donat* OR plasma dono* OR plasma donat* OR platelet dono* OR platelet donat* OR donate blood OR donated blood OR donating blood OR give blood OR gave blood OR giving blood OR donate plasma OR donated plasma OR donating plasma OR give plasma OR gave plasma OR giving plasma OR donate platelet OR donated platelet OR donating platelet OR give platelet OR gave platelet OR giving platelet

Clinicaltrials.gov

(“blood donor” OR “blood donation” OR “plasma donor” OR “plasma donation” OR “platelet donor” OR “platelet donation” OR “donate blood” OR “donated blood” OR “donating blood” OR “give blood” OR “gave blood” OR “giving blood” OR “donate plasma” OR “donated plasma” OR “donating plasma” OR “give plasma” OR “gave plasma” OR “giving plasma” OR “donate platelet” OR “donated platelet” OR “donating platelet” OR “give platelet” OR “gave platelet” OR “giving platelet”)

AND INFLECT EXACT NOT ("Recruiting" OR "Not yet recruiting" OR "Available") [OVERALL-STATUS] AND INFLECT EXACT "Interventional" [STUDY-TYPES] AND INFLECT EXACT "Completed" [OVERALL-STATUS] AND NOTEXT [OVERALL-STATUS-OUTDATED] AND NOT NOTEXT [FIRST-RECEIVED-RESULTS-DATE] AND INFLECT EXACT "Interventional" [STUDY-TYPES] AND INFLECT EXACT ("Phase 3" OR "Phase 4") [PHASE]

ProQuest Dissertations & Theses Full text

all(((blood or plasma or platelet*) N/5 (donor* or donat*)) or ((give or gave or giving)) N/1 blood) and all(random* or trial* or "controlled study" or placebo* or assign* or allocat* or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or crossover or "cross over" or factorial* or "latin square")

EconLit (Ebsco)

1. (blood or plasma or platelet*) and (donor* or donat*)
2. (give or gave or giving) N1 blood
3. 1 or 2
4. random* or trial* or "controlled study" or placebo* or assign* or allocat* or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or crossover or "cross over" or factorial* or "latin square" or groups
5. 3 and 4

CENTRAL (The Cochrane Library)

1. (blood or plasma or platelet) near/5 (donor or donat*)
2. (give or gave or giving) near/1 blood
3. donor:ti,kw
4. blood or plasma or platelet
5. 3 and 4
6. 1 or 2 or 5

Table A.1.1: Summary of Included Studies

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
Cioffi 1998	USA	Novice and repeat donors	1,121	NR	NR	1: Active-Yes and response option email 2: Active-No and response option email 3: Forced choice email 4: Information only email 5: No email control	6-7 days prior to blood drive	Donation	1: 20/242 (8.3%) 2: 30/244 (12.3%) 3: 14/247 (5.7%) 4: 12/241 (5.0%) 5: 7/129 (5.4%)
Ferrari 1985	USA	NR	78	NR	NR	1: Telephone reminder 2: No prompt	2 days prior to blood drive	Donation	1: 27/29 (93.1%) 2: 22/39 (56.4%)
Germain 2016	Canada	Repeat donors	3,454	41.8 (14.3)	51.5%	1: Motivational interview telephone call 2: Non-personal recruitment email 3: Motivational interview telephone call + non-personal recruitment email	4 days prior to blood drive	Donation	1: NR/1,176 (15.7%) 2: NR/1,091 (13.2%) 3: NR/1,187 (18.5%)
Gimble 1994	USA	4.7-6.6% novice donors	65,874	NR	37-43%	1: New recruitment brochure 2: No brochure	1-2 weeks prior to blood drive	Donation	1: 4,092/30,990 (13.2%) 2: 4,200/34,884 (12.0%)
Godin 2008	Canada	Repeat donors	4,672	NR	38.4%	1: Mailed intention questionnaire + reminder 2: No contact	1 month after donation	Donation at 6 months Donation at 12 months	1: NR/2,900 (53.7%) 2: NR/1,772 (49.2%) 1: NR/2,900 (69.9%) 2: NR/1,772 (65.2%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
Godin 2010	Canada	Novice donors	5,000	30.4 (12.9)	53.0%	1: Mailed behavioural intention-only questionnaire 2: Mailed behavioural intention + regret questionnaire 3: Mailed implementation intention-only questionnaire 4: Mailed implementation intention + regret questionnaire 5: No contact	3 weeks prior to becoming eligible to donate again	Donation at 6 months Mean (SD)	1: 0.45 (0.76) 2: 0.46 (0.71) 3: 0.50 (0.83) 4: 0.49 (0.80) 5: 0.44 (0.70)
								Donation at 12 months Mean (SD)	1: 0.82 (1.17) 2: 0.83 (1.14) 3: 0.91 (1.39) 4: 0.90 (1.27) 5: 0.81 (1.09)
Godin 2014	Canada	Lapsed donors (no donation in 24 months)	7,000	38.2 (13.8)	50.2%	1: Mailed intention-only questionnaire 2: Mailed interrogative intention questionnaire 3: Mailed intention + regret questionnaire 4: Mailed intention + moral norm questionnaire 5: Mailed intention + positive self-image questionnaire 6: Mailed implementation intention questionnaire 7: No contact	Any time after being classified as lapsed donor	Donation at 6 months Mean (SD)	1: 0.20 (0.49) 2: 0.20 (0.49) 3: 0.21 (0.47) 4: 0.18 (0.46) 5: 0.21 (0.48) 6: 0.22 (0.52) 7: 0.17 (0.45)
								Donation at 12 months Mean (SD)	1: 0.43 (0.86) 2: 0.43 (0.79) 3: 0.43 (0.84) 4: 0.39 (0.78) 5: 0.42 (0.82) 6: 0.44 (0.88) 7: 0.37 (0.77)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
Goette 2009 S1	Switzerland	Non-donors	2,824	NR (NR)	48.7%	1: Mailed invitation 2: Mailed invitation + appeal 3: Mailed invitation + appeal + cholesterol test	3 weeks prior to blood drive	Change in frequency of donation	1: Base 2: -0.005 (0.019) 3: 0.016 (0.018)
Goette 2009 S2	Switzerland	Repeat donors	8,269	44.6 (NR)	38.8%	1: Mailed invitation 2: Mailed invitation + appeal 3: Mailed invitation + appeal + cholesterol test	3 weeks prior to blood drive	Change in frequency of donation	1: Base 2: -0.005 (0.019) 3: 0.016 (0.018)
Iajya 2010	Argentina	NR	18,500	32.0 (NR)	41%	1: Mailed flyer 2: Mailed flyer + information 3: Mailed flyer + information + T-shirt 4. Mailed flyer + information + newspaper mention 5. Mailed flyer + information + AR$20 supermarket voucher 6. Mailed flyer + information + AR$60 supermarket voucher 7. Mailed flyer + information + AR$100 supermarket voucher	3 weeks donation behaviour follow-up	Donation	1: 0/2,360 (0.0%) 2: 0/2,366 (0.0%) 3: 0/2,248 (0.0%) 4: 0/2,411 (0.0%) 5: 0/2,253 (0.0%) 6: 10/2,336 (0.43%) 7: 27/3,264 (0.83%)
LaTour 1989 S1	USA	NR	800	NR	NR	1: Informational influence (letter) + normative influence (telephone) 2: Informational influence only (letter) 3: Normative influence only (telephone) 4. No contact	Letter: 3-4 weeks prior to blood drive Telephone call: 1-2 weeks prior to blood drive	Donation	1: 33/151 (21.9%) 2: 8/180 (4.4%) 3: 11/149 (7.4%) 4: 4/200 (2.0%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
LaTour 1989 S2	USA	NR	1,200	NR	NR	1: Strong informational influence (letter) + normative influence (telephone) 2: Weak informational influence (letter) + normative influence (telephone) 3: Normative influence only (telephone) 4: Strong informational influence only (letter) 5: Weak informational influence only (letter) 6: No contact	Letter: 3-4 weeks prior to blood drive Telephone call: 1-2 weeks prior to blood drive	Donation (at either target drive or blood drive held 2 months later)	1: 36/200 (18.2%) 2: 17/200 (8.3%) 3: 12/200 (5.8%) 4: 7/200 (3.6%) 5: 3/200 (1.5%) 6: 1/200 (0.5%)
Maghsudlu 2017	Iran	Novice donors	1,356	NR	10.4%	1: Reminder telephone call 2: Educational letter 3: Emotional letter 4: T-shirt after initial donation 5: Lecture after initial donation 6: No contact	Letters + telephone call: 3 months after initial donation	Donation	1: NR/NR (31%) 2: NR/NR (33%) 3: NR/NR (36%) 4: NR/NR (30%) 5: NR/NR (22%) 6: NR/NR (22%)
Masser 2016	Australia	Novice donors making their first appointment	3,646	32.0 (12.3)	65.2%	1: Mailed brochure + telephone call 2: Mailed brochure only 3: Email brochure + telephone call 4: Email brochure only 5: Telephone call only 6: No contact	Brochure/email: 1 week prior to blood drive Telephone call: 5-6 days prior to blood drive	Donation	1: 429/609 (70.4%) 2: 432/609 (70.9%) 3: 460/615 (74.8%) 4: 414/606 (68.3%) 5: 431/604 (71.4%) 6: 399/603 (66.2%)
Mellström 2008	Sweden	Novice donors	262	NR	58.0%	1: Hypothetical SEK 50 cash	Compensation offered to entice	Agreed to health examination	1: 28/85 (32.9%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
						2: Choice of hypothetical SEK 50 cash or donation to charity 3: No offer	participants to agree to the preliminary health examination		2: 39/88 (44.3%) 3: 38/89 (42.7%)
Mines 2000	New Zealand	Lapsed one-time donors (no donation in 6 months)	325	25.0 (9.9)	62.8%	1: Commitment enhancing letter 2: Telephone call 3: Standard letter + questionnaire 4: Commitment enhancing letter + questionnaire 5: Standard letter only 6: Blood Donor service secure mailer	6 days prior to blood drive	Donation	1: 4/53 (7.5%) 2: 4/18 (22.2%) 3: 5/48 (10.4%) 4: 6/58 (10.3%) 5: 7/54 (13.0%) 6: 12/148 (8.1%)
Myhal 2017	Canada	Novice (10.3%) and repeat (89.7%) donors	7,399	38.9 (16.2)	51.7%	1: Reward tool 2: Action planning questionnaire 3: Control	Post-donation with 6 months donation behaviour follow-up	Donation	1: 1,424/2,397 (59.4%) 2: 1,530/2,585 (59.2%) 3: 1,490/2,417 (61.7%)
Ou-Yang 2017	China	Lapsed donors	1,188	NR	NR	1: Telephone call 2: SMS message 3: No contact	≥2 years post donation with 7 months donation behaviour follow-up	Donation	1: 19/396 (4.8%) 2: 11/396 (2.8%) 3: 7/396 (1.8%)
Reich 2006	USA	Novice donors	6,919	NR	48.6%	1: T-shirt + empathy and altruism script by email 2: T-shirt + empathy and altruism script by telephone 3: Empathy and altruism script by email only	Open invitation with 12 months donation behaviour follow-up	Donation (2nd donation)	T-shirt: 712/3,478 (20.5%) No T-shirt: 709/3,441 (20.6%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
						4: Empathy and altruism script by telephone only 5: T-shirt + self-esteem script by email 6: T-shirt + self-esteem script by telephone 7: Self-esteem script by email only 8: Self-esteem script by telephone only			Empathy/altruism script: 763/3,431 (22.2%) Self-esteem script: 658/3,488 (18.9%) Email: 141/1,068 (13.2%) Telephone: 287/1,033 (27.8%)
Royse 1999	USA	Novice donors	1,003	NR	54%	1: Two movie tickets 2: Altruistic commitment letter 3: Volunteer request letter 4: Standard letter	Post-donation with 14 months donation behaviour follow-up	Donation (2nd donation)	1: NR/NR (53.2%) 2: NR/NR (49.6%) 3: NR/NR (56.2%) 4: NR/NR (53.2%)
Sinclair 2010	USA	Novice and repeat donors	427	31.1 (13.5)	59.1%	1: Telephone interview post donation 2: No interview	1 month after donation with 12 month donation behaviour follow-up	Donation (9 months) Donation (12 months)	OR=1.60 (95% CI: 0.93-2.78) OR=2.48 (95% CI: 1.27-4.87)
Sinclair-Miracle 2018	USA	Repeat donors	195	37.2 (13.5)	27.2%	1: Telephone interview post donation 2: Follow-up questionnaires	1 month after donation with 12 month donation behaviour follow-up	Donation	1: NR/86 (82.6%) 2: NR/109 (73.5%)
Sun 2016	China	Repeat donors	80,000	31.3	32.8%	1: Reminder message 2: Reminder message + supermarket voucher 3: Group orientated reminder message	15-day experiment using mobile collection vehicles	Donation	1: 108/11,000 (0.98%) 2: 120/11,000 (1.09%) 3: 95/11,000 (0.86%) 4: 112/11,000 (1.11%) 5: 129/11,000 (1.17%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
						4. Group orientated reminder message + supermarket voucher 5. Group orientated reminder + conditional supermarket reminder 6. Group orientated reminder + additional gifts 7. No message control			6: 124/11,000 (1.13%) 7: 99/14,000 (0.71%)
Upton 1973	USA	Repeat donors (half lapsed)	1,261	NR	NR	1: $10 cash 2: No cash	Telephone recruitment	Donation	1: 492/640 (76.9%) 2: 546/621 (87.9%)
van Dongen 2013 S1	The Netherlands	Novice donors	7,008	33.4 (12.1)	66.6%	1: Posted recruitment letter + questionnaire 2: Posted recruitment letter	10 days before first appointment + 6 months donation behaviour follow-up	Repeat donation	1: 2,154/3,518 (61.2%) 2: 2088/3490 (59.8%)
van Dongen 2013 S2	The Netherlands	Repeat donors	11,789	44.8 (13.0)	51.1%	1: Posted recruitment letter + questionnaire 2: No contact	6 month donation behaviour follow-up	Donation	1: 3,612/5,789 (62.4%) 2: 3,646/6,000 (60.8%)
Wevers 2015	The Netherlands	Newly registered novice donors	937	NR	70.5%	1: Information sheet only 2: Information sheet + implementation intentions 3: Information sheet + explicit commitment 4: Information sheet + implementation intentions + explicit commitment 5: No information sheet	2 week donation behaviour follow-up	Donation	1: 120/197 (60.9%) 2: 98/180 (54.5%) 3: 108/188 (57.4%) 4: 126/196 (64.3%) 5: 93/176 (52.8%)

Reference	Country	Prior donation history	Sample (N) ITT	Age (years): Mean (SD)	Female	Interventions	Delivery / Follow-up	Outcomes	Results: Donations/Sample
Weisenthal 1989	Canada	Novice donors	209	NR	NR	1: Schedule information only call 2: Social reinforcement + schedule information call 3: Information on blood's uses + schedule information call 4: Social reinforcement + information on blood's use plus schedule information call 5: No contact	1 week after index donation	Repeat donation (within 6 months)	1: 21/40 (52.5%) 2: 12/40 (30.0%) 3: 15/40 (37.5%) 4: 18/40 (45.0%) 5: 15/40 (37.5%)

AR = Argentine peso; ITT = intention to treat, NR = not reported; OR = odds ratio; SD = standard deviation; SEK = Swedish krona; SMS = short message service

Table A.1.2: Existing Practice

Reference	Country	Prior donation history	Sample (N)	Intervention designated existing practice
Cioffi 1998	USA	Novice and repeat donors	1,121	No message sent ahead of campus blood drive
Ferrari 1985	USA	NR	78	Not calling those who have pledged to give at upcoming campus blood drive
Gimble 1994	USA	4.7-6.6% novice donors	65,874	Not sending a questionnaire to donors
Godin 2008	Canada	Repeat donors	4,672	Not sending a questionnaire to repeat donors
Godin 2010	Canada	Novice donors	5,000	Not sending a questionnaire to novice donors
Godin 2014	Canada	Lapsed donors	7,000	Not sending a questionnaire to lapsed donors
LaTour 1989 S1	USA	NR	800	Not calling or sending letters to individuals on commercial mailing list ahead of blood drive
LaTour 1989 S2	USA	NR	1,200	Not calling or sending letters to individuals on commercial mailing list ahead of blood drive
Maghsudlu 2017	Iran	Novice donors	1,356	Not calling or emailing after initial donation
Masser 2016	Australia	Novice donors making their first appointment	3,646	Not sending a brochure or email or calling ahead of the blood drive
Mellström 2008	Sweden	Novice donors	262	No offer of compensation to sign up to preliminary health examination
Myhal 2017	Canada	Novice and repeat donors	7,399	No post-donation intervention
Ou-Yang 2017	China	Lapsed donors	1,188	Not calling or texting lapsed donors
Sun 2016	China	Repeat donors	80,000	Not texting experienced donors
van Dongen 2013 S1	The Netherlands	Novice donors	7,008	No questionnaire sent to new donors
van Dongen 2013 S2	The Netherlands	Repeat donors	11,789	No questionnaire sent to experienced donors
Wevers 2015	The Netherlands	Newly registered novice donors	937	No information sheet given during new donor medical check-up
Wiesenthal 1989	Canada	Novice donors	209	No post-donation telephone call

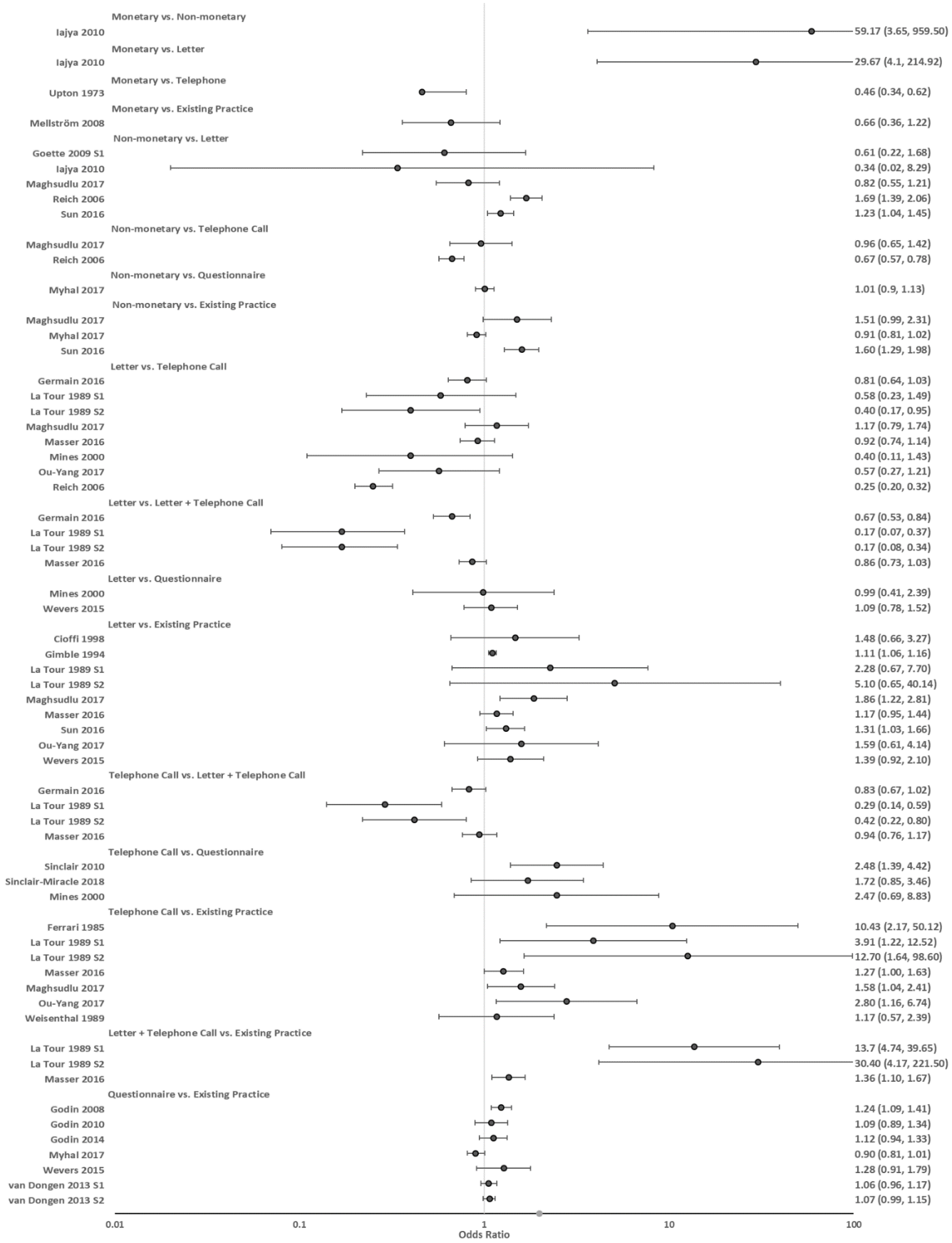

Figure A.1.1: Forest Plot of Included Studies by Comparison

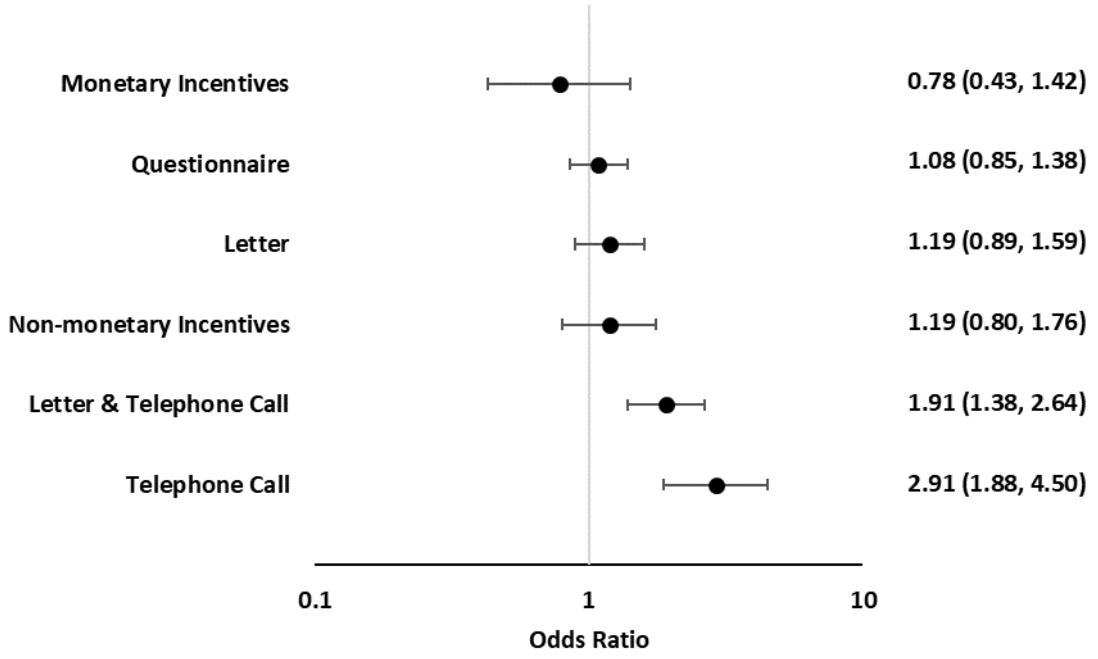

Figure A.1.2: Sensitivity Analysis – Developed Economies

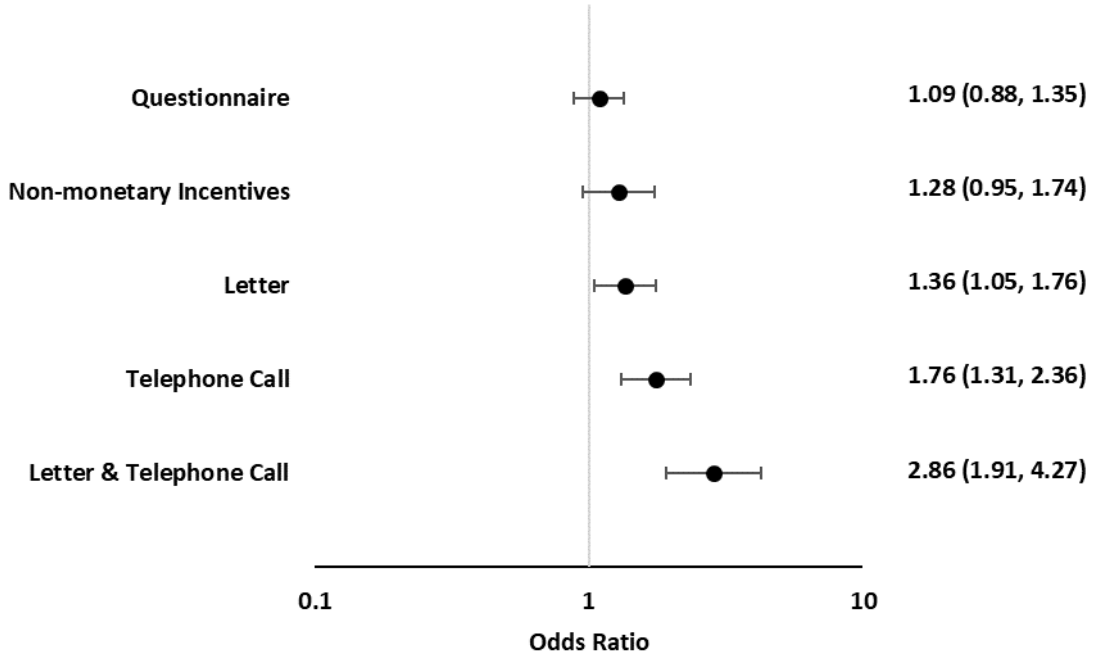

Figure A.1.3: Sensitivity Analysis – Risk of Bias

A.3 Appendix for Chapter 3

A.4 Discharge model

Data were collected on whether patients were discharged to another acute hospital, a long-term care facility, rehabilitation, or home after their index hospitalization. For patients discharged to another acute hospital this was likely to be one closer to their home but information on length of stay at this secondary acute hospital was not available. For these patients, total ward length of stay was predicted based on a linear regression of ward length of stay on treatment group, APACHE III risk of death score, haemoglobin at randomisation, blood group, age, and hospital site for patients who were not discharged to another acute hospital.

Hospital readmission days reported at 6-month follow-up were then allocated up to the point where the total hospital length of stay, including any time spent discharged to a second hospital, did not exceed 6 months or time until death. Days spent in rehabilitation, long-term care, or at home were then sequentially assigned to the point where the total length of stay in all locations equalled the shorter of 6 months or time until death. Patients who were originally discharged to another acute hospital were assumed to be subsequently discharged to rehabilitation, long-term care, or home in the same proportions as those from the index hospitalization.

After rehabilitation, based on data from the Australasian Rehabilitation Outcomes Centre[137], it was assumed that 52.3% of these patients were discharged to long-term care and 47.7% to their homes for the remainder of the follow up period. Patients discharged to long-term care or sent home after either their index or second hospitalization were assumed to remain in their discharge destination for the remainder of follow up less any hospital readmission days reported at 6-month follow-up.

Rehabilitation length of stay was calculated using the mix of Acute Physiology and Chronic Health Evaluation III diagnosis codes recorded in the trial for rehabilitation patients and the average length of stay for matched impairments from the Australasian Rehabilitation Outcomes Centre[138]. Rehabilitation length of stay for public and private patients was calculated separately and applied to patients whose index hospitalization was in a public or private hospital respectively.

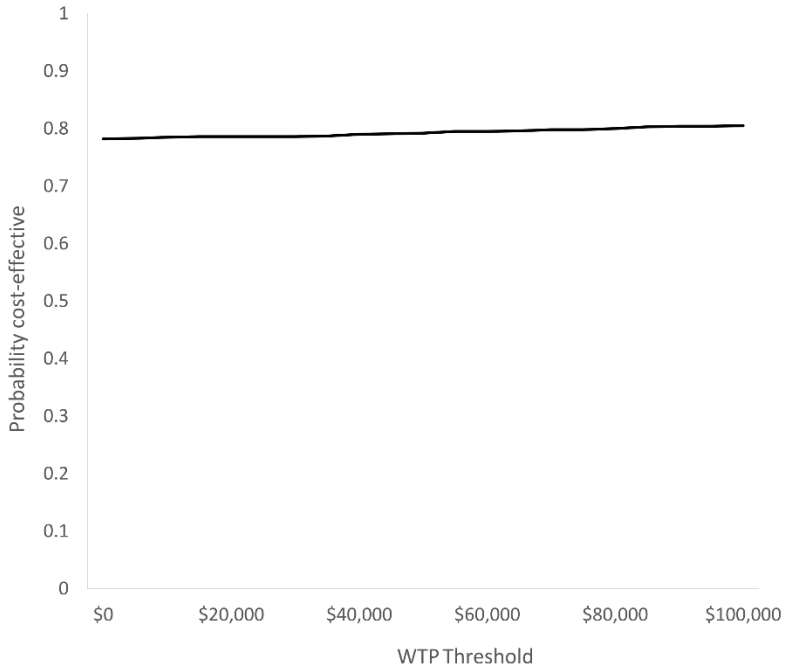

Figure A.2.1: Cost-effectiveness Acceptability Curve for Short-term vs. Long-term Storage

A.5 Appendix for Chapter 4

Table A.3.1: General Surgery Recommendations

No.	Recommendation	Evidence
R1	Health-care services should establish a multidisciplinary, multimodal perioperative patient blood management program. This should include preoperative optimisation of red cell mass and coagulation status; minimisation of perioperative blood loss, including meticulous attention to surgical haemostasis; and tolerance of postoperative anaemia.	Grade C
R4	In surgical patients with, or at risk of, iron deficiency anaemia, preoperative oral iron therapy is recommended.	Grade B
R5	In patients with preoperative anaemia, where an erythropoietin stimulating agent is indicated, it must be combined with iron therapy.	Grade A
R6	In patients with postoperative anaemia, early oral iron therapy is not clinically effective, its routine use in this setting is not recommended.	Grade B
R11	The routine use of preoperative autologous donation is not recommended because, although it reduces the risk of allogeneic RBC transfusion, it increases the risk of receiving any RBC transfusion (allogeneic and autologous)	Grade C
R12	In patients undergoing surgery, measure to prevent hypothermia should be used	Grade A
R14	In adult patients undergoing surgery in which substantial blood loos (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of acute normovolemic haemodilution should be considered.	Grade C
R15	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, intraoperative cell salvage is recommended.	Grade C
R22	The prophylactic or routine therapeutic use of rFVIIa is not recommended because concerns remain about its safety profile, particularly in relation to thrombotic adverse events.	Grade C

Table A.3.2: Cardiac Surgery-Specific Recommendations

No.	Recommendation	Evidence
R2	In patients undergoing cardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay.	Grade C
R7	In patients undergoing CABG either with or without CPB, clopidogrel therapy should be stopped, where possible, at least 5 days before surgery.	Grade C
R16	In adult patients undergoing cardiac surgery, the use of thromboelastography should be considered.	Grade C
R17	In adult patients undergoing cardiac surgery, the use of intravenous tranexamic acid is recommended.	Grade A
R19	In adult patients undergoing cardiac surgery, the use of Ɛ-aminocaproic acid is recommended.	Grade C
R20	In adult patients undergoing cardiac surgery or total knee arthroplasty, in whom significant postoperative blood loss is anticipated, postoperative cell salvage should be considered.	Grade C
R21	The prophylactic use of fresh-frozen plasma in cardiac surgery is not recommended.	Grade B

Table A.3.3: Evidence Guide

Grade A	Body of evidence can be trusted to guide practice
Grade B	Body of evidence can be trusted to guide practice in most situations
Grade C	Body of evidence provides some support for recommendation but care should be taken in its application
Grade D	Body of evidence is weak and recommendations must be applied with caution

Table A.3.4: Full Red Blood Cell Regressions

	Total red blood cell units						Red blood cell transfusion rate						Conditional red blood cell units					
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.323	0.044	<0.001	-0.345	0.096	<0.001	-0.039	0.006	<0.001	-0.044	0.018	0.015	-0.473	0.102	<0.001	-0.507	0.161	0.002
Overall yearly trend	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040	0.040
Change in yearly trend	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011	0.011
Age	-0.004	0.001	0.005	-0.003	0.002	0.090	0.001	0.000	0.001	0.001	0.000	0.071	-0.014	0.003	<0.001	-0.012	0.004	0.001
Male	-0.397	0.026	<0.001	-0.392	0.046	<0.001	-0.169	0.004	<0.001	-0.168	0.010	<0.001	0.365	0.055	<0.001	0.329	0.089	<0.001
BMI	-0.007	0.002	0.002	-0.009	0.003	0.001	-0.004	0.000	<0.001	-0.004	0.001	<0.001	0.007	0.005	0.172	0.005	0.005	0.331
Cardiac catheterisation	-0.177	0.049	<0.001	-0.400	0.140	<0.001	-0.010	0.006	0.093	-0.040	0.017	0.017	-0.454	0.136	0.001	-0.832	0.276	0.003
Cardiogenic shock	1.908	0.432	<0.001	1.958	0.723	0.007	0.186	0.026	<0.001	0.198	0.036	<0.001	1.591	0.583	0.006	1.613	0.904	0.074
Congestive heart failure	0.322	0.032	<0.001	0.325	0.061	<0.001	0.037	0.004	<0.001	0.036	0.009	<0.001	0.420	0.068	<0.001	0.443	0.077	<0.001
Cerebrovascular disease	0.217	0.042	<0.001	0.207	0.043	<0.001	0.034	0.005	<0.001	0.033	0.007	<0.001	0.223	0.086	0.009	0.219	0.087	0.012
Diabetes	0.102	0.024	<0.001	0.102	0.031	0.001	0.046	0.004	<0.001	0.046	0.005	<0.001	-0.137	0.057	<0.001	0.227	0.209	0.278
ln(eGFR)	-1.025	0.044	<0.001	-1.035	0.062	<0.001	-0.211	0.006	<0.001	-0.211	0.011	<0.001	-0.684	0.082	<0.001	-0.712	0.082	<0.001
Infective endocarditis	1.605	0.151	<0.001	1.563	0.187	<0.001	0.209	0.013	<0.001	0.201	0.017	<0.001	1.475	0.261	<0.001	1.433	0.271	<0.001
Myocardial infarction	0.056	0.027	0.040	0.062	0.033	0.064	0.026	0.004	<0.001	0.027	0.004	<0.001	-0.034	0.064	0.596	-0.015	0.064	0.815
Peripheral vascular disease	0.247	0.049	<0.001	0.234	0.066	<0.001	0.044	0.006	<0.001	0.043	0.007	<0.001	0.233	0.096	0.015	0.203	0.122	0.096
Respiratory disease	0.194	0.037	<0.001	0.211	0.037	<0.001	0.032	0.005	<0.001	0.035	0.006	<0.001	0.208	0.080	0.010	0.236	0.074	0.001
Dialysis	0.369	0.171	0.031	0.376	0.167	0.024	-0.008	0.017	0.629	-0.004	0.020	0.833	0.213	0.235	0.365	0.227	0.209	0.278
Intra-aortic balloon pump	3.553	0.231	<0.001	3.477	0.540	<0.001	0.254	0.012	<0.001	0.230	0.019	<0.001	3.852	0.315	<0.001	3.841	0.649	<0.001
Previous cardiac surgery	0.370	0.033	<0.001	0.390	0.065	<0.001	0.045	0.004	<0.001	0.048	0.009	<0.001	0.511	0.074	<0.001	0.527	0.110	<0.001
Angina – CCS classification																		
1	0.031	0.034	0.370	-0.070	0.070	0.316	0.015	0.005	0.008	-0.003	0.008	0.676	-0.084	0.083	0.312	-0.219	0.131	0.096
2	0.043	0.305	0.159	-0.086	0.053	0.108	0.022	0.005	<0.001	-0.003	0.006	0.631	-0.095	0.075	0.201	-0.222	0.110	0.044
3	0.053	0.036	0.141	-0.027	0.058	0.642	0.032	0.006	<0.001	0.013	0.007	0.066	-0.134	0.083	0.108	-0.187	0.128	0.144
4	0.182	0.052	<0.001	0.040	0.089	0.654	0.066	0.008	<0.001	0.035	0.008	<0.001	-0.083	0.111	0.452	-0.172	0.174	0.321
Ejection fraction																		
Mild 46-60%	-0.005	0.026	0.837	0.024	0.023	0.309	-0.004	0.004	0.286	0.003	0.005	0.490	0.036	0.066	0.585	0.047	0.058	0.419
Moderate 30-45%	0.021	0.043	0.629	0.031	0.053	0.556	0.023	0.006	<0.001	0.025	0.007	<0.001	-0.117	0.095	0.217	-0.104	0.102	0.310
Severe <30%	0.039	0.108	0.716	0.037	0.209	0.861	0.052	0.011	<0.001	0.055	0.017	0.001	-0.212	0.202	0.293	-0.227	0.316	0.472
Coronary artery bypass	0.408	0.045	<0.001	0.453	0.102	<0.001	0.120	0.005	<0.001	0.125	0.014	<0.001	-0.087	0.094	0.352	0.010	0.155	0.950
Valve surgery	0.546	0.041	<0.001	0.532	0.096	<0.001	0.112	0.005	<0.001	0.110	0.008	<0.001	0.453	0.084	<0.001	0.440	0.152	0.004
Constant	1.248	0.049	<0.001	1.191	0.198	<0.001	0.340	0.007	<0.001	0.339	0.030	<0.001	3.742	0.107	<0.001	3.514	0.264	<0.001
Hospital fixed-effects	×			✓			×			✓			×			✓		
N	77,122			77,122			77,214			77,214			26,504			26,504		
R^2	0.0969			0.1153			0.1519			0.1870			0.0605			0.0758		

Monthly trend scaled up to yearly; Coef - coefficient; BMI - body mass index; CCS - Canadian Cardiovascular Society; eGFR - estimated Glomerular filtration rate; SE - standard error

Table A.3.5: Full Platelet Regressions

	Total platelet units						Platelet transfusion rate						Conditional platelet units					
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.090	0.053	0.087	-0.056	0.070	0.421	-0.009	0.006	0.101	-0.014	0.015	0.360	-0.285	0.233	0.221	-0.085	0.290	0.770
Overall yearly trend	0.011	0.012	0.391	0.024	0.026	0.344	0.010	0.001	<0.001	0.010	0.004	0.009	-0.096	0.054	0.075	-0.045	0.097	0.646
Change in yearly trend	-0.022	0.014	0.103	-0.042	0.037	0.255	-0.018	0.002	<0.001	-0.017	0.004	<0.001	0.153	0.059	0.009	0.046	0.149	0.756
Age	-0.002	0.002	0.152	-0.003	0.002	0.208	-0.000	0.000	0.399	0.000	0.000	0.787	-0.010	0.008	0.222	-0.013	0.009	0.141
Male	0.070	0.020	<0.001	0.086	0.021	<0.001	0.021	0.003	<0.001	0.022	0.004	<0.001	0.066	0.087	0.447	0.132	0.065	0.041
BMI	-0.011	0.002	<0.001	-0.010	0.003	<0.001	-0.004	0.000	<0.001	-0.004	0.000	<0.001	-0.004	0.008	0.609	-0.000	0.007	0.957
Cardiac catheterisation	0.043	0.039	0.273	-0.163	0.074	0.029	-0.005	0.005	0.353	-0.029	0.016	0.069	0.295	0.176	0.094	-0.359	0.189	0.058
Cardiogenic shock	1.059	0.410	0.010	1.091	0.389	0.005	0.076	0.033	0.006	0.085	0.035	0.016	2.278	1.002	0.023	2.323	0.846	0.006
Congestive heart failure	0.035	0.021	0.088	0.080	0.040	0.043	0.021	0.004	<0.001	0.019	0.006	0.001	-0.123	0.080	0.125	0.123	0.118	0.296
Cerebrovascular disease	0.070	0.026	0.008	0.056	0.033	0.093	0.017	0.005	<0.001	0.014	0.005	0.004	0.109	0.102	0.284	0.001	0.083	0.993
Diabetes	-0.091	0.019	<0.001	-0.066	0.013	<0.001	-0.022	0.003	<0.001	-0.021	0.002	<0.001	-0.179	0.096	0.062	-0.076	0.086	0.380
ln(eGFR)	-0.226	0.041	<0.001	-0.201	0.042	<0.001	-0.056	0.005	<0.001	-0.054	0.004	<0.001	-0.293	0.169	0.083	-0.209	0.154	0.175
Infective endocarditis	0.810	0.135	<0.001	0.700	0.181	<0.001	0.128	0.013	<0.001	0.119	0.016	<0.001	1.173	0.344	0.001	0.684	0.375	0.068
Myocardial infarction	-0.023	0.034	0.485	-0.006	0.035	0.871	0.005	0.003	0.122	0.003	0.003	0.390	-0.172	0.168	0.308	-0.059	0.150	0.693
Peripheral vascular disease	0.038	0.028	0.174	0.044	0.039	0.259	0.002	0.005	0.708	0.000	0.006	0.961	0.155	0.116	0.182	0.134	0.097	0.168
Respiratory disease	0.050	0.028	0.070	0.046	0.034	0.179	0.004	0.004	0.390	0.005	0.005	0.328	0.194	0.120	0.107	0.115	0.117	0.327
Dialysis	0.169	0.153	0.271	0.221	0.128	0.085	0.053	0.016	0.001	0.059	0.015	<0.001	-0.070	0.511	0.891	0.175	0.446	0.695
Intra-aortic balloon pump	1.704	0.130	<0.001	1.665	0.235	<0.001	0.280	0.013	<0.001	0.263	0.024	<0.001	1.763	0.229	<0.001	1.861	0.349	<0.001
Previous cardiac surgery	0.221	0.024	<0.001	0.205	0.046	<0.001	0.052	0.004	<0.001	0.055	0.008	<0.001	0.271	0.095	0.004	0.182	0.120	0.130
Angina – CCS classification																		
1	-0.066	0.034	0.051	-0.092	0.060	0.126	0.004	0.005	0.374	-0.007	0.007	0.335	-0.412	0.153	0.007	-0.265	0.176	0.133
2	-0.042	0.037	0.259	-0.074	0.044	0.096	0.005	0.004	0.165	-0.0012	0.005	0.038	-0.278	0.184	0.132	-0.198	0.172	0.249
3	-0.008	0.408	0.851	-0.089	0.056	0.113	0.011	0.005	0.019	-0.002	0.005	0.732	-0.169	0.207	0.416	-0.327	0.223	0.142
4	0.090	0.055	0.102	-0.030	0.070	0.673	0.023	0.007	0.001	0.012	0.006	0.086	0.191	0.267	0.474	-0.250	0.350	0.475
Ejection fraction																		
Mild 46-60%	0.008	0.024	0.732	-0.007	0.025	0.788	0.003	0.003	0.396	0.006	0.004	0.111	-0.003	0.112	0.979	-0.108	0.119	0.362
Moderate 30-45%	0.015	0.033	0.637	-0.020	0.039	0.616	0.013	0.005	0.017	0.012	0.006	0.074	-0.079	0.135	0.559	-0.234	0.155	0.130
Severe <30%	-0.008	0.056	0.877	-0.053	0.063	0.401	0.037	0.010	<0.001	0.038	0.015	0.008	0.344	0.182	0.059	-0.670	0.243	0.006
Coronary artery bypass	0.164	0.034	<0.001	0.166	0.063	0.009	0.051	0.005	<0.001	0.056	0.010	<0.001	0.058	0.128	0.652	-0.050	0.118	0.669
Valve surgery	0.347	0.027	<0.001	0.326	0.072	<0.001	0.114	0.004	<0.001	0.113	0.009	<0.001	0.115	0.106	0.276	0.027	0.127	0.833
Constant	0.572	0.043	<0.001	-0.003	0.002	0.208	0.154	0.006	<0.001	0.154	0.019	<0.001	3.594	0.182	<0.001	3.268	0.450	<0.001
Hospital fixed-effects	×			✓			×			✓			×			✓		
N	77,322			77,322			77,322			77,322			14,560			14,560		
R^2	0.0199			0.0358			0.0520			0.0732			0.0124			0.0945		

Monthly trend scaled up to yearly; Coef - coefficient; BMI - body mass index; CCS - Canadian Cardiovascular Society; eGFR - estimated Glomerular filtration rate; SE - standard error

Table A.3.6: Full Cryoprecipitate Regressions

	Total cryoprecipitate units			Cryoprecipitate transfusion rate			Conditional cryoprecipitate units											
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	0.086	0.077	0.269	0.065	0.123	0.596	0.011	0.004	0.007	0.007	0.013	0.587	-0.267	0.793	0.736	-0.044	0.729	0.952
Overall yearly trend	0.032	0.014	0.022	0.036	0.033	0.270	0.001	0.001	0.513	0.001	0.003	0.700	0.350	0.150	0.019	0.221	0.172	0.198
Change in yearly trend	-0.050	0.017	0.004	-0.050	0.042	0.237	0.000	0.001	0.891	-0.001	0.004	0.860	-0.564	0.167	0.001	-0.291	0.238	0.222
Age	-0.003	0.002	0.209	-0.001	0.004	0.748	-0.001	0.000	<0.001	-0.001	0.000	0.026	0.025	0.020	0.199	0.042	0.036	0.245
Male	0.031	0.065	0.636	0.034	0.053	0.518	0.007	0.002	0.005	0.007	0.003	0.015	-0.308	0.733	0.674	-0.294	0.615	0.633
BMI	-0.016	0.004	<0.001	-0.020	0.006	0.001	-0.003	0.000	<0.001	-0.003	0.000	0.000	0.088	0.060	0.141	0.084	0.071	0.240
Cardiac catheterisation	-0.059	0.056	0.291	-0.244	0.136	0.074	-0.017	0.004	<0.001	-0.019	0.012	0.101	0.864	0.426	0.043	-0.770	0.462	0.095
Cardiogenic shock	0.110	0.248	0.658	0.161	0.315	0.608	0.012	0.020	0.547	0.016	0.024	0.504	1.056	1.013	0.297	1.380	0.821	0.093
Congestive heart failure	-0.068	0.052	0.191	-0.031	0.119	0.795	-0.003	0.003	0.214	0.006	0.004	0.081	-0.424	0.451	0.347	-0.850	1.199	0.479
Cerebrovascular disease	0.065	0.043	0.132	0.043	0.044	0.329	0.008	0.003	0.023	0.006	0.003	0.050	-0.041	0.346	0.905	-0.092	0.386	0.812
Diabetes	-0.172	0.034	<0.001	-0.162	0.041	<0.001	-0.015	0.002	<0.001	-0.014	0.003	0.000	-0.497	0.357	0.164	-0.562	0.462	0.224
ln(eGFR)	-0.202	0.036	<0.001	-0.158	0.055	0.004	-0.025	0.003	<0.001	-0.022	0.004	0.000	0.134	0.292	0.646	0.312	0.408	0.445
Infective endocarditis	0.689	0.140	<0.001	0.676	0.162	<0.001	0.064	0.011	<0.001	0.063	0.012	0.000	0.567	0.511	0.267	0.132	0.470	0.779
Myocardial infarction	-0.149	0.027	<0.001	-0.167	0.032	<0.001	-0.013	0.002	<0.001	-0.013	0.003	0.000	-0.436	0.258	0.091	-0.623	0.213	0.003
Peripheral vascular disease	0.114	0.050	0.024	0.128	0.073	0.082	0.008	0.004	0.030	0.011	0.005	0.030	0.520	0.448	0.246	0.370	0.522	0.478
Respiratory disease	0.019	0.061	0.752	0.050	0.043	0.248	0.001	0.003	0.813	0.002	0.003	0.533	0.171	0.625	0.784	0.523	0.422	0.216
Dialysis	-0.045	0.121	0.708	0.040	0.122	0.743	-0.009	0.011	0.383	-0.003	0.012	0.825	0.353	0.746	0.636	0.708	0.750	0.345
Intra-aortic balloon pump	2.324	0.193	<0.001	2.304	0.452	<0.001	0.166	0.012	<0.001	0.158	0.028	0.000	3.570	0.535	<0.001	3.510	0.687	<0.001
Previous cardiac surgery	0.366	0.037	<0.001	0.383	0.081	<0.001	0.038	0.003	<0.001	0.040	0.007	0.000	0.193	0.320	0.546	0.664	0.221	0.003
Angina – CCS classification																		
1	0.027	0.051	0.598	-0.086	0.057	0.129	0.004	0.003	0.269	-0.009	0.006	0.137	-0.019	0.486	0.969	-0.112	0.517	0.829
2	0.022	0.040	0.579	-0.118	0.052	0.022	0.007	0.003	0.008	-0.007	0.004	0.129	-0.447	0.389	0.250	-0.614	0.346	0.076
3	-0.036	0.041	0.384	-0.120	0.064	0.061	0.003	0.003	0.328	-0.006	0.005	0.279	-0.770	0.386	0.046	-0.773	0.355	0.029
4	-0.084	0.051	0.097	-0.084	0.085	0.323	-0.006	0.004	0.143	-0.001	0.007	0.841	-0.260	0.507	0.608	-1.121	1.087	0.302
Ejection fraction																		
Mild 46-60%	0.010	0.034	0.764	0.010	0.033	0.761	0.000	0.002	0.956	0.002	0.002	0.427	0.092	0.350	0.793	-0.134	0.317	0.673
Moderate 30-45%	0.006	0.041	0.889	-0.017	0.045	0.702	0.002	0.004	0.611	0.000	0.004	0.992	-0.059	0.303	0.847	-0.116	0.215	0.589
Severe <30%	-0.056	0.085	0.511	-0.057	0.102	0.580	0.013	0.007	0.075	0.012	0.009	0.166	-0.834	0.484	0.085	-0.487	0.527	0.355
Coronary artery bypass	0.046	0.062	0.458	0.108	0.090	0.230	0.014	0.004	0.000	0.018	0.007	0.014	-0.877	0.530	0.098	-0.732	0.719	0.308
Valve surgery	0.550	0.041	<0.001	0.537	0.097	<0.001	0.063	0.003	<0.001	0.061	0.010	0.000	0.181	0.233	0.437	0.384	0.370	0.299
Constant	0.532	0.050	<0.001	0.511	0.133	<0.001	0.073	0.004	<0.001	0.072	0.011	0.000	7.326	0.472	<0.001	7.666	0.769	<0.001
Hospital fixed-effects	×			✓			×			✓			×			✓		
N	77,322			77,322			77,322			77,322			6,493			6,493		
R^2	0.0070			0.0136			0.0329			0.0674			0.0046			0.0272		

Monthly trend scaled up to yearly; Coef - coefficient; BMI - body mass index; CCS - Canadian Cardiovascular Society; eGFR - estimated Glomerular filtration rate; SE - standard error

Table A.3.7: Full Fresh Frozen Plasma Regressions

	Total fresh frozen plasma units						Fresh frozen plasma transfusion rate						Conditional fresh frozen plasma units					
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.110	0.036	0.002	-0.111	0.076	0.143	-0.009	0.005	0.089	-0.010	0.014	0.459	-0.297	0.149	0.047	-0.283	0.250	0.258
Overall yearly trend	0.014	0.009	0.117	0.009	0.028	0.743	0.007	0.001	<0.001	0.005	0.005	0.234	-0.080	0.038	0.034	-0.057	0.068	0.404
Change in yearly trend	-0.108	0.011	<0.001	-0.080	0.034	0.020	-0.027	0.002	<0.001	-0.022	0.006	<0.001	0.000	0.048	0.999	-0.002	0.080	0.982
Age	-0.002	0.001	0.077	-0.001	0.001	0.442	0.000	0.000	0.050	0.000	0.000	0.825	-0.004	0.004	0.354	-0.004	0.005	0.389
Male	0.077	0.019	<0.001	0.076	0.020	<0.001	0.009	0.003	0.005	0.009	0.004	0.019	0.254	0.084	0.003	0.256	0.089	0.004
BMI	-0.015	0.002	<0.001	-0.018	0.003	0.000	-0.004	0.000	<0.001	-0.005	0.001	<0.001	0.001	0.009	0.922	-0.008	0.007	0.300
Cardiac catheterisation	-0.170	0.043	<0.001	-0.311	0.103	0.003	-0.016	0.005	0.001	-0.040	0.015	0.008	-0.598	0.202	0.003	-0.893	0.227	<0.001
Cardiogenic shock	0.406	0.199	0.042	0.447	0.344	0.194	0.103	0.027	<0.001	0.113	0.032	<0.001	-0.083	0.432	0.847	-0.061	0.660	0.927
Congestive heart failure	0.158	0.029	<0.001	0.158	0.040	<0.001	0.027	0.004	0.000	0.024	0.006	<0.001	0.218	0.121	0.072	0.316	0.099	0.001
Cerebrovascular disease	0.124	0.043	0.004	0.113	0.036	0.002	0.013	0.004	0.005	0.010	0.004	0.007	0.369	0.209	0.078	0.359	0.154	0.020
Diabetes	-0.075	0.019	<0.001	-0.061	0.023	0.007	-0.017	0.003	<0.001	-0.015	0.003	<0.001	-0.073	0.103	0.481	-0.015	0.077	0.849
ln(eGFR)	-0.254	0.033	<0.001	-0.219	0.040	0.000	-0.056	0.004	<0.001	-0.049	0.005	<0.001	-0.188	0.155	0.224	-0.167	0.153	0.277
Infective endocarditis	0.822	0.238	0.001	0.782	0.265	0.003	0.109	0.013	<0.001	0.101	0.018	<0.001	1.042	0.742	0.160	0.941	0.726	0.195
Myocardial infarction	-0.032	0.019	0.088	-0.052	0.021	0.013	-0.001	0.003	0.644	-0.006	0.005	0.210	-0.080	0.091	0.376	-0.077	0.098	0.435
Peripheral vascular disease	0.069	0.034	0.042	0.072	0.050	0.150	0.007	0.005	0.125	0.007	0.006	0.216	0.228	0.149	0.125	0.201	0.159	0.205
Respiratory disease	0.018	0.025	0.469	0.042	0.027	0.123	0.003	0.004	0.454	0.008	0.004	0.066	0.007	0.111	0.948	0.052	0.101	0.602
Dialysis	-0.076	0.097	0.433	-0.042	0.111	0.708	-0.027	0.015	0.068	-0.018	0.016	0.265	0.160	0.339	0.637	0.105	0.373	0.779
Intra-aortic balloon pump	1.725	0.130	<0.001	1.686	0.312	<0.001	0.208	0.013	<0.001	0.199	0.029	<0.001	2.182	0.253	<0.001	2.206	0.388	<0.001
Previous cardiac surgery	0.233	0.025	<0.001	0.269	0.049	<0.001	0.037	0.003	<0.001	0.043	0.007	<0.001	0.353	0.111	0.002	0.445	0.133	0.001
Angina – CCS classification																		
1	0.091	0.028	0.001	-0.019	0.069	0.779	0.004	0.004	0.408	-0.012	0.008	0.108	0.455	0.128	<0.001	0.052	0.149	0.728
2	0.031	0.022	0.164	-0.075	0.039	0.056	0.006	0.004	0.088	-0.012	0.006	0.036	0.055	0.106	0.610	-0.184	0.128	0.152
3	0.014	0.026	0.591	-0.059	0.048	0.216	0.010	0.004	0.020	-0.003	0.007	0.658	-0.177	0.121	0.142	-0.308	0.163	0.059
4	0.018	0.034	0.602	-0.073	0.055	0.182	0.013	0.006	0.040	-0.002	0.009	0.790	-0.191	0.160	0.233	-0.379	0.164	0.021
Ejection fraction																		
Mild 46-60%	0.014	0.025	0.575	0.033	0.026	0.206	-0.002	0.003	0.558	0.003	0.003	0.398	0.131	0.137	0.339	0.110	0.129	0.395
Moderate 30-45%	0.044	0.030	0.144	0.050	0.031	0.110	0.015	0.005	0.003	0.016	0.005	0.003	-0.049	0.118	0.679	-0.038	0.103	0.710
Severe <30%	0.128	0.065	0.049	0.134	0.112	0.231	0.054	0.010	<0.001	0.055	0.014	<0.001	-0.299	0.194	0.122	-0.285	0.250	0.255
Coronary artery bypass	0.066	0.033	0.042	0.084	0.069	0.225	0.036	0.005	<0.001	0.038	0.010	<0.001	-0.420	0.120	<0.001	0.340	0.146	0.020
Valve surgery	0.390	0.030	<0.001	0.381	0.087	<0.001	0.098	0.004	<0.001	0.097	0.010	<0.001	0.118	0.104	0.255	0.131	0.190	0.491
Constant	0.807	0.044	<0.001	0.805	0.147	<0.001	0.164	0.006	<0.001	0.165	0.023	<0.001	4.863	0.189	<0.001	4.691	0.311	<0.001
Hospital fixed-effects	×			✓			×			✓			×			✓		
N	77,322			77,322			77,322			77,322			12,205			12,205		
R^2	0.0391			0.0640			0.0589			0.0948			0.0280			0.0561		

Monthly trend scaled up to yearly; Coef - coefficient; BMI - body mass index; CCS - Canadian Cardiovascular Society; eGFR - estimated Glomerular filtration rate; SE - standard error

Table A.3.8: Full Patient Outcome Regressions

	ICU length of stay (hours)			Hospital length of stay (days)			30-day readmissions/1,000 patients			30-day mortality/1,000 patients		
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-1.635	2.075	0.431	-0.941	0.324	0.004	-5.850	7.716	0.448	-0.782	2.023	0.699
Overall yearly trend	2.941	1.171	0.012	0.411	0.103	<0.001	-0.505	2.215	0.819	0.425	0.521	0.415
Change in yearly trend	-2.014	1.356	0.138	-0.334	0.117	0.004	2.203	2.845	0.439	-0.388	0.588	0.509
Age	0.011	0.067	0.865	0.016	0.011	0.138	-0.332	0.140	0.018	0.136	0.057	0.017
Male	-2.190	1.272	0.085	-0.536	0.126	<0.001	-10.79	2.850	<0.001	-5.218	1.233	<0.001
BMI	1.305	0.125	<0.001	0.110	0.013	<0.001	1.352	0.284	<0.001	0.548	0.114	<0.001
Cardiac catheterisation	-7.895	2.033	<0.001	-1.646	0.334	<0.001	-5.648	4.620	0.222	-5.904	2.271	0.009
Cardiogenic shock	59.10	16.31	<0.001	9.747	2.262	<0.001	-9.908	16.84	0.556	31.03	17.10	0.070
Congestive heart failure	10.57	1.679	<0.001	1.644	0.202	<0.001	10.40	3.141	0.001	10.79	1.999	<0.001
Cerebrovascular disease	4.173	1.141	<0.001	0.986	0.141	<0.001	9.157	4.204	0.029	8.363	1.836	<0.001
Diabetes	3.262	1.287	0.011	0.649	0.152	<0.001	14.34	2.886	<0.001	1.229	1.271	0.334
ln(eGFR)	-24.79	2.293	<0.001	-2.732	0.333	<0.001	-12.67	3.977	0.001	-21.48	2.009	<0.001
Infective endocarditis	18.65	4.084	<0.001	9.775	0.994	<0.001	1.339	9.149	0.884	15.46	3.859	<0.001
Myocardial infarction	0.733	1.183	0.535	1.414	0.225	<0.001	1.308	2.834	0.644	-1.236	1.260	0.326
Peripheral vascular disease	6.481	1.776	<0.001	1.129	0.199	<0.001	6.294	4.430	0.155	10.78	2.720	<0.001
Respiratory disease	11.65	1.829	<0.001	1.863	0.231	<0.001	16.71	3.434	<0.001	9.016	1.915	<0.001
Dialysis	1.609	5.289	0.761	4.234	1.258	0.001	60.94	25.18	0.016	8.825	8.671	0.309
Intra-aortic balloon pump	81.21	10.53	<0.001	5.314	0.761	<0.001	-20.25	10.82	0.061	135.8	17.21	<0.001
Previous cardiac surgery	4.221	1.021	<0.001	0.123	0.182	0.500	6.597	3.694	0.074	9.302	1.827	<0.001
Angina – CCS classification												
1	-2.394	1.443	0.097	-0.222	0.236	0.348	-3.249	3.713	0.382	-0.301	1.965	0.878
2	-3.435	1.628	0.035	-0.110	0.238	0.644	-2.975	3.132	0.342	-2.857	1.292	0.027
3	-2.066	1.552	0.183	0.416	0.186	0.026	-0.581	3.877	0.881	0.018	2.172	0.993
4	-1.529	2.506	0.542	1.573	0.373	<0.001	9.791	5.704	0.086	3.007	3.187	0.345
Ejection fraction												
Mild 46-60%	2.179	0.831	0.009	0.272	0.123	0.027	2.202	1.932	0.254	2.475	1.226	0.044
Moderate 30-45%	8.382	1.639	<0.001	1.428	0.225	<0.001	6.742	4.234	0.111	2.759	2.118	0.193
Severe <30%	23.60	5.538	<0.001	3.841	1.063	<0.001	7.565	8.054	0.348	3.799	5.908	0.520
Coronary artery bypass	2.036	2.576	0.429	0.341	0.346	0.324	-2.969	3.981	0.456	0.128	2.275	0.955
Valve surgery	8.896	2.301	<0.001	1.176	0.296	<0.001	17.91	3.497	<0.001	7.165	1.881	<0.001
Constant	53.58	4.075	<0.001	9.859	0.471	<0.001	101.3	10.04	<0.001	15.76	2.512	<0.001
Hospital fixed-effects	✓			✓			✓			✓		
N	66,684			77,258			76,240			77,322		
R^2	0.1074			0.088			0.0186			0.0410		

Monthly trend scaled up to yearly; Coef - coefficient; BMI - body mass index; CCS - Canadian Cardiovascular Society; eGFR - estimated Glomerular filtration rate; ICU - intensive care unit; SE - standard error

Table A.3.9: Resource Saving Over 5 Years (March 2012 to March 2017)

	Red blood cells (units)	Platelets (units)	Fresh frozen plasma (units)	Hospital length of stay (days)	Total
Reduction	18,398	3,826	9,691	41,069	N/A
Cost per unit/day (2017 USD)	$278	$192	$122	$594	N/A
Total resource saving	$5,121,205	$736,258	$1,181,979	$24,398,217	$31,437,658
Per patient (48,595 patients)	$105	$15	$24	$502	$647

Reduction assumes that under a counterfactual without the guidelines the estimated resource use at March 2012 would have continued for 5 years (monthly trend = 0)
Cost per blood product unit taken from National Blood Authority Annual Report 2016/17, cost per hospital bed calculated as a weight average based on separations of coronary artery bypass graft and valve replacement surgery AR-DRGs from the National Hospital Cost Data Collection, Round 21 (2016/17) and converted from AUD to USD using 2017 PPP from the OECD

Table A.3.10: Subgroup Analyses

	Public vs. private hospitals						Devolved vs. non-devolved hospitals					
	Total RBC units			RBC transfusion rate			Total RBC units			RBC transfusion rate		
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.401	0.109	<0.001	-0.049	0.023	0.029	-0.443	0.106	<0.001	-0.050	0.027	0.061
Guideline shift * Private / Devolved	0.282	0.663	0.671	0.164	0.119	0.169	0.165	0.199	0.405	0.016	0.048	0.743
Overall yearly trend	0.060	0.041	0.147	0.007	0.006	0.269	0.064	0.041	0.121	0.009	0.006	0.165
Overall yearly trend * Private / Devolved	-0.038	0.107	0.719	0.008	0.014	0.593	0.007	0.040	0.857	-0.004	0.005	0.366
Change in yearly trend	-0.075	0.042	0.079	-0.013	0.007	0.051	-0.110	0.039	0.005	-0.024	0.007	0.001
Change in yearly trend * Private / Devolved	-0.006	0.105	0.956	-0.021	0.017	0.219	0.008	0.063	0.903	0.016	0.010	0.099
Hospital fixed-effects	✓			✓			✓			✓		
N	77,122			77,124			58,731			58,798		
R^2	0.1154			0.1872			0.1083			0.1778		

	Isolated CABG patients only					
	Total RBC units			RBC transfusion rate		
	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.042	0.022	0.058	-0.253	0.088	0.004
Overall yearly trend	0.006	0.005	0.310	0.016	0.032	0.614
Change in yearly trend	-0.013	0.007	0.048	-0.040	0.030	0.185
Hospital fixed-effects	✓			✓		
N	38,454			38,411		
R^2	0.1870			0.1163		

Monthly trend scaled up to yearly; Regressions contain the same control variables as the base-case analysis; Coef – coefficient; RBC – red blood cell; SE – standard error

Table A.3.11: Sensitivity Analyses

	Total red blood cell units									Red blood cell transfusion rate								
	Quadratic			Cubic			Multiple imputation			Quadratic			Cubic			Multiple imputation		
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	-0.181	0.098	0.065	-0.001	0.146	0.996	-0.344	0.096	0.001	-0.010	0.015	0.500	0.012	0.016	0.453	-0.044	0.018	0.018
Overall yearly trend	0.090	0.123	0.453	-0.189	0.186	0.309	0.051	0.038	0.183	0.013	0.021	0.540	-0.012	0.030	0.699	0.008	0.006	0.147
Overall yearly trend ^{2}	-0.000	0.001	0.725	0.007	0.004	0.080	-	-	-	0.000	0.000	0.820	0.001	0.001	0.407	-	-	-
Overall yearly trend ^{3}	-	-	-	0.000	0.000	0.057	-	-	-	-	-	-	0.000	0.000	0.385	-	-	-
Change in yearly trend	-0.173	0.121	0.153	-0.116	0.207	0.577	-0.076	0.038	0.053	-0.043	0.023	0.055	-0.050	0.037	0.181	-0.017	0.007	0.014
Change in yearly trend ^{2}	0.002	0.001	0.065	0.014	0.008	0.063	-	-	-	0.000	0.000	0.027	0.002	0.001	0.102	-	-	-
Change in yearly trend ^{3}	-	-	-	0.000	0.000	0.805	-	-	-	-	-	-	-0.000	0.000	0.742	-	-	-
Hospital fixed-effects	✓			✓			✓			✓			✓			✓		
N	77,122			77,122			77,958			77,214			77,214			78,064		
R^2	0.1156			0.1156			-			0.1877			0.1875			-		

Monthly trend scaled up to yearly; Regressions contain the same control variables as the base-case analysis; Coef – coefficient; SE – standard error

Table A.3.12: Falsifications Tests

	Inotropes			Intravenous Nitrates			Steroids		
	Coef.	SE	p	Coef.	SE	p	Coef.	SE	p
Guideline shift	0.004	0.009	0.655	0.002	0.007	0.728	-0.004	0.003	0.215
Overall yearly trend	0.007	0.006	0.302	0.006	0.005	0.240	0.001	0.001	0.197
Change in yearly trend	-0.002	0.004	0.639	-0.003	0.003	0.249	-0.002	0.002	0.254
Hospital fixed-effects	✓			✓			✓		
N	77,321			77,321			76,892		
R^2	0.2391			0.2033			0.0223		

Monthly trend scaled up to yearly; Regressions contain the same control variables as the base-case analysis; Coef – coefficient; SE – standard error

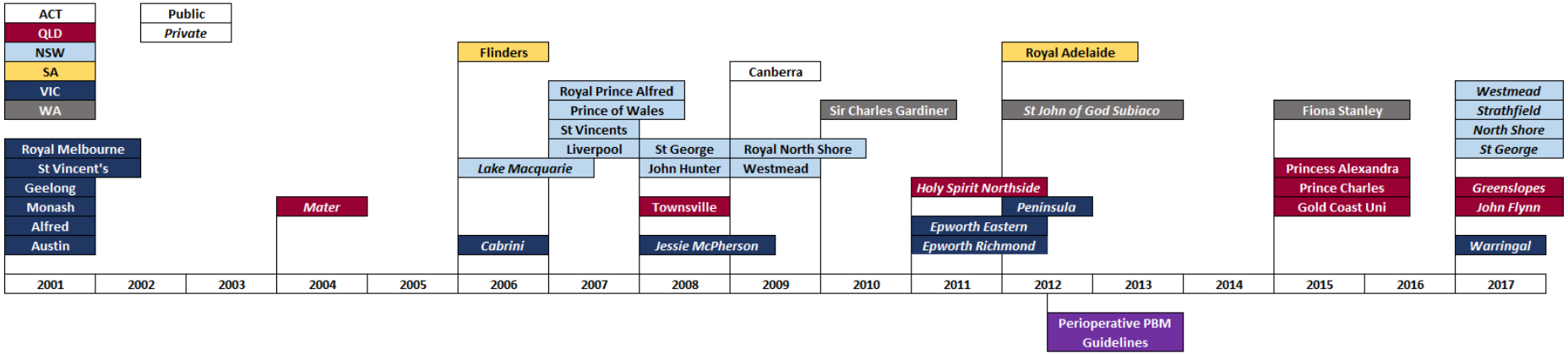

Figure A. 3.1: Hospital Enrolment Timeline

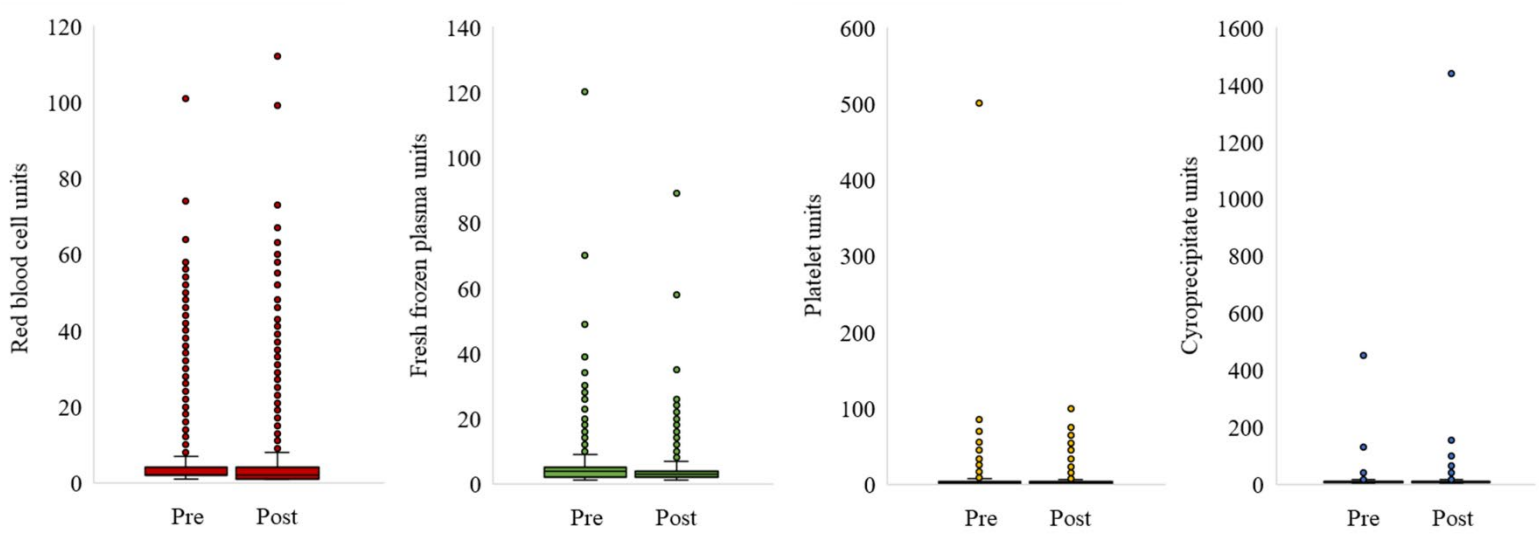

Figure A.3.2: Blood Product Box and Whisker Plots

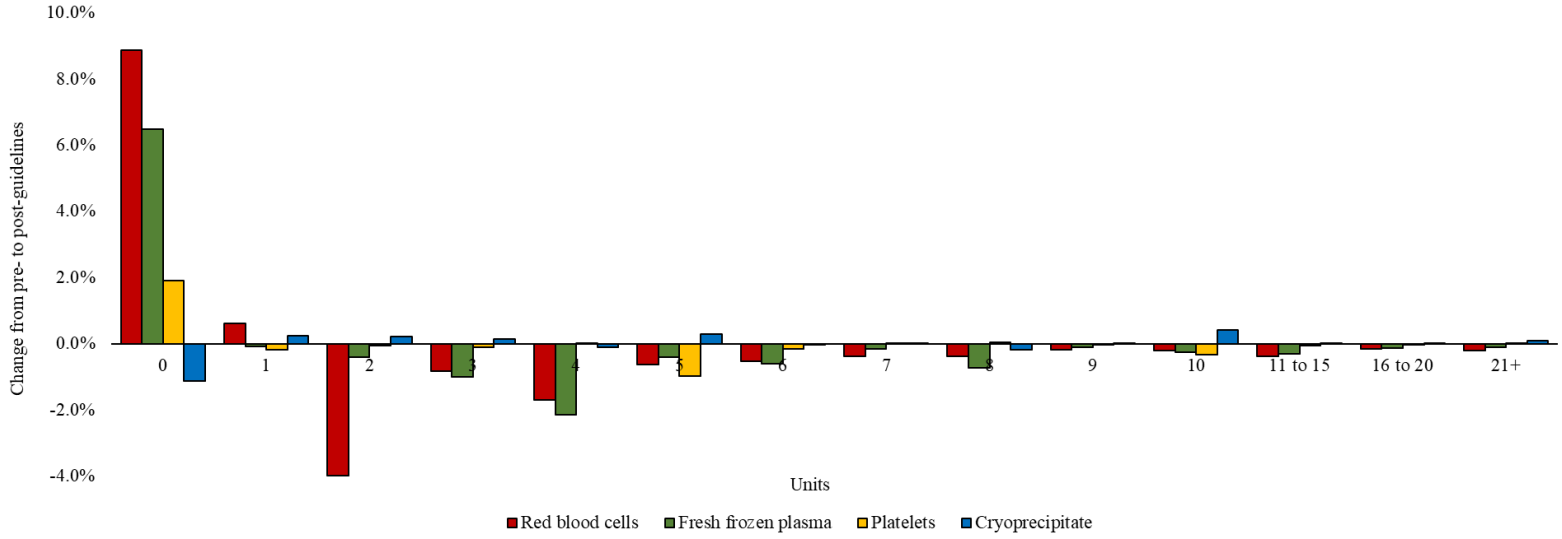

Figure A.3.3: Blood Product Histograms

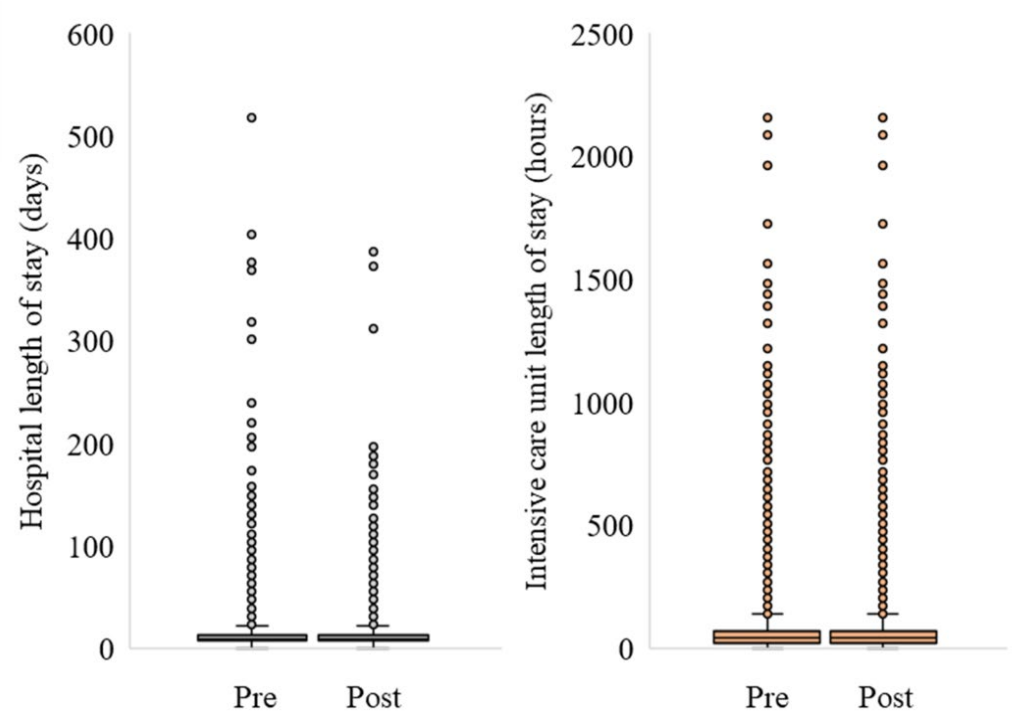

Figure A.3.4: Hospital and Intensive Care Unit Length of Stay Box and Whisker Plots

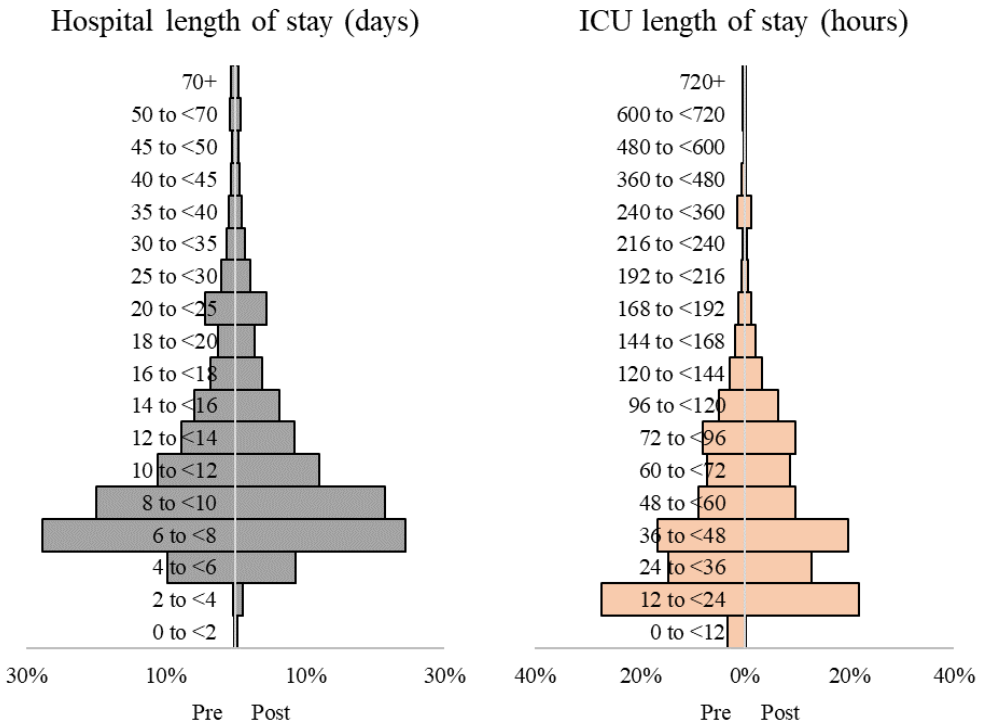

Figure A.3.5: Hospital and Intensive Care Unit Length of Stay Histograms

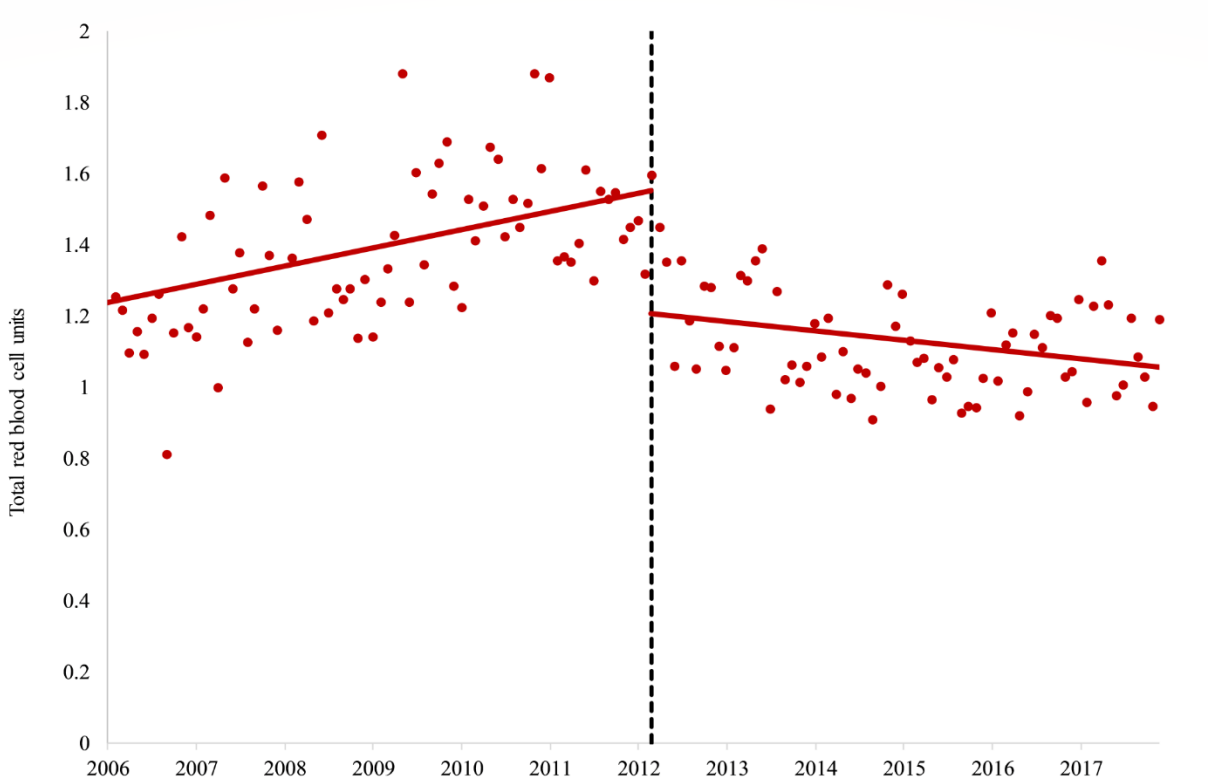

Figure A.3.6: Total Red Blood Cell Units

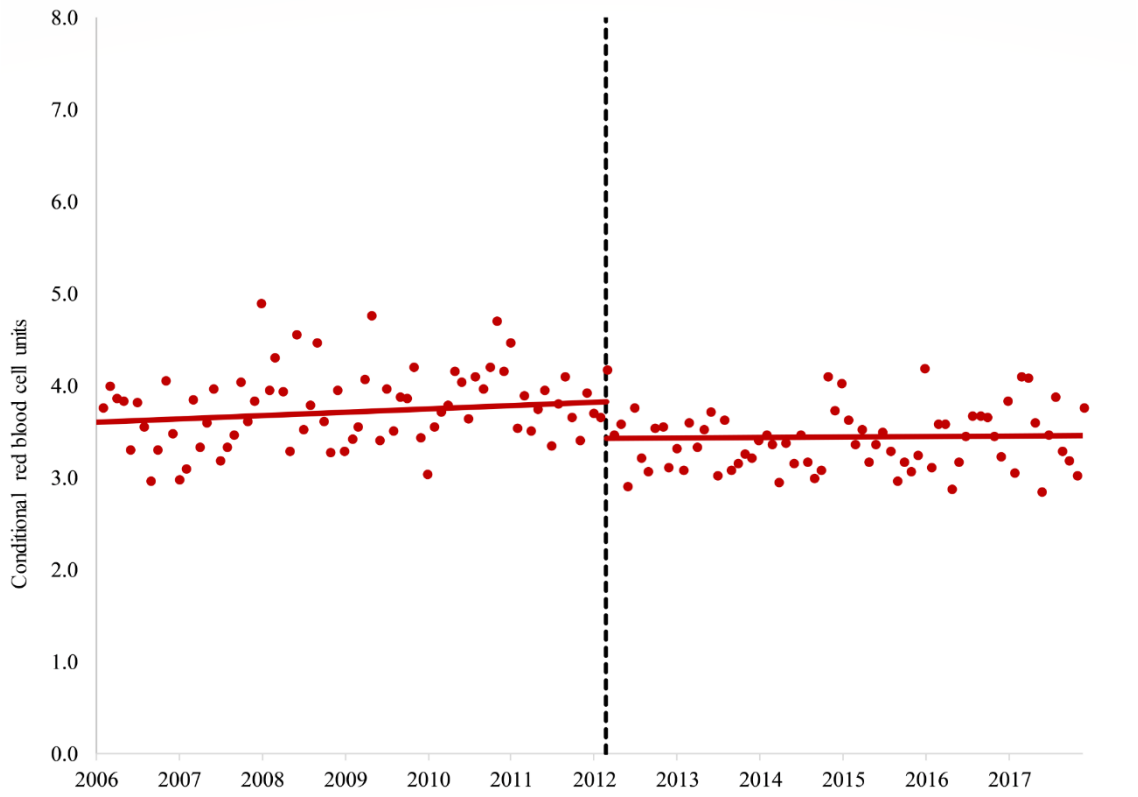

Figure A.3.7: Conditional Red Blood Cell Units

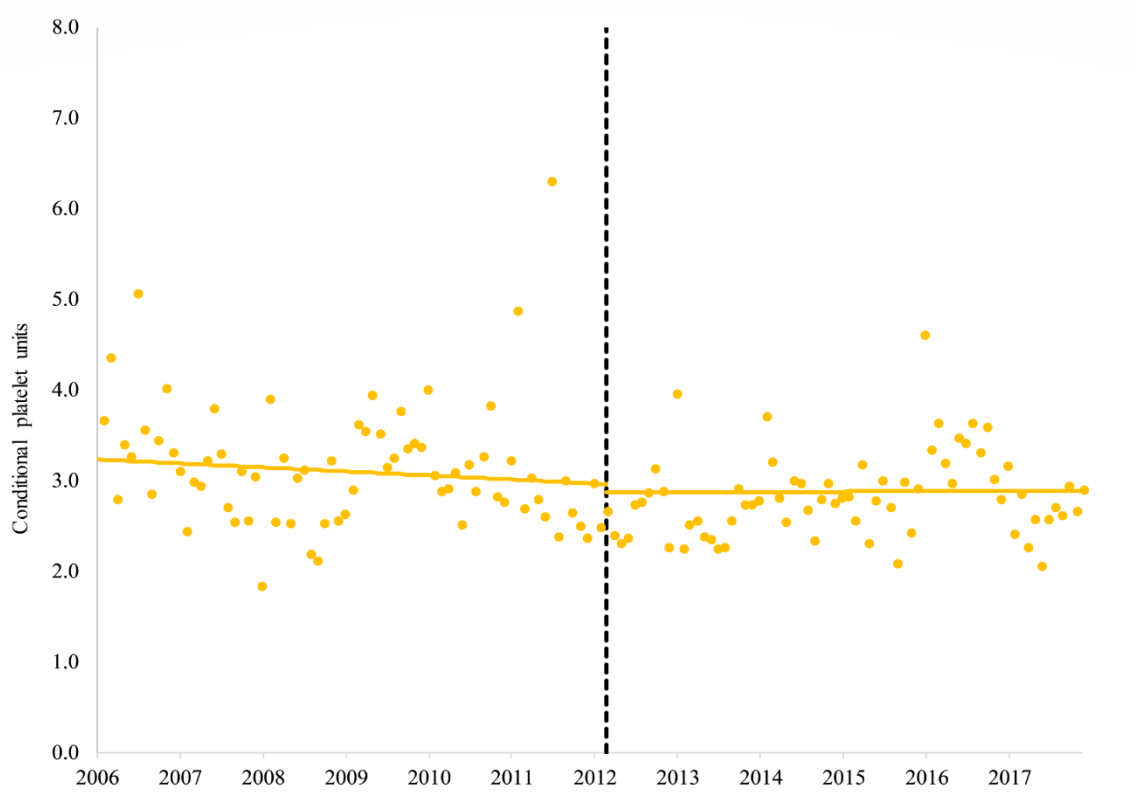

Figure A.3.8: Total Platelet Units

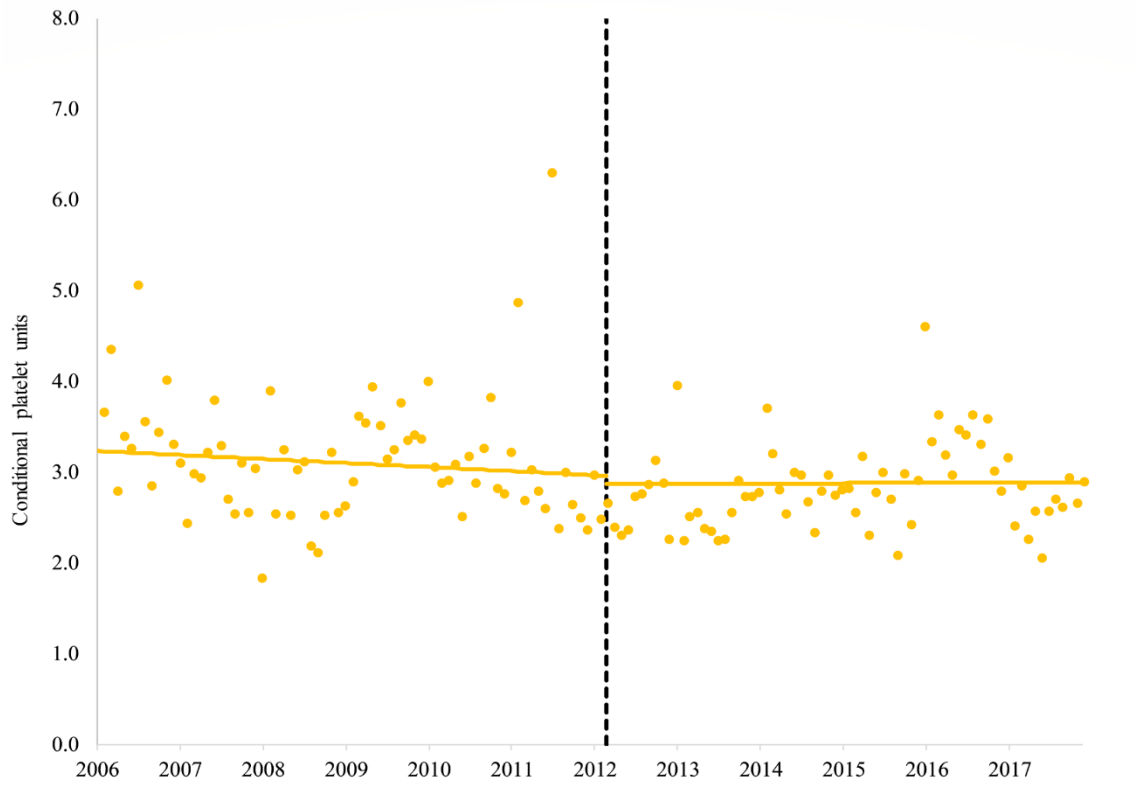

Figure A.3.9: Conditional Platelet Units

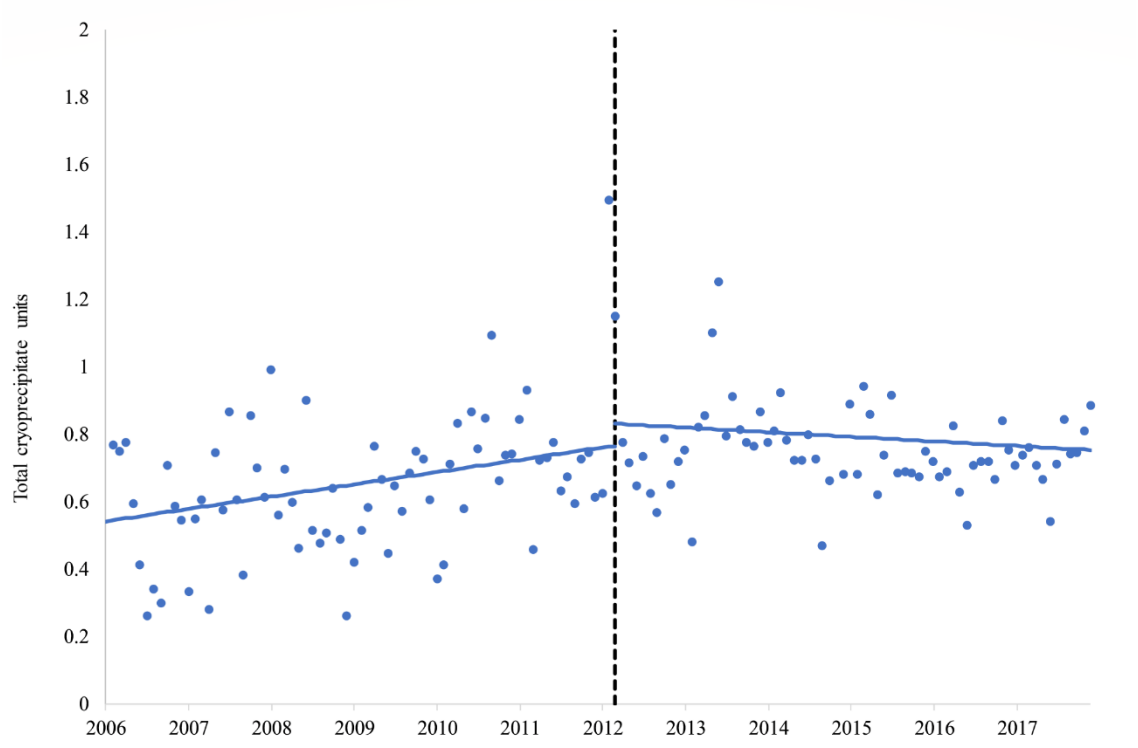

Figure A.3.10: Total Cryoprecipitate Units

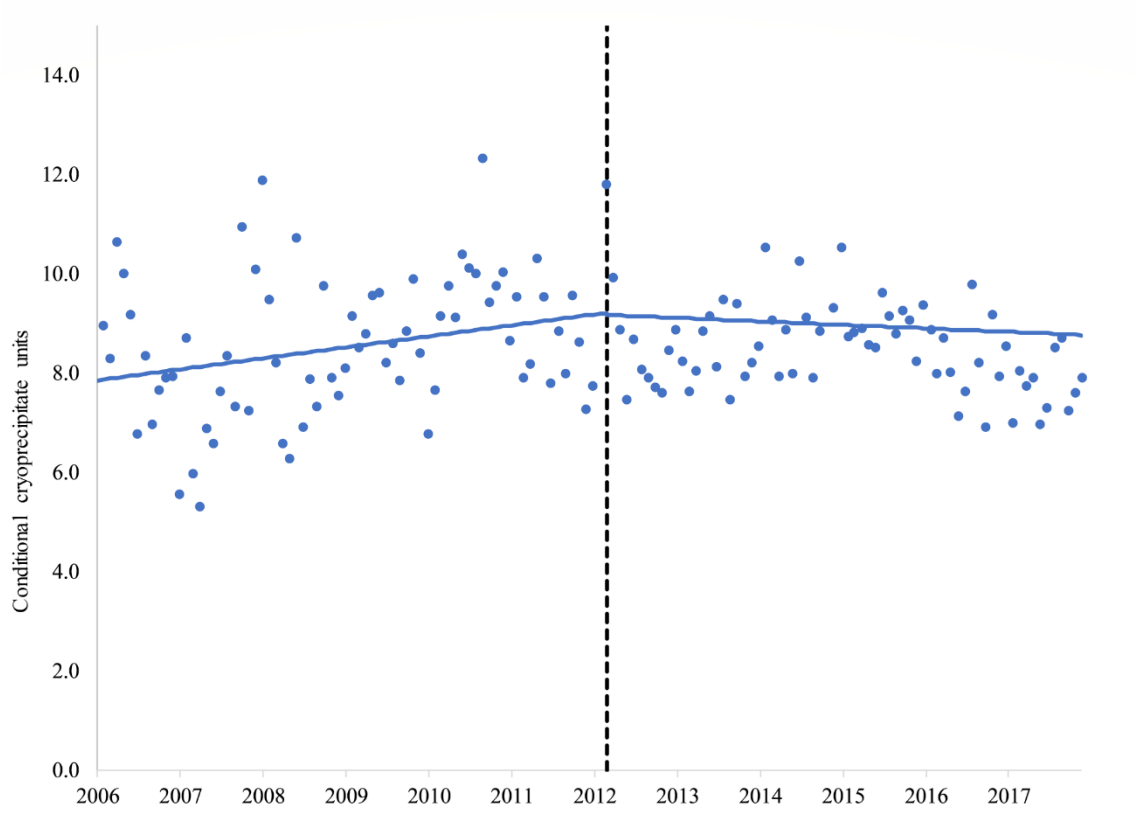

Figure A.3.11: Conditional Cryoprecipitate Units

Figure A.3.12: Total Fresh Frozen Plasma Units

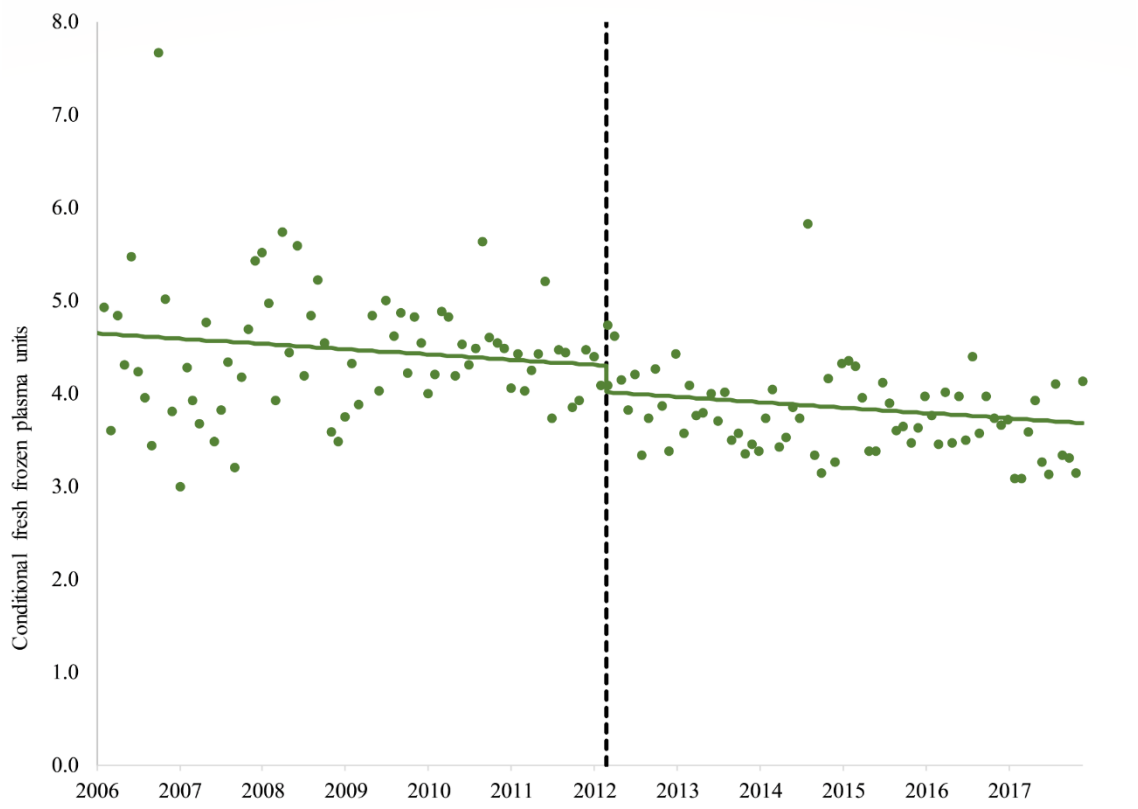

Figure A.3.13: Conditional Fresh Frozen Plasma Units

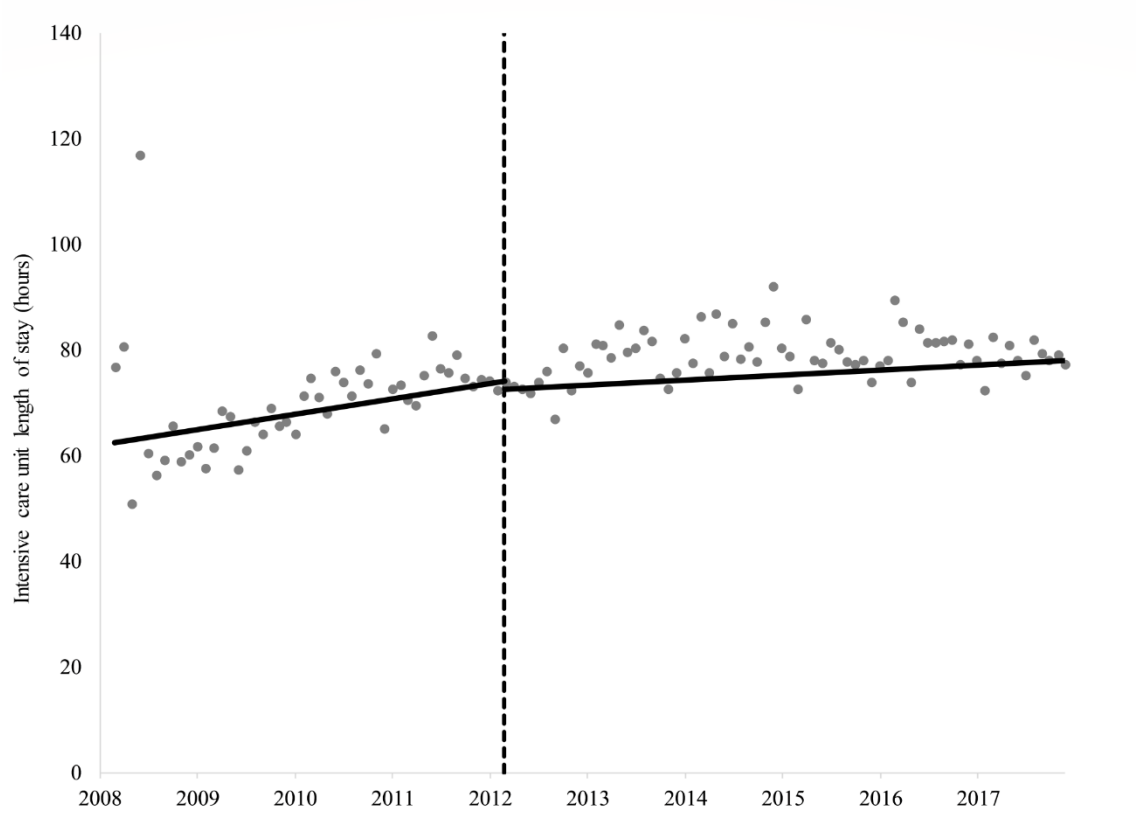

Figure A.3.14: Intensive Care Unit Length of Stay

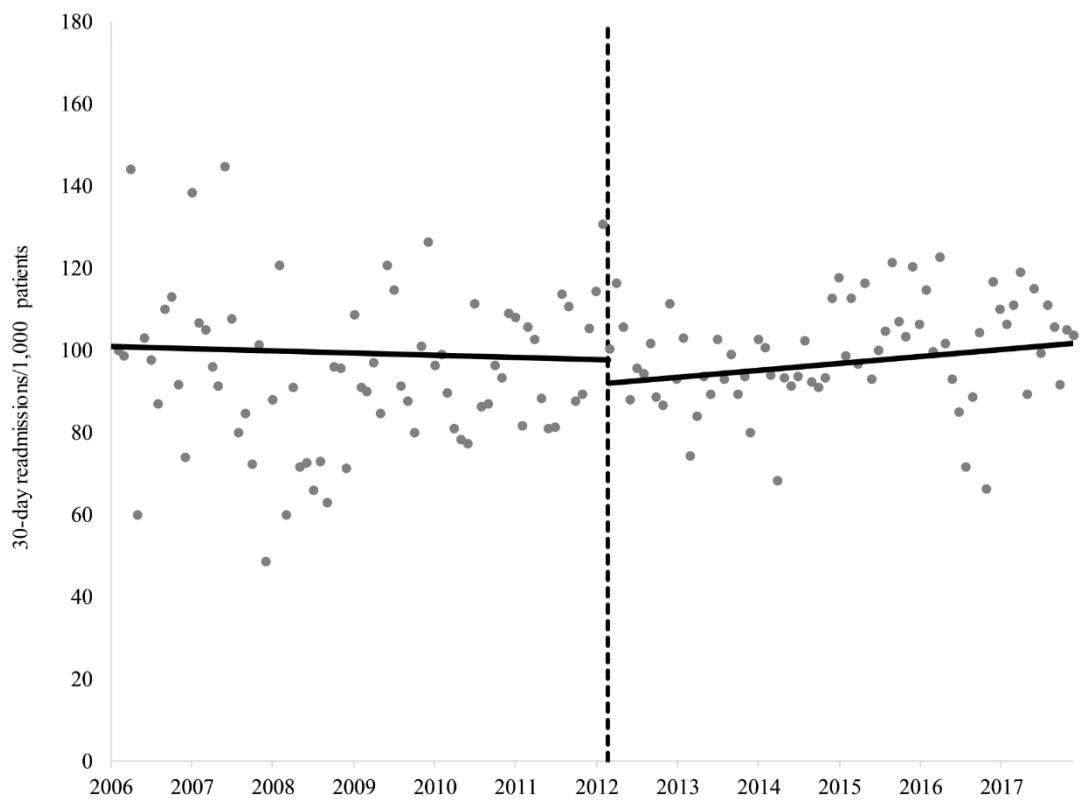

Figure A.3.15: 30-day Readmissions

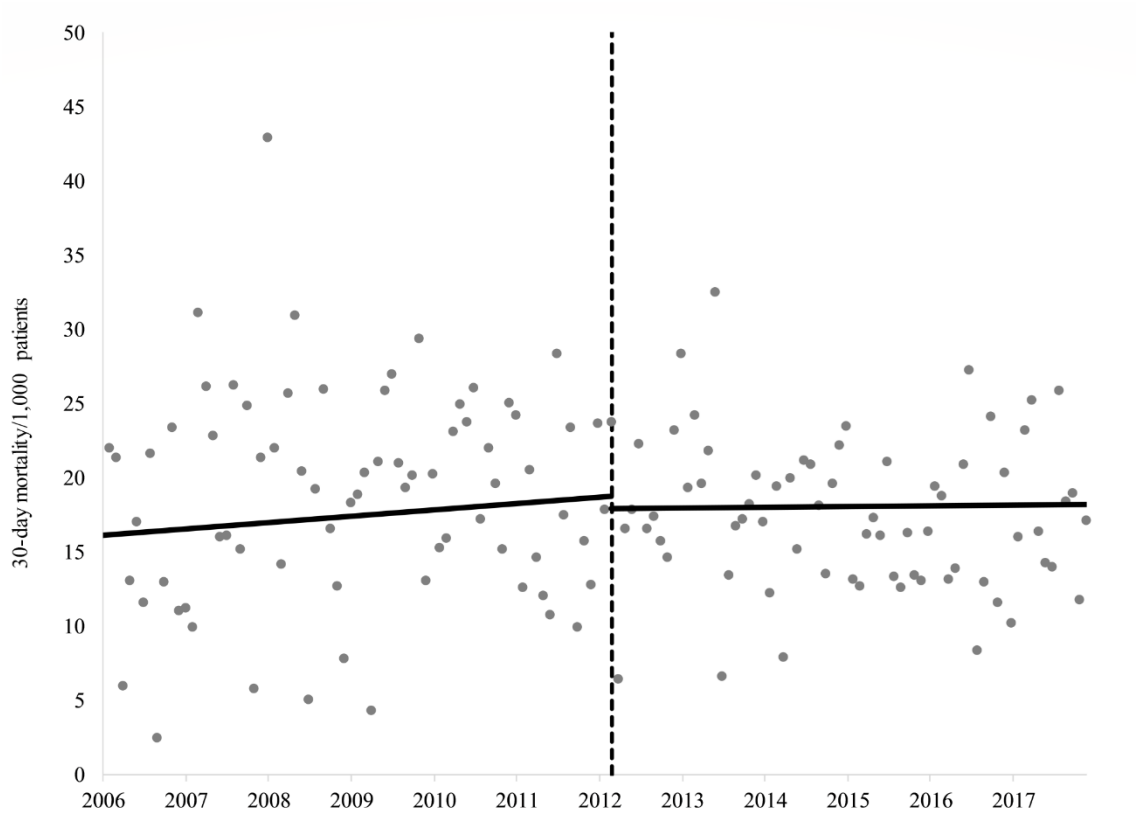

Figure A.3.16: 30-day Mortality

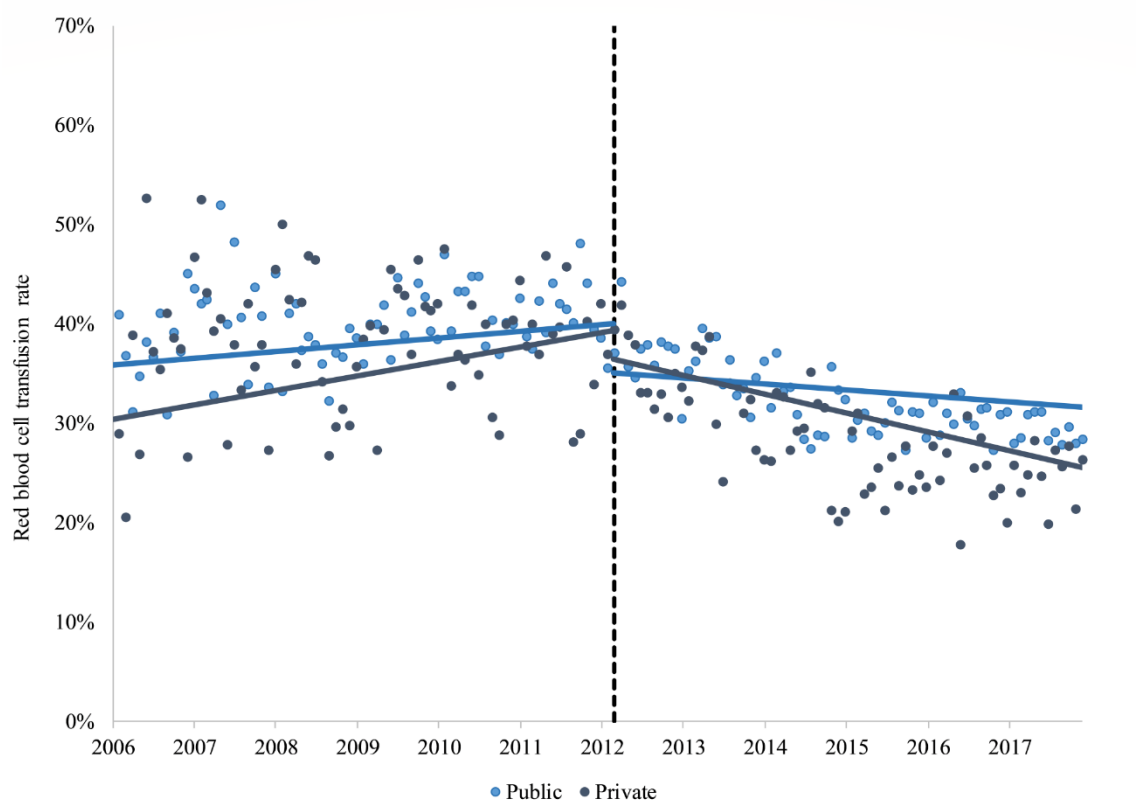

Figure A.3.17: Public vs. Private Hospitals: Red Blood Cell Transfusion Rate

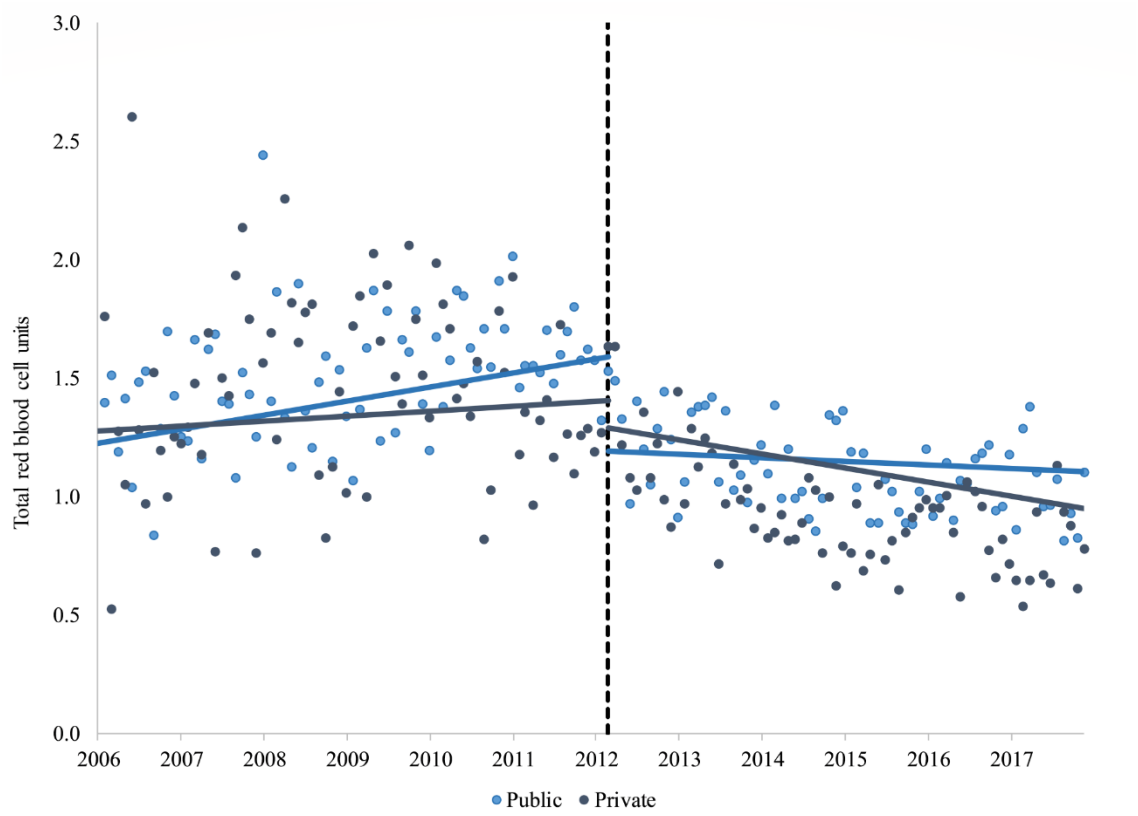

Figure A.3.18: Public vs. Private Hospitals: Total Red Blood Cell Units

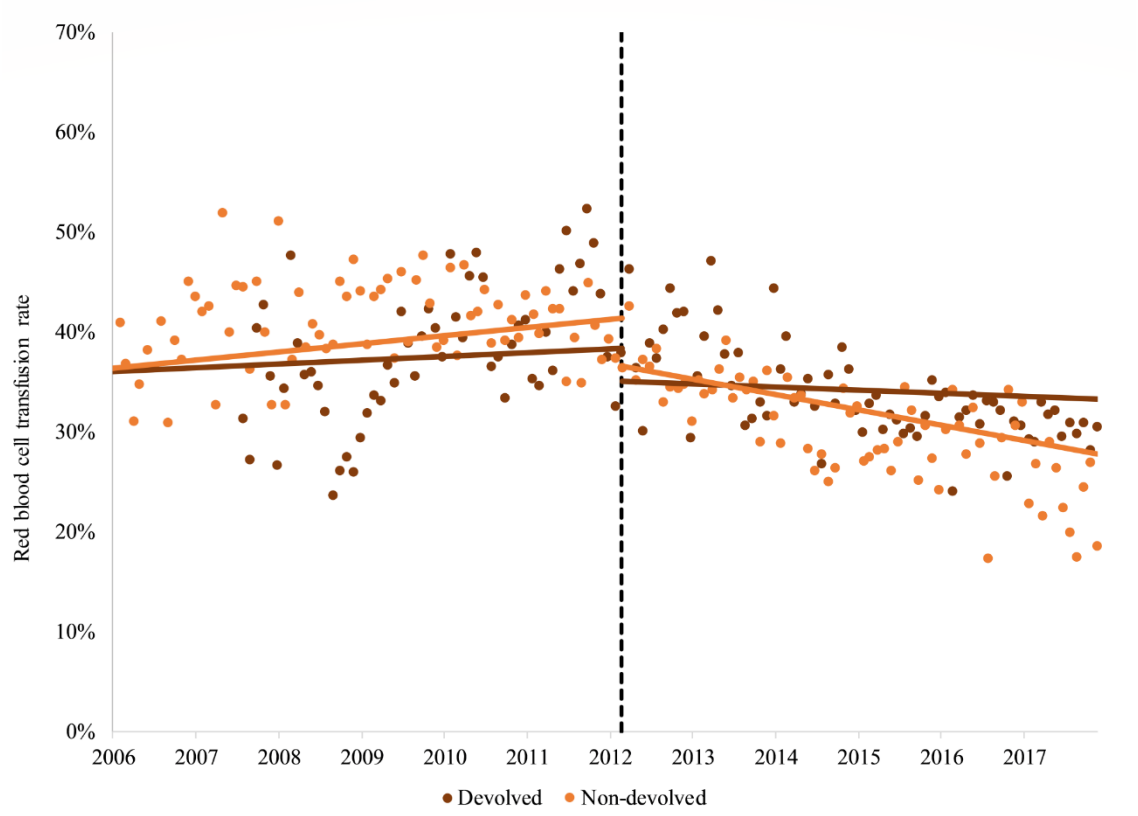

Figure A.3.19: Devolved vs. Non-devolved Hospitals: Red Blood Cell Transfusion Rate

Figure A.3.20: Devolved vs. Non-devolved Hospitals: Total Red Blood Cell Units

Figure A.3.21: Threshold Analysis: Red Blood Cell Transfusion Rate

Figure A.3.22: Threshold Analysis: Total Red Blood Cell Units

A.6 Appendix for Chapter 5

Table A.4.1: Patient Characteristics

	Pre-guideline		Post-guideline		p-value
	Missing	N=21,208	Missing	N=27,296	
Age - years, mean ± SD	<0.1%	66.0 ± 13.1	<0.1%	66.2 ± 13.1	0.064
Male - n (%)	<0.1%	15,045 (70.9%)	<0.1%	19,590 (71.8%)	0.045
BMI - kg/m^2, mean ± SD	0.3%	28.4 ± 5.5	0.2%	28.7 ± 5.6	<0.001
Cardiac catheterisation - n (%)	0.4%	18,870 (89.0%)	0.1%	24,854 (91.1%)	<0.001
Cardiogenic shock - n (%)	0.2%	98 (0.5%)	0.1%	122 (0.5%)	0.075
Congestive heart failure - n (%)	0.3%	4,777 (22.5%)	<0.1%	5,640 (20.7%)	<0.001
Cerebrovascular disease - n (%)	0.2%	2,415 (11.4%)	0.2%	2,647 (9.7%)	<0.001
Diabetes - n (%)	0.2%	5,957 (28.1%)	0.1%	7,855 (28.8%)	0.158
eGFR- mL/min/1.73m^2, mean ± SD	1.1%	4.21 ± 0.5	0.2%	4.29 ± 0.5	<0.001
Infective endocarditis - n (%)	0.2%	327 (1.5%)	0.2%	463 (1.7%)	0.184
Myocardial infarction - n (%)	0.3%	6,171 (29.1%)	<0.1%	7,068 (25.9%)	<0.001
Peripheral vascular disease - n (%)	0.2%	2,010 (9.5%)	0.2%	2,176 (8.0%)	<0.001
Respiratory disease - n (%)	0.2%	2,810 (13.3%)	0.2%	3,552 (13.0%)	0.282
Dialysis - n (%)	0.2%	300 (1.4%)	0.2%	346 (1.3%)	0.370
Intra-aortic balloon pump - n (%)	0.2%	464 (2.2%)	<0.1%	544 (2.0%)	<0.001
Previous cardiac surgery - n (%)	0.2%	4,075 (19.2%)	0.1%	5,533 (20.3%)	0.003
Angina – CCS classification - n (%)	0.6%		0.1%		<0.001
0		8,676 (40.9%)		13,112 (48.0%)	
1		2,475 (11.7%)		2,913 (10.7%)	
2		5,702 (26.9%)		6,654 (24.4%)	
3		3,143 (14.8%)		3,190 (11.7%)	
4		1,092 (5.2%)		1,391 (5.1%)	
Ejection fraction - n (%)	<0.1%		<0.1%		<0.001
Normal >60%		13,633 (64.3%)		18,323 (67.1%)	
Mild 46-60%		4,939 (23.3%)		5,857 (21.5%)	
Moderate 30-45%		2,023 (9.5%)		2,383 (8.7%)	
Severe <30%		613 (2.9%)		733 (2.7%)	
Coronary artery bypass - n (%)	<0.1%	13,989 (66.0%)	<0.1%	16,473 (60.4%)	<0.001
Valve surgery - n (%)	0.1%	9,657 (45.5%)	<0.1%	13,494 (49.4%)	<0.001

Table A.4.2: Regression Results

	Transfusion rate	
Overall monthly trend	0.001***	0.001***
	(0.000)	(0.000)
Change in monthly trend	-0.002***	-0.002***
	(0.000)	(0.000)
Age	0.001***	0.001***
	(0.000)	(0.000)
Male	-0.174***	-0.174***
	(0.005)	(0.005)
BMI	-0.005***	-0.005***
	(0.000)	(0.000)
Cardiac catheterisation	-0.057***	-0.047***
	(0.008)	(0.008)
Cardiogenic shock	0.239***	0.234***
	(0.030)	(0.031)
Congestive heart failure	0.044***	0.040***
	(0.006)	(0.006)
Cerebrovascular disease	0.029***	0.031***
	(0.007)	(0.007)
Diabetes	0.046***	0.048***
	(0.005)	(0.005)
ln(eGFR)	-0.209***	-0.210***
	(0.007)	(0.007)
Infective endocarditis	0.215***	0.221***
	(0.017)	(0.017)
Myocardial infarction	0.031***	0.030***
	(0.005)	(0.005)
Peripheral vascular disease	0.044***	0.043***
	(0.007)	(0.008)
Respiratory disease	0.028***	0.031***
	(0.006)	(0.006)
Dialysis	0.002	-0.001
	(0.021)	(0.021)
Intra-aortic balloon pump	0.214***	0.227***
	(0.017)	(0.014)
Previous cardiac surgery	0.051***	0.050***
	(0.005)	(0.005)
Angina – CCS classification		
1	-0.004	0.001
	(0.007)	(0.007)
2	0.005	0.008
	(0.006)	(0.006)
3	0.026***	0.027***
	(0.007)	(0.007)
4	0.038***	0.044***
	(0.010)	(0.010)
Ejection fraction		
Mild 46-60%	0.010*	0.007
	(0.005)	(0.005)
Moderate 30-45%	0.027***	0.025**
	(0.007)	(0.007)
Severe <30%	0.058***	0.054***
	(0.013)	(0.013)
Coronary artery bypass	0.120***	0.124***
	(0.006)	(0.006)
Valve surgery	0.119***	0.119***
	(0.006)	(0.006)
Constant	1.301***	1.136***
	(0.042)	(0.040)
Fixed effects	Hospital-Surgeon	Hospital only

***p<0.01, **p<0.05, *p<0.10, BMI = body mass index; CCS = Canadian Cardiovascular Society; eGFR = estimated Glomerular filtration rate; ICU = intensive care unit. Hospital-Surgeon fixed effects controls for all hospital and surgeon combinations.

A.7 Alternative Estimation Strategy

The estimation strategy for the base-case analysis comprised two separate one-way linear regressions with fixed effects at the hospital level and then at the hospital-surgeon level with all hospital-surgeon combinations having an estimated effect. With this approach, the hospital effect reflects a weighted average of the hospital-surgeon effects and thus neither approach attempts to distinguish between separate hospital and surgeon effects or responses.

A single two-way fixed effect linear regression containing both hospital and surgeons fixed effects simultaneously is an alternative estimation strategy that attributes any differences in the performance of surgeons that work across multiple hospitals as a relative hospital effect. This allows us to estimate not only the relative difference between hospitals in their effect (after controlling for their quality of surgeons) but also the relative difference between surgeons (after controlling for the quality of the hospitals they operate in). The disadvantage of the two-way fixed effect strategy is that when a hospital contains no switching surgeons we are unable to identify separate hospital and surgeon effects, as the hospital effects will be collinear with the surgeon effects. In addition, when one network of hospitals and surgeons have no connections with another network we are unable to compare across networks in terms of the relative surgeon and relative hospital effects.

We conducted an exploratory analysis using the two-way fixed estimation strategy to determine what additional inference can be made using this method. Using the same notation as the one-way estimation strategy our additional regression is as follows:

$$y_{ijt} = \beta X_{it} + \varphi M_t^0 + \gamma M_t^1 + s_k^0 + s_k^1 + h_j^0 + h_j^1 + \varepsilon_{ijt}$$

In order to perform comparisons on identical selections of patients we also estimate our main results using the one-way fixed effect model using the same hospitals within each network. We present the results for two networks of hospitals that contained switching surgeons – one pair of hospitals that contained the same three switching surgeons (Network 1) and a group of six hospitals that contained 23 surgeons, 6 of which operated across multiple hospitals within the cohort (Network 2).

One- and two-way fixed effect models were run on the subsamples of Network 1 and Network 2 surgeries separately. Controlled predictions of the pre- and post-guideline transfusion rates were obtained with variation across hospitals and across surgeons estimated as $\hat{\tau}^2$ from the random error model.

Table A.4: Network 1

One-way				Two-way			
Variation Across	Pre	Post	Change	Variation Across	Pre	Post	Change
Hospitals	0.001	0.005	0.004	Hospitals	0.000	0.003	0.003
Hospital-surgeons	0.017	0.004	-0.013	Surgeons	0.017	0.002	-0.015

For Network 1, which contained two hospitals, variation across hospitals controlling for surgeons (two-way) in the pre- and post-guideline periods was lower than the corresponding variation across hospitals (one-way). This suggests there has been some surgeon selection; inspection of the raw data indicates the surgeon with the lowest transfusion rate performed twice as many surgeries in one hospital than the other – creating variation across hospitals in the one-way model that is appropriately attributed instead to the surgeon in the two-way model. Variation across surgeons controlling for hospitals (two-way) is lower than the variation across hospital-surgeons (one-way) in the post-guideline period. While, the two-way model predicts that variation across surgeons after controlling for hospital has decreased significantly it also suggests that variation across hospitals after controlling for surgeon has marginally increased – this is due to the hospital with the lower pre-guideline transfusion rate experiencing a larger response to the guidelines.

Table A.5: Network 2

One-way				Two-way			
Variation Across	Pre	Post	Change	Variation Across	Pre	Post	Change
Hospitals	0.008	0.007	-0.001	Hospitals	0.005	0.003	-0.002
Hospital-surgeons	0.007	0.007	-0.001	Surgeons	0.004	0.002	-0.002

The findings are similar for the six hospitals in Network 2 with lower variation across hospitals controlling for surgeons (two-way) in both periods compared with variation across hospitals (one-way). Variation across surgeons controlling for hospitals (two-way) is also lower than variation across hospital-surgeons (one-way). Overall, the two-way model suggests that variation across hospitals after controlling for surgeons and variation across surgeons after controlling for hospitals has decreased.

That only a subset of the surgeons in our dataset switch hospitals precludes the ability to make a full comparison however, it is likely that our conclusions from the base-case analysis - the heterogeneous response across hospitals and surgeons correlated with pre-guideline performance and the reduction in variation in care would remain the same.

Addenda

B.1 Addendum for Chapter 4

B.1.1 OLS versus Logit

While linear probability models can produce individual predictions that are less than zero or greater than one, their coefficients often provide an accurate and robust estimate of the average marginal effect which is easy to interpret. Alternatively, coefficients from binary choice models such as the logit or probit do not have a direct interpretation and instead are usually presented as odds ratios. These non-linear models can also suffer from the inconsistent parameter problem which causes bias when a large number of fixed effects are estimated. In addition, for an ITS analysis the logit and probit models no longer assume a linear trend in the probability but instead assume a constant odds ratio trend (which translates into a non-linear trend in the probability). However, as long as the linear trend in the probability does approach a probability of zero or one then the trend from the linear probability model will approximate the trend from a non-linear model. The analysis of the dichotomous outcomes in Chapter 4 used a linear probability model estimated by ordinary least squares (OLS) regressions. The sensitivity of this modelling framework was assessed by comparing the predicted transfusion rates of the OLS analysis with those from an equivalent logit model.

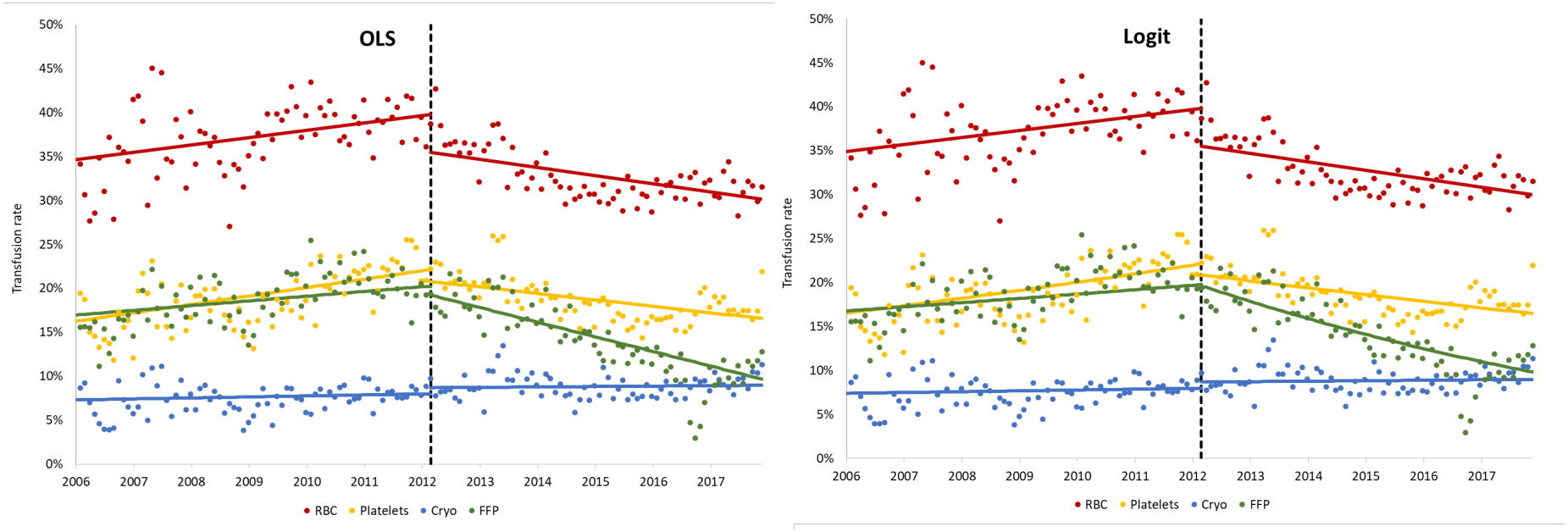

Figure B.1: OLS versus logit

Both the OLS and logit models presented in Figure B.1 include fixed effects for hospital. There appears to be only very small differences in the predicted transfusion rates for all blood products when comparing the OLS and logit models, providing assurance that our conclusions are robust to the functional form assumptions in this setting.

Commentary: Adjudicating a blood sport?

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Central Message

Following rules that govern blood transfusion might work.

See Article page XXX.

In this article, Irving and colleagues chronicle the effect of the implementation of blood management guidelines on blood product utilization.[1] The account adds to a growing body of evidence that suggests that implementation of blood management guidelines might significantly reduce utilization and, as in this account, hospital length of stay. Somewhat remarkably, however, there was no significant improvement in mortality, readmission rate(s), or intensive care unit length of stay. The study is sufficiently powered and draws upon a broad multistate denominator derived from a national data set representative of cardiac surgery patients treated at several hospitals, public and private, each subject to adherence to a single set of national guidelines. The account provides a somewhat stark contrast to reports from health systems such as that in the United States where, with the absence of a national health system, individual hospitals are not beholden to blood product transfusion practices stipulated by the federal government.

The strength of the conclusion is attenuated somewhat, however, by the absence of a suitable control group. This raises the potential for confounding as a direct result of the influence of external factors, independent of the guidelines. It is also worthy of mention that, aside from the guidelines themselves, governmental provisions allowing for monetary incentives to hospitals that show a surplus in annual blood budget(s), are a tacit endorsement of restrictive transfusion policies. Independently this serves undoubtedly, as a potent motivator. Whereas the authors might have addressed the broader support for restrictive blood management, they have also simultaneously, perhaps inadvertently, pointed out the need for an evaluation of perioperative practices that might themselves reduce transfusion needs. These include such methods as hemodilution, retrograde autologous priming, use of short circuit length(s), and intensive care unit anemia protocols among several others. In this vein, a broader multidimensional evaluation of blood usage will remain necessary. As such, blood management guidelines will likely remain a topical issue of vigorous debate.

Admittedly, the growing momentum of support for restrictive policies reads more like a referendum on physician decision-making rather than an unequivocal stance predicated on irrefutable evidence of oxygen deficit as the objective guide to transfusion. Indeed, decisions regarding transfusions as a whole continue to be driven by what might be deemed an emotional response to low hemoglobin level rather than objective metrics of physiological decline. This has been fueled further by the lack of consensus from meta-analyses, thus far.[2] As such, indication for transfusion solely on the basis of laboratory results will likely remain as much a behavioral as indeed a physiological science. In the interim, however, this report, founded upon a national set of guidelines, provides more evidence that adjudication and policy-making at the national level, replete with monetary incentives, might successfully influence and even reduce the utilization of blood products. On extrapolation, this might serve to reduce health care expenditure because, despite a lack of demonstrable effect on survival, the financial incentives and merits of cost reduction might independently promote the survival of the health system as a whole.

References

1. Irving, et al. Impact of patient blood management guidelines on blood transfusions and patient outcomes during cardiac surgery. *J Thorac Cardiovasc Surg*. 2019. XX:XXX-XXX.
2. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, et al. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. *Eur Heart J*. 2018;40:1081-8.

B.2 Addendum for Chapter 5

B.2.1 Data Window

In Chapter 5, 10-year data window was selected for the base-case analysis – 5 years before and 5 years after the publication of the PBM guidelines in March 2012. The sensitivity of the results to this decision was assessed by conducting an identical analysis, presented in Figure B.2 on a shorter, 6-year data window – 3 years before and 3 years after March 2012.

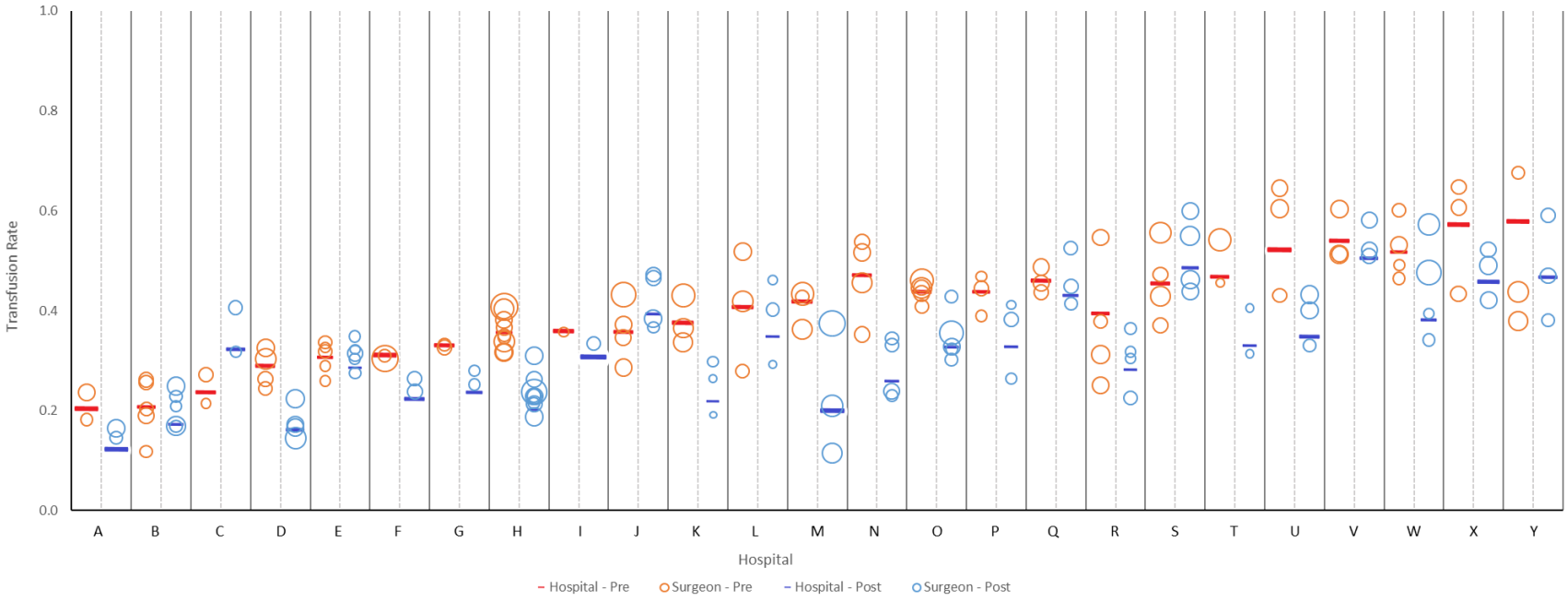

Figure B.2: 6-year data window

When reducing the data window from 10 down to 6 years, the number of surgeons who performed at least 50 surgeries in both the pre- and post-guideline periods falls from 88 to 86. Overall, reducing the data window does not impact the main conclusions that the variation across hospitals and within hospitals reduced after the publication of the PBM guidelines.

B.2.2 Post-guideline prediction month

The predicted RBC transfusion rate from surgeries occurring in different months will be affected by the significant pre- and post-guideline monthly trend identified in Chapter 4. Therefore, in Chapter 5 the hospital- and surgeon-level RBC transfusion rates were predicted at a consistent, fixed month rather than the actual month the surgery occurred. In the base-case analysis, for the pre-guideline predictions the fixed month was the last month in the period, just before the guidelines were published and for the post-guideline predictions the fixed month was the middle month of the 5-year post-guideline period. Given the increasing pre-guideline trend, the selection of the fixed month for the pre-guideline predictions appears to be appropriate. However, it would have been possible to also select the last month in the post period, rather than the middle month. The decision to use the middle month was made in order to take a conservative approach to estimating the impact of the PBM guidelines on the RBC transfusion rate. In order to assess the validity of this claim, Table B.1 presents a comparison of surgeon post-guideline RBC transfusion rate predictions taken at the middle versus the last month of the post-guideline period.

Table B.1: Comparing post-guideline prediction months

Surgeon RBC transfusion rate					
Prediction month	Mean	Lower 95% CI	Upper 95% CI	Min	Max
Middle month	32.5%	30.2%	34.9%	10.5%	60.1%
Last month	29.3%	27.0%	31.6%	7.4%	57.0%

Given the significant downward trend in the post-guideline period, predicting the RBC transfusion rate at the last month of the period uniformly shifts the predictions downwards. This confirms that the approach in the base-case analysis represents a conservative estimate of the reduction in RBC transfusion rate that may be attributable to the PBM guidelines.

Chapter 5 used variation in the RBC transfusion rate as the only outcome under evaluation. However, variation may exist in other important outcomes including the number of RBC units transfused – which is more closely aligned with resource use. The main analysis was performed using the number of RBC units transfused to confirm that the conclusions regarding the impact of the PBM guidelines on variation in blood transfusion practices remain consistent.

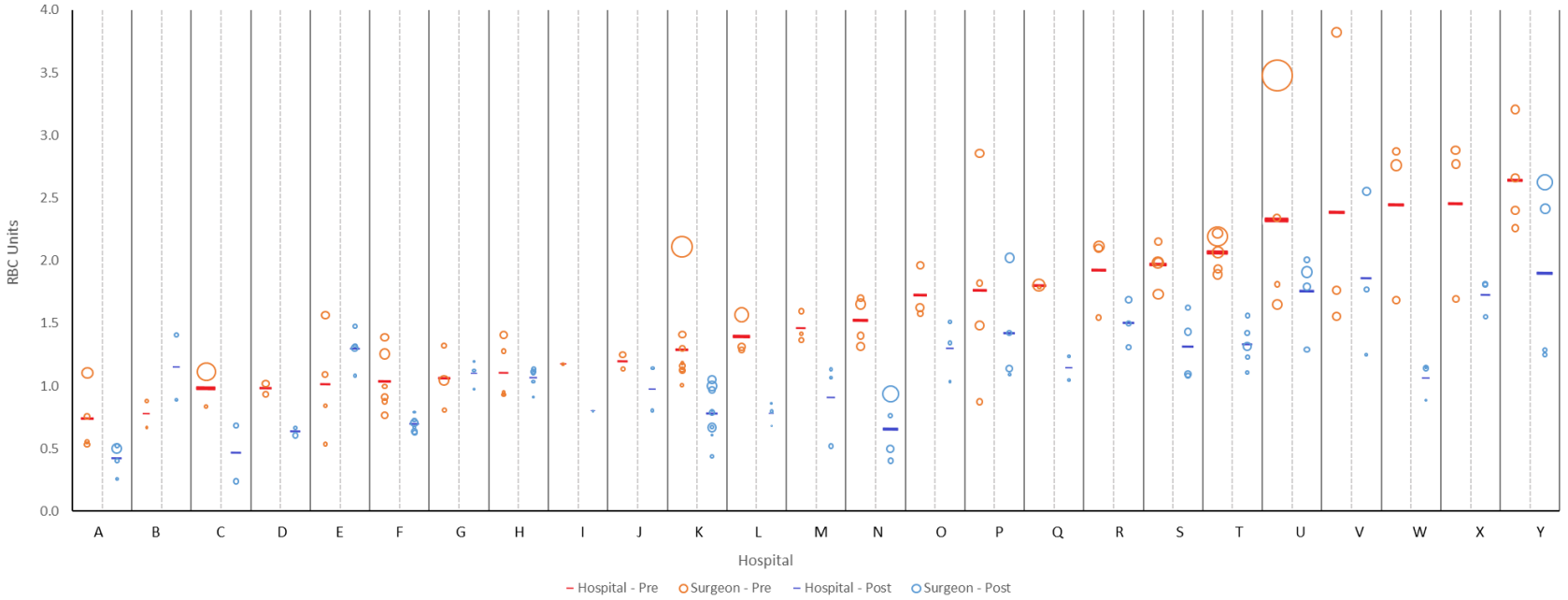

Figure B.3: RBC Units Outcome

Figure B.3 shows that when moving from the pre- to post-guideline period, variation across surgeons has generally decreased. Consistent with the RBC transfusion rate analysis, variation in the number of RBC units transfused across surgeons within hospitals as also decreased in most hospitals. Variation across surgeons as measured by $\hat{\tau}^2$ decreased significantly from 0.2928 in the pre-guideline period to 0.1168 in the post-guideline period.