Factors influencing variation in blood product usage: an international perspective

Stefan Laspina MD FFPath FRCPath

A thesis submitted in fulfilment of the requirement for the degree of Doctor of Philosophy (PhD)

Warwick Medical School, University of Warwick

March 2017

Table of Contents Page

Acknowledgements

I would like to thank my supervisor Professor Peter Spurgeon, for all the help, guidance, support and patience he has afforded. I also would like to thank Dr William Murphy, my co-supervisor, for his help and support and for being an inspiring mentor during my formative years.

I would like to thank my colleagues on the Board of the European Blood Alliance for providing me with information on red cell use in their country. I would like to thank Dr Liberato Camilleri and Dr Neville Calleja for statistical support and much more.

I would like to thank my work colleagues for providing cover while I worked on the thesis.

Finally I would like to thank my wife Mary-Ann and my children Karl and Lisa for always being there through thick and thin, and for their love and patience.

Declaration

This thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree.

All the work presented was carried out by the author except in the case outlined below:

Part of the data on regional use of red cells in Tables 3.7 – 3.14 were provided by colleagues from the European Blood Alliance as outlined:

- Denmark – data for 2015
- Finland – data for 2014
- Austria – data for 2013, 2014, 2015
- Switzerland – data for 2012. Colleagues in Switzerland also provided the corrected figures for the more in-depth analysis in Table 2.17
- Colleagues in France and Italy indicated sources for the data
- Colleagues in the UK and Belgium provided part of the data for their country

_____

Stefan Laspina

Abstract

Introduction and Aims

Despite the availability of evidence-based guidelines, blood transfusion, one of the commonest procedures in health care, manifests significant variation across different countries that appear to have comparable health systems. This is corroborated by extensive data on blood usage in coronary artery bypass graft surgery, a sentinel procedure, which also suggests that the variation may be related to institutional practice. Regional use of red cells within the same country, data for which had not yet been collated to date, was elicited, and it confirmed the same pattern of variation where the highest-using regions tend to transfuse double the red cells transfused in the lowest-using ones.

Methods

Since the reasons for it are largely unknown, analyses of available data from Australia, New Zealand, Canada, the USA, and 24 countries in Europe, were performed using linear correlation and regression analysis, to identify potential predictors and possible effectors of this variation.

Results

Apart from confirming a known demographic predictor, proportion of the population over 65 years ($p = 0.01$), another 4 predictors were identified including clinical activity as represented by coronary artery bypass graft surgery ($p = 0.001$) and health funding ($p = 0.007$), which together explained 70% of the variation in red cell usage. Similar regression models for platelets and plasma showed an R square value of 0.31 and 0.247 respectively.

The variation in blood product use did not correlate at all with health service outcomes and performance, but correlated quite tightly with markers of supply sensitive care making a strong case for unwarranted variation in blood transfusion. Red cell use, for example, correlated with the availability of diagnostic technology as represented, amongst others, by the number of MRI units ($r = 0.665$, $p = 0.001$). Moreover, it was shown that countries that use more of one product use more of the others. A relationship was also found between blood product usage and cultural constructs capturing the notions of professional uncertainty and difficulty with accepting new evidence.

Conclusions

Irrational and evidence-denying variation in blood transfusion practice exists and can be measured relatively easily. Comparison of clinical use of blood in discrete geographical regions may be useful as a general measure of the effectiveness of the implementation of different tools to improve practice, not just within the context of blood transfusion but in clinical practice in general.

Abbreviations

ABS	Australian Bureau of Statistics
ANVISA	Agencia Nacional de Vigilancia Sanitaria
APTT	Activated Partial Thromboplastin Time
ASBT	Australasian Society of Blood Transfusion
BSE	Bovine Spongiform Encephalopathy
CABG	Coronary Artery Bypass Graft
CBS	Canadian Blood Service
CDC	Center for Disease Control
CMS	Centers for Medicare and Medicaid Services
CNCRH	Conference Nationale des Coordonnateurs Regionaux d'Hemovigilance
CT	Computerised Tomography
DHHS	Department of Health and Human Services
DoH	Department of Health
EBA	European Blood Alliance
EDQM	European Directorate for the Quality of Medicines and Healthcare
EFTA	European Free Trade Association
EU	European Union
FFP	Fresh Frozen Plasma
GBD	Global Burden of Disease
GDP	Gross Domestic Product
HDI	Human Development Index
HL	Hodgkin's Lymphoma
ICU	Intensive Care Unit
IDV	Individualism vs Collectivism Index
IOM	Institute of Medicine
JRCS	Japanese Red Cross Society
MDS	Ministero Della Salute

MI	Myocardial Infarct
MM	Multiple Myeloma
MRI	Magnetic Resonance Imaging
NA	Not Available
NBA	National Blood Authority
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
OECD	Organisation for Economic Co-operation and Development
PBM	Patient Blood Management
PDI	Power Distance Index
PHE	Public Health England
PT	Prothrombin Time
QI	Quality Indicator
RC	Red Cells
SHOT	Serious Hazards of Transfusion
TIR	Transfusion Incident Reports
UAI	Uncertainty Avoidance Index
UNDP	United Nations Development Programme
vCJD	Variant Creutzfeldt Jacob Disease
WHO	World Health Organisation

Chapter 1

Introduction

1. Introduction

1.1 Background

As a result of the civil disasters of HIV and hepatitis C, transfusion medicine in Europe and elsewhere has led in the fields of governance and risk management in health care during the last 15 years. As a direct outcome of the tragedies of the 70's and 80's, the international community has brought to bear considerable pressure on Blood Establishments, the institutions responsible for the production of blood components for transfusion. This drive has effectively forced a total re-organisation of the service provided by these institutions. In Europe this led to the enactment of 4 European Union (EU) Directives in the field of blood transfusion (European Union, 2003; European Union, 2004; European Union, 2005a; European Union, 2005b). Consequently, large amounts of money have been spent on blood safety, and quality systems have been introduced in the vast majority of blood services. Moreover, haemovigilance, a system of nation-wide surveillance for complications associated with transfusion, an initiative taken by a number of countries on a voluntary basis, was also taken up by the EU Commission and transformed into a mandatory process. All this activity has therefore ensured that the blood products reaching hospitals are at a level of safety never present before.

Once the products reach hospital blood banks they are transfused to patients. This part of the process has undergone much less scrutiny and is very physician-dependent. Through the data generated by haemovigilance systems (Department of Health and Human Services, 2011; Japanese Red Cross Society, 2010; National Blood Authority, 2011; Williamson, 1998) the medical community has become even more aware that despite all the efforts to minimise risk, blood transfusion still carries a very specific known

complication rate, which does not even take into consideration other possible difficult-to-measure hazards such as transmission of novel infective agents like variant Creudtzfeldt Jacob Disease (vCJD).

All the Blood Services in Europe subscribe to best practice in Transfusion Medicine and to evidence-based use of blood products. Testament to this is the *Manual of Optimal Blood Use* (McClelland *et al.*, 2010), the main deliverable of a health-related project funded by the EU Commission. It is a resource containing information and practical materials to deliver quality assurance throughout the clinical transfusion process; to promote best practice in blood transfusion; and to guide with compliance with relevant EU directives. It was written by a group of experts from the European Blood Alliance (EBA), an association of not-for-profit Blood Establishments, with 25 members from within the European Union and 2 members from European Free Trade Association (EFTA) states. The board of the EBA meets twice a year and is composed of the national medical director and the chief executive of every Blood Establishment represented. The author is one of the two members representing Malta on the Board. This manual is complemented by a large number of guidelines on blood component use that have been published in most developed countries. All this has been put in place in an effort to guarantee standard practice.

Establishing uniform best practice has however been quite difficult. A cursory look at a simple statistic such as the number of red cells transfused per thousand inhabitants across European countries, shows that there is an extensive variation (Janssen *et al.*, 2011). A number of studies on sentinel surgical procedures such as coronary artery bypass graft surgery have also shown striking differences in blood product use even between institutions within the same country (Surgenor *et al.*, 1998). The nature of this variation is mostly unknown bar a couple of papers whose authors have argued that it may be dependent on demographic differences (Ali *et al.*, 2010; Seifried *et al.*, 2011). The thesis will probe this variation extensively in order to better

define the true core issues, as any variation in practice, especially as apparently extensive as this, is bound to have a significant impact on the appropriateness of blood product use.

Conclusions may be drawn to the effect that local tradition in the practice of transfusion medicine is most likely the one single factor that mostly contributes to the variation in blood component use (Jin *et al.*, 2013). In many hospitals, it is left to the individual clinicians and their teams to adopt or discard practice based on guidelines as they please. In many other hospitals, it is the remit of the transfusion laboratory to be the gatekeeper for these blood products (Pena & Dzik, 2014). Within yet other systems, what started off as a haemovigilance exercise, i.e. a process for collating and analysing transfusion reactions, has slowly transformed itself into a surrogate system for optimisation of the use of blood components. As part of this haemovigilance drive, nurses were recruited to posts to perform the associated tasks. These members of staff have gone on, in some cases, to take on the mantle of educationists / trainers in the use of blood products (Freedman *et al.*, 2008). Also, mainly in hospitals in the United Kingdom (UK) and Ireland, due to the National Health Service (NHS) Better Blood Transfusion Initiative, it became common to have a Hospital Transfusion Committee involved in the governance of blood product utilisation (UK Department of Health, 2007). This latter practice was also adopted by the World Health Organisation (WHO) in its guidance on blood transfusion as a specific recommendation (World Health Organisation, 2010).

Anecdotally, change in practice in Transfusion Medicine has been mostly effective in hospitals where Transfusion Medicine 'champions' have emerged. These leaders, mainly clinicians, mostly Transfusion Medicine Specialists / Haematologists or Anaesthetists, have made a difference within their hospital and even abroad, as they have pioneered systems within their hospitals which went on to be used internationally (Murphy, 2012a; Rehm *et al.*, 1998). This set of events over the past 20 years has presented both the opportunity

and the need to test the hypothesis that a champion or leader in a hospital setting can or must be engaged to ensure that internationally established norms of best practice are employed, and that without such, money, time and opportunities are wasted. In other words, that in order to complete the 'Vein to Vein' process in Transfusion Medicine and to complement the huge efforts made by the blood establishments, a Transfusion Medicine leader / champion must be engaged by hospitals where blood products are used with the specific role of implementing Patient Blood Management (PBM) strategies.

1.2 Scope of Thesis

The scope of the project has been to use transfusion medicine practice, where motive (history of previous disasters from HIV and hepatitis C among other problems), opportunity (differences in current practices across Europe within a fairly small professional community) and means (excellent history of collaboration and high quality information sharing within the European and indeed the global transfusion community) exist, to explore the nature of international and local variation in practice in blood product usage and to try to understand the different parameters contributing to the significant variation therein. It is probably pertinent to mention that the spirit of collaboration on an international level between Blood Transfusion Services is really quite significant and possibly unique within the different disciplines in medicine.

More specifically the project will look at

- The historical context to this variation and the continued threats to the blood supply
- A review of the literature and of available data sources highlighting variation in blood product usage

- Securing and analysing additional data that confirms this variation in practice
- The relationship between this variation and other measures of health care
- Effectors of variation in different countries

In summary, the Doctoral thesis will seek to unravel the reasons behind the variation in practice in blood product usage and to confirm the necessity of the implementation of Patient Blood Management strategies within hospitals to ensure the achievement of appropriate blood use.

Chapter 2

Context and Threats

2. Context and Threats

2.1 Historical Context

Blood has been surrounded by a mystical aura since the time of antiquity (Greenwalt, 1997). This sentiment persevered through the ages and, though its history is also associated with tragedy, there still lingers a strong belief in its inherent power to do good. Despite the soaring levels of modern research activity and the strong shift to evidence based practice, the use of blood components still seems to be resistant to recommendations on appropriate use as evidenced by the apparent large differences in practice across countries (Cobain *et al.*, 2006) and even across institutions within the same country (Stover *et al.*, 1998). The modern history of blood transfusion owes its origin to three important developments at the turn of the previous century.

2.1.1 Developments that allowed safe practice of blood transfusion

1. The erstwhile extremely complicated and dangerous transfusion procedure, which required that the radial artery of the person donating blood, and the proximal end of a large superficial vein of the person receiving the blood, were dissected out and attached to each other over a canula as the arms lay parallel to each other, was simplified by the design of specific apparatus. In 1913, Dr Edward Lindeman in New York thought of using paraffin-lined syringes containing anticoagulant and paraffin-lined jars and needles obviating the need to cut open the patients' and donors' arms (Pair, 1929). This strategy was further improved upon by Dr Lester J Unger, who

designed a stopcock, and connected the two needles with rubber tubing and a four-way valve, thus enabling the drawing of blood from the donor and its re-direction into the recipient to occur uninterruptedly.

2. The second development was the determination of the appropriate concentration of anticoagulant that would allow physicians enough time to perform the transfusion process, beyond the three to five minutes it took for the blood to clot and block their needles and tubes. Citrate had a long-standing history as a superior anticoagulant used in laboratories but the 1% concentration at which it was used was extremely toxic. Dr Richard Lewisohn, a physician in Mount Sinai Hospital in New York, showed that a concentration of 0.1% was perfectly adequate to maintain anticoagulation but low enough not to precipitate any harmful events (Lewisohn, 1916).

3. Karl Landsteiner, a German physician, made the third and most significant contribution for which he won the Nobel Prize in 1930 (www.nobelprize.org/nobel_prizes/medicine/laureates/1930/). In his haemagglutinin experiments performed in his laboratory in 1900 using blood from 6 individuals including his own, he showed that antibodies present in serum combined to the homologous antigen (Landsteiner & van der Scheer, 1924). On the basis of his results he deduced three blood groups which he designated A, B and C (later changed to O). The fourth group, AB, was discovered by his colleagues some time later. This allowed for the performance of crossmatch tests that reduced the occurrence of acute haemolytic post-transfusion reactions from 35% to zero.

2.1.2 Universal availability

Though during the First World War there was some use of blood, albeit in a limited way, it was the Second World War that really gave the necessary impetus for the development of the logistical operations of blood collection, storage and transport with ad hoc blood banks being established in close proximity to the battle front (Maycock, 1940). Inevitably, its use in these circumstances endowed blood with an almost supernatural aura as the article written in the New York Times by Marine Corps correspondent Ralph W Myers attests: "The primary item in each Medical Corps man's front line survival kit, whole blood …. brought a new smile to the lips and blood shot eyes of overworked Navy Doctors in the forward areas. In a few minutes the wine-colored bottles were held aloft above the prone bodies and the stuff was doing its miraculous work" (Myers, 1945). Brigadier General Doug B Kendrick, the US army's transfusion chief in his book Blood Program in World War 2 highlights a comment made by Carl Mydans in his book 'More Than Meets The Eye', on "combat medics on bouncing jeeps who … kneeling and balancing and clinging miraculously with one arm, raised the other higher, as one would a torch, holding a bottle of plasma, pouring life into a broken body. I think I have never seen a soldier kneeling thus who was not in some way shrouded with a god-like grace and who did not seem sculptured and destined for immortality" (Kendrick, 1964).

2.1.3 Serious set-back

A very powerful symbolism became attached to the use of blood and its products and this persevered well into the unfortunate subsequent era of hepatitis and HIV transmission. The fault for these tragic developments, mainly associated with infusion of fractionated blood products, as starkly exemplified by one particular group of patients – people with haemophilia, was laid squarely at the door of transfusion services.

Cryoprecipitate, a white residue that forms in a blood bag after frozen plasma is thawed slowly at 4^{o}C, was discovered in 1965 in Stanford University (Pool & Shannon, 1965). This was used as treatment for people with haemophilia on account of its concentration of coagulation Factor 8. A further development in the late 60's saw thousands of units of plasma being pooled to make large amounts of cryoprecipitate which was then further processed to make highly concentrated Factor 8 (Brinkhous *et al.*, 1968) which could be carried around easily and injected using a syringe, a change that liberated people with haemophilia from their total dependence on hospitals. In order to satisfy the consequent high requirement for this product, paid donations were resorted to by companies in the United States of America (USA). Low income and marginalized groups were highly represented in this particular donor population (Seeff, 1988). Homosexual men also became an important source since drug companies valued their plasma for hepatitis antibodies and were thus unconsciously selectively including plasma from high-risk groups (McHenry & Khoshnood, 2014). Though originally most blood services in Europe were self-sufficient, once the demand for these products exploded in the late 1970's, many nations imported these plasma derivatives from the USA, as did countries from the rest of the world, including Japan.

In the first half of 1982, three men with haemophilia contracted *Pneumocystis carinii* pneumonia. This condition had recently become prevalent in previously healthy homosexual men. Specialists within the Centers for Disease Control and Prevention (CDC) in the USA became suspicious that some novel causative virus was being transmitted by blood (Centers for Disease Control and Prevention, 1982). However, it was only in March 1983 that the Public Health Service of the USA issued recommendations related to AIDS and blood donation (Centers for Disease Control and Prevention, 1983). Significantly, a resolution voted on by the World Haemophilia Federation in June 1983 stated that 'There is insufficient evidence to recommend, at this time, any changes in the treatment of haemophilia, therefore present

treatment should continue with whatever products are available' (Starr, 1998). Many countries took this to mean unlimited use of Factor 8!

Though evidence showing that heat treatment inactivated the virus was reported in August 1984 (Evatt, 2006), and a new screening test for what was then known as HTLV III became available in the USA in spring 1985 (Centers for Disease Control and Prevention, 1986), these precautions were not universally applied. A number of patients, both ones with haemophilia and whole blood recipients, were infected due to the inertia of governments / transfusion services which failed to adopt these measures, and other simple interventions such as questionnaires delving into donor behaviour. Lawsuits were instituted in a number of countries claiming negligence and a small number of blood service medical personnel were very publicly indicted for crimes related to HIV contamination. Some were convicted and jailed. Twenty-two countries including most of Europe, Canada and Japan established funds to compensate infected recipients.

The result of all this in the subsequent years has been a concerted effort by the medical and pharmaceutical communities to totally sanitise blood products. No expense was spared to institute very robust testing for known infectious diseases with some authors claiming that, with the ever-decreasing potential risk for transmission through transfusion, this has gone well beyond reasonable proportions (Davidson *et al.*, 2011; Marshall *et al.*, 2004), an opinion not necessarily universally endorsed (Murphy, 2012c).

2.2 Continued Threats to Supply of Blood

2.2.1 Novel transmissible agents

Variant Creutzfeldt-Jakob Disease, a new form of transmissible encephalopathy was first described in 1996 (Will *et al.*, 1996). All 6 patients

affected had a specific neuropathological profile that was distinct from classical CJD. Studies showed that these features were similar to those produced in macaques inoculated by bovine spongiform encephalopathy (BSE) (Lasmezas *et al.*, 1996), an epidemic condition that had peaked in UK cattle in the early 1990's. In 1998 an independent risk assessment was commissioned by the UK Health Department to assess the risk of transmission of vCJD through transfusion and to make recommendations to mitigate this risk (Comer & Huntly, 2003). Testing for this potentially transmissible agent was not an option. On the basis of the precautionary principle a number of measures were adopted primarily by the UK and Ireland (Murphy, 2013; Thomas *et al.*, 2013); but also by most other countries where a ban was introduced on blood donors who had resided in the UK for a cumulative period of more than six months between the years 1980 and 1996. Despite these measures, in 2004 the first case of transfusion transmitted vCJD was reported in the UK (Llewellyn *et al.*, 2004). vCJD has not turned out to be of the epidemic proportions originally feared (Ghani *et al.*, 2000); 178 cases in the UK and 53 in the rest of the world (The National CJD Research & Surveillance Unit, 2017) and only 4 cases have been transmitted through transfusion. However at the time of discovery and immediately subsequent to that, it inevitably raised past spectres and spurred much activity that was specifically targeted. A realization did however start to set in that the greatest protection from this and from any future threats from novel transmissible agents was in fact one of the least expounded upon strategies - that of optimizing blood use i.e. only appropriate transfusions should be administered (Ludlam & Turner, 2005).

2.2.2 Cost issues

In this context it would also be appropriate to highlight the issue of cost, a major concern of hospital administrators who are constantly in search of additional savings in an effort to satisfy budgetary demands. Blood product

usage like every other in-patient treatment modality has come under scrutiny, and focus has been strongly re-oriented towards appropriate use.

The cost of healthcare has continued to spiral upwards in the last few years. The 2011 edition of the Organisation for Economic Co-operation and Development (OECD) publication 'Health at a Glance' reports that, on average, per capita health spending has risen in real terms by four percentage points annually between 2000 and 2009 (Lafortune & de Looper, 2011). The United States continues to outspend all other countries by a wide margin with health care spending having increased from $1.8 trillion in 2004 to $2.6 trillion in 2010 and is projected to grow to $4.6 trillion in 2020, comprising 19.8% of GDP (Centers for Medicare and Medicaid Services, 2009). These figures have, of necessity, forced governments to rethink the way health care provision is delivered. In the UK for example, the structure of the NHS will be altered by the setting up of an independent commissioning board and the abolition of strategic health authorities and primary care trusts, and by the use of markets instead of targets to drive improvements in performance (Ham, 2010). The price of blood products has also followed the same trend. According to a recent trans-national appraisal, the population weighted mean cost of transfusing 2 units of red cells in Western Europe was estimated at around €900, a significant burden (Abraham & Sun, 2012). An analysis of the transfusion process in the United States wherein each step was mapped out, has shown that the full cost of a red cell transfusion to a surgical patient is $1148 and each transfusion episode costs $3433 when one takes into consideration also the indirect costs (Shander *et al.*, 2009). Though not necessarily a universally held view, some recent publications have repeatedly argued that further application of testing procedures to continue to improve blood safety have gone far beyond what would rationally be expected in cost-effectiveness terms (Davidson *et al.*, 2011). Given the already increasing pressures on hospitals to maintain their spending within budgets and the evident financial burden that can be attributed to transfusion, it is understandable that cost and the savings that can be made

through eliminating unnecessary transfusions have become an issue requiring attention.

2.2.3 Decrease in blood supply

A number of publications have alerted the transfusion community to the effect of changing society demographics on the blood supply. Shortages have been forecast and potential remedies, some quite drastic, have been suggested. Ali et al, in an analysis of the Finnish Red Cross Blood Service national database, suggested that in the future unprecedented measures, such as reversing some donor deferrals, and hence altering the safety profile of the transfused blood, or else shifting blood around from country to country, therefore risking higher rates of transfusion transmissible diseases in some countries on account of different epidemiological backgrounds, should be taken to meet the growing requirement (Ali *et al.*, 2010). They came to this conclusion after simulating the red cell usage in different age groups in Finland upon the population demographics of other countries and projected that into the future on the assumption that Finish practice in transfusion medicine was entirely appropriate. According to their projection, by 2015 all countries would have been using more than 40 units per 1,000 population and by 2025 that would have climbed to above 50 per 1,000 population in most countries evaluated. This prediction came on foot of an earlier publication from Germany that studied Mecklenburg-West Pomerania as a model region for the rest of Europe (Greinacher *et al.*, 2007). The authors concluded that a shortfall of a little more than 30% in red cell provision would occur and this was primarily due to changes in demographics. This projected trend seems to have been acknowledged in different countries (Currie *et al.*, 2004; Seifried *et al.*, 2011; Vamvakas & Taswell, 1994). These projections were based entirely on the transfusion medicine practice current at the time of publication. The whole argument about appropriateness of use was not discussed. Though, soon enough, a few dissenters did voice their doubts about this trend as they started bringing into play other

considerations apart from the aging population and the disproportionate use of blood in this fraction of the population (Benjamin & Whitaker, 2011). A publication from the Netherlands highlighted that more variables need to be taken into account, such as potential changes in clinical use, apart from population demographics (Borkent-Raven *et al.*, 2010). Neither has the trend in Meckleberg-West Pomerania been borne out as predicted (Greinacher *et al.*, 2016).

2.3 Conclusion

It is evident from the above that unnecessary transfusions, carrying risk without benefit, must be avoided. Tailoring the use of blood components to the patient's specific requirements is the single most effective method of ensuring optimal treatment while eliminating the risk associated with undue use and at the same time improving equity of access to a limited blood supply whilst reducing the cost footprint of this treatment modality (Murphy *et al.*, 2011; Seifried *et al.*, 2011). A large effort to address this began in the 1980's and continues up to the present. Large differences in usage of blood transfusion have evolved in different countries with similar economies and levels of health care. Germany uses twice as many red blood cells per capita as the Netherlands (Janssen *et al.*, 2011), for example, without clear benefit or disadvantage; the United States transfuses 30% more red cells as Canada in very similar clinical systems (Canadian Blood Services, 2010; Department of Health and Human Services, 2011; Hema-Quebec, 2010). This phenomenon – variations in practice where no clear reasons exist to account for the variations - provides an opportunity to explore the underlying forces at work in apparently geographically defined irrational clinician behaviour in the presence of clear evidence of risk and benefit, and to develop a measure to analyse the effects of measures to change such behaviours.

Chapter 3

The Evidence for Variation in Blood Transfusion Practice

3. The Evidence for Variation in Blood Transfusion Practice

3.1 Evidence in the Literature

As explained in the previous chapter, since its inception, blood transfusion, has been largely considered a benign form of treatment. Trials to establish appropriate blood product usage under different clinical scenarios were not performed at the outset as would normally happen with more modern new treatment modalities. In many circumstances, blood was considered to be a lifesaver and therefore, most naturally, *more became better*. Patients would be transfused to as close to a *normal range* as possible. It was in fact commonplace for physicians to use a transfusion trigger for red cells of 10mg/dL. In the same way patients were transfused platelets to counts well beyond $50x10^9$/L or $100x10^9$/L, and plasma was often used as a volume expander, all practices now labelled as inappropriate. It was only in 1999 that the first seminal trial held by Hebert and co showed unequivocally that *more is in fact worse*, with regard to red cell transfusion in patients in an Intensive Care Unit (ICU) setting (Hebert *et al.*, 1999). Since then, other publications have shown this in a number of different scenarios (Table 3.1) (Carson *et al.*, 2011; Cooper *et al.*, 2011). Parallel publications could be highlighted with regards to platelet and plasma use (Slichter *et al.*, 2010; Williamson *et al.*, 1999), even though less comprehensively than has been the case for red cells.

First Author / Year	Name of Trial	Clinical Setting	Transfusion Trigger (mg/dL)	No of Patients
Hebert 1999	TRIC	Adult ICU	7 vs 9	838
Kirpalani 2006	PINT	Infants < 1Kg	10 vs 12	457
Lacroix 2007	-	Paediatric ICU	7 vs 9.5	637
Hajjar 2010	TRAC	Cardiac Surgery	8 vs 10	502
Cooper 2011	CRIT	Acute MI	8 vs 10	45
Carson 2011	FOCUS	Hip Surgery	8 vs 10	2,016
Villaneuva 2013	-	UGI bleed	7 vs 9	921

Table 3.1: Randomised control trials involving a variety of patient and clinical settings, studying transfusion triggers. Adapted from (Pena & Dzik, 2014)

A number of evidence-based guidelines on appropriate use of blood components were also published in various countries and were widely disseminated for local adoption within hospitals (Australasian Society of Blood Transfusion, 2001; Crosby *et al.*, 1997; Murphy *et al.*, 2001). Despite this wave of mostly similar guidelines with almost identical recommendations, the usage of all three blood components still continued to vary widely (Gombotz *et al.*, 2014; Jin *et al.*, 2013; Likosky *et al.*, 2014; McQuilten *et al.*, 2014; Mitra *et al.*, 2015; Norgaard *et al.*, 2014).

These differences may be analysed by looking at transfusion practices surrounding a very well defined sentinel surgical procedure that is highly standardised across health care systems, such as coronary artery bypass graft (CABG) surgery. CABG continues to be a procedure with one of the heaviest usage of blood products. Around 20% of blood transfusions in the United States are associated with this type of surgery (Snyder-Ramos *et al.*, 2008; Stover *et al.*, 1998).

3.1.1 Variation in blood usage in coronary artery bypass grafting

In the last 25 years a number of studies evaluating blood use in CABG surgery have shown a significant variation of blood product use both within and across a number of countries (Andreasen *et al.*, 2007; Bennett-Guerrero *et al.*, 2010; Gombotz *et al.*, 2014; Goodnough *et al.*, 1991; Jin *et al.*, 2013; Likosky *et*

al., 2014; McQuilten *et al.*, 2014; Snyder-Ramos *et al.*, 2008; Stover *et al.*, 1998).

In 1991 Goodnough et al performed a study reviewing blood use in 30 consecutive adult patients undergoing first-time elective CABG surgery, in 18 institutions in the USA. They found that the number of patients transfused varied between 17% and 100% (Goodnough *et al.*, 1991) in different institutions. A further study involving 24 academic institutions, each reviewing between 100 and 108 randomly selected patients who underwent CABG surgery, concluded that blood use in 713 low-risk patients varied between 27% and 92% (Stover *et al.*, 1998). A large review of blood product use involved 82,446 patients undergoing isolated primary CABG operations using a cardiopulmonary bypass machine, performed between January 1st 2008 and December 31st 2008, in 408 hospitals performing at least 100 eligible on pump CABG operations per year. This study showed a frequency of blood transfusion rates ranging from 7.8% to 92.8% for red cells, 0% to 97.5% for fresh frozen plasma and 0.4% to 90.4% for platelets (Bennett-Guerrero *et al.*, 2010). A more recent study also showed significant variability in red cell usage (7% - 77%) and in usage of fresh frozen plasma (1% - 31%) and platelets (1% - 38%) (Jin *et al.*, 2013). Likosky et al studied 11,200 patients undergoing CABG who received 2 or less red cell units (low-volume transfusion). The hypothesis was that in this group, since no emergency was involved, decisions could be made in a more calculated fashion and consistency was more likely. However usage varied between 9.1% and 31.7% across 56 centres (Likosky *et al.*, 2014). A study in Australia which recruited 24,222 patients across 25 centres showed similar variation (McQuilten *et al.*, 2014).

In Europe this has been echoed by similar studies, including one in Denmark in four public, university-affiliated hospitals that between them perform 77% of all CABG operations in that country. This showed a more modest 2-fold variation in the percentage of patients transfused with allogeneic red blood

cells ranging from 30.0% to 64.2% (Andreasen *et al.*, 2007). Similar variation in usage of red cells (30% - 49%) in 6 centres in Austria (Gombotz *et al.*, 2014) was reported in a follow-up study to an original similar study 4 years previously (Gombotz *et al.*, 2007). Despite having communicated the findings of the original study to the individual centres, presumably to raise awareness and prompt a change in behaviour, transfusion rates in CABG procedures in the second study remained the same.

An international study performed in 69 medical institutions across 16 countries on 5065 patients scheduled to undergo CABG surgery showed similar variation. Two thirds of the patients enrolled received red cell transfusions. The rate varied from 100% in Thailand to 8.7% in the two study centres in France, which had the lowest transfusion rate per country. Similar variation was observed in the transfusion of fresh frozen plasma (0% to 98.3%) and platelets (0% to 50.5%) (Snyder-Ramos *et al.*, 2008).

Study	Year of enrolment	No. of Patients	No. of Institutions	Country/ies	Range of Use (%)
Goodnough LT	1991	540	18	USA	RC: 17-100
Stover EP	1991-1993	714	24	USA	RC: 27-92
Bennett Guerrero E	2008	82,446	408	USA	RC: 7.8-92.8 FFP: 0-97.5 Plt: 0.4-90.4
Andreasen JJ	2004	571	4	Denmark	RC: 30-64.2
Snyder-Ramos S	1996-2000	5065	69	USA, Germany, UK, Canada, India, France, Hungary, Thailand, Colombia, Romania, Austria, Netherlands, Italy, Israel, Mexico, Poland	RC: 8.7-100 FFP: 0-98.3 Plt: 0-50.5
Jin R	2008-2011	5744	12	USA	RC: 7-77 FFP: 1-31 Plt: 1-38
McQuilten ZK	2005-2011	24,222	25	Australia	RC: 16-66 FFP: 4-34 Plt: 6-32
Likosky DS (LV)	2009-2012	11,200	56	USA	RC: 9.1-31.7
Gombotz H	2009-2010	714	6	Austria	RC: 30-49

Table 3.2: CABG studies showing variation (LV = low volume; RC = red cells; FFP = fresh frozen plasma; Plt = platelets)

3.1.1.1 Some causes for variation in blood usage in CABG

Use of blood products during CABG depends on a number of different factors. Pre-operative factors including haematocrit, age, gender, previous CABG procedure, active cigarette smoking, catheterisation on the same admission, coagulation defects, insulin-dependent diabetes, associated transmural myocardial infarction and severe complications such as cardiogenic shock or renal failure have all been associated with a higher likelihood of transfusion (Surgenor *et al.*, 1998). Preoperative medication with anti-platelet therapy and anticoagulants as well as pre-operative transfusion of blood products may impact intra- and post-operative transfusion needs (Picker *et al.*, 2007). Perioperative variables such as red cell volume lost (Stover *et al.*, 1998), whether the surgery is performed on-pump or off-pump, duration, urgency and additional procedures such as mitral valve replacement, also contribute strongly to the risk of transfusion (Slight *et al.*, 2006). A critical issue is the skill of the operating surgeon, which is highly variable, as is the decision to adopt specific techniques that can have a profound effect on bleeding (Bracey, 2008). The use of cell saver devices and antifibrinolytics are also relevant factors (Brown *et al.*, 2007; Niranjan *et al.*, 2006). Other issues such as priming volumes and fluid management can also influence the necessity for transfusion (Slight *et al.*, 2006). Despite the fact that these variables will certainly impact the extent of blood usage, they cannot explain away the sheer inconsistency highlighted in the quoted studies.

A central determinant is the *transfusion trigger* the anaesthetist / surgeon subscribes to, if at all. Traditionally a Haemoglobin value of 8 – 10 g/dL was considered a suitable threshold for transfusion. A recent prospective, randomised, noninferiority controlled trial of 502 patients scheduled for CABG elective surgery comparing a restrictive transfusion strategy to a liberal one suggested that the former, targeting a haematocrit of 24%, was as safe as the latter (Haematocrit = 30%), with respect to a composite end-point of 30-day mortality and inpatient clinical complications (Hajjar *et al.*, 2010).

Though indicative, the transfusion trigger cannot be isolated from the contextual setting and a number of additional considerations need to be reviewed in order to ensure that blood is used optimally, a point eloquently made in a thorough review (Slight *et al.*, 2009).

3.1.1.2 Effect of the institution on variation in blood usage in CABG

Throughout the various studies on variation in blood product use, the institution itself was found to be a significant variable in its own right. Early studies showed that after patient related factors and surgical factors were controlled for, red cell transfusions still varied significantly among institutions. This difference was thought to be associated with transfusion practice-related factors (Goodnough *et al.*, 1991). A study performed in 5 separate hospitals in the United States performed a two-step logistic regression analysis of the enrolled cases. Factors that had previously been found to significantly influence the likelihood of red cell transfusion were entered as a first step, with the specific hospital entered as the second step. This revealed that the hospital was also a significant factor for red cell transfusion. This study concluded that the effects of the specific hospital on blood transfusion practice was the result of deeply ingrained institutional differences in training and hierarchical practices within the hospitals (Surgenor *et al.*, 1998).

Some studies correlated some institutional characteristics to blood use. Patients in hospitals with higher volumes of surgery tend to be transfused less, and patients in hospitals with residency / academic programmes tend to receive more red cells (Bennett-Guerrero *et al.*, 2010; Maddux *et al.*, 2009). In a single country based study, after adjusting for patient-, drug-, and procedure-related risk factors, in what were already comparable patient populations, the institutional effect was thought to be notable (Andreasen *et al.*, 2007).

3.2 Data Sources Highlighting Variation in Practice

3.2.1 Haemovigilance programmes

Haemovigilance is defined as a set of surveillance procedures covering the whole transfusion chain from the donation of blood and its components to the follow-up of its recipients. It is intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products and to prevent the occurrence and recurrence. Haemovigilance was taken up in many countries mainly as a voluntary initiative of the Transfusion Services; although some schemes also had a basis in national law, as was the case in France where a database of Transfusion Incident Reports (TIR) was set up in 1994 under the responsibility of the French Blood Agency (Andreu, 2002). The first report of the Haemovigilance scheme in the UK, Serious Hazards of Transfusion (SHOT) was published in 1998 (Williamson, 1998). By 1999, ten countries out of the then fifteen EU member states had put in place a structure for haemovigilance and most came together as a single forum – the European Haemovigilance Network (Faber, 2002) which has since (in 2010) become the International Haemovigilance Network also encompassing countries outside Europe. In 2003 the European Union published binding directives which mandated reporting of serious adverse events and reactions associated with transfusion, thus enshrining haemovigilance in the member states' legislative framework (European Union, 2003; European Union, 2005a).

Comparison of data arising from these haemovigilance schemes has been somewhat hampered by a lack of standardised definitions. However the risk of occurrence of the better-characterised adverse events and reactions associated with blood component transfusion has been reported for various

countries. Table 3.3 shows an example of the data collated from different sources, indicated in the table itself, for 2009/2010.

Country	**Total number of components transfused**	**Overall incidence of adverse reactions per 100,000 components**	**Events per 100,000 components transfused**			
			Anaphylaxis	TACO	TRALI	ABO Haemolysis
Australia[1]	1,157,394	25.40	0.70	0.50	0.30	N/A
Belgium[2]	678,627	9.30	0.90	0.30	0.30	0.70
Brazil[3]	3,387,984	77.00	0.50	2.20	0.60	0.20
Czech Republic[2]	640,833	4.20	1.40	0	0.90	0.30
Finland[2]	342,083	3.80	0.60	0.30	0	0.30
France[2]	2,928,807	6.40	2.00	3.00	0.80	0.10
Germany[2]	6,421,480	0.40	0.10	0	0.06	0.10
Ireland[2]	173,393	36.90	12.70	8.60	0	0
Italy[2]	3,214,887	9.10	7.60	0.40	0.10	0.40
Japan[4]	4,903,649	35.00	8.60	N/A	0.70	0.04
Malta[2]	22,537	17.70	4.40	0	4.40	0
Switzerland[2]	414,084	8.20	4.30	1.40	0	0.50
UK[2]	2,810,673	6.40	2.70	0.60	0.20	0.10
USA[5]	23,669,000	0.70	N/A	6.00	1.90	0.20

Table 3.3: Haemovigilance data for 2009/2010 [1 - (National Blood Authority, 2011); 2 - (Janssen *et al.*, 2011); 3 **-** (Agencia Nacional de Vigilancia Sanitaria, 2010); 4 - (Japanese Red Cross Society, 2010); 5 - (Department of Health and Human Services, 2011); TACO = Transfusion Associated Circulatory Overload; TRALI = Transfusion Related Acute Lung Injury]

In order to be able to compare rates of complications, authors of national haemovigilance reports started to include, as a denominator, the amount of blood products distributed to hospitals or transfused. This allowed them to calculate the incidence of adverse reactions. The inadvertent outcome was the potential to start comparing the number of blood components distributed to hospitals or transfused in the different countries publishing reports.

3.2.2 International benchmarking

The Council of Europe has been involved in the field of blood transfusion since the 1950s. It has been active in promoting optimal use of blood and blood products, and is responsible for a major publication called the *Guide to the preparation, use and quality assurance of blood components* now in its 20th edition. In 2007, the scientific secretariat with responsibility for blood transfusion was transferred to the European Directorate for the Quality of Medicines and Healthcare (EDQM).

Since 2001, a sub-committee of the European Committee on Blood Transfusion (CD-P-TS) has been responsible for the collation of an *Annual report on the collection, testing and use of blood and blood components in Europe*. According to the 2009 report (Janssen *et al.*, 2011), red cell use per thousand population in Europe varies significantly (Figure 3.1).

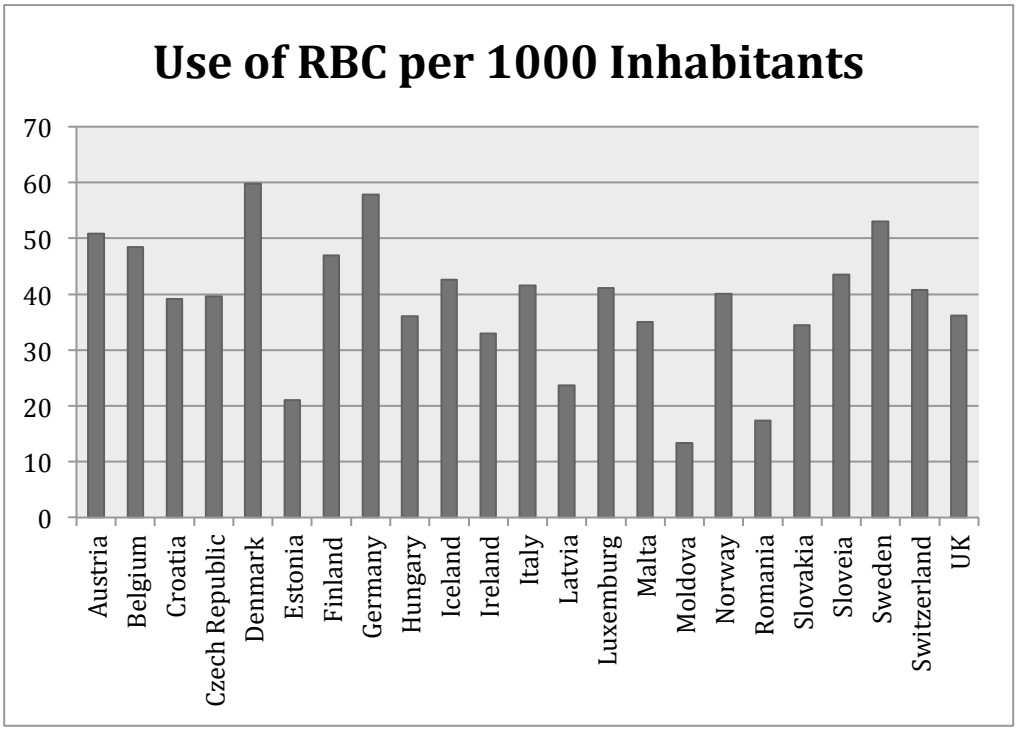

Figure 3.1: Red cell use: compiled from data in the *Annual Report on The Collection, Testing and Use of Blood and Blood Products in Europe in 2009* (Janssen *et al.*, 2011).

3.2.2.1 Data

The data in Table 3.4 on blood product usage in 2009/2010 have been compiled from a number of sources: annual reports published by the Australian National Blood Authority (National Blood Authority, 2011), the American Department of Health and Human Services (Department of Health and Human Services, 2011), the Canadian Blood Service (Canadian Blood Services, 2010), Hema-Quebec (Hema-Quebec, 2010), the New Zealand Blood Service Haemovigilance Report (NZBLOOD, 2010) and the 2009 and 2010 EDQM reports (Janssen *et al.*, 2011; Janssen *et al.*, 2014). Data from two years were used to populate as much of the table as possible and as realistically as possible. Where possible, these figures were discussed with colleagues in the European Blood Alliance (EBA), as a means of validation, ensuring their faithfulness to the actual state of affairs. Importantly, though they are labelled as blood component usage, the figures presented in the reports by a number of countries for the various components, refer to the number of units distributed by the transfusion services, a closely related but slightly inflated value that also incorporates a relatively minor amount of components that are eventually not transfused.

Countries	Blood Component Usage - Per 1000 Population		
	Red Cells	Platelets	Plasma
Australia	36.8	5.9	7.4
Austria	50.9	4.4	8.9
Belgium	48.4	6.4	8.1
Canada	31.2	4.3	8.7
Croatia	39.1	NA	15.7
Czech Republic	39.6	3.1	19.0
Denmark	59.8	5.9	12.6
Estonia[1]	39.8	4.5	5.3
Finland	47.0	7.5	9.4
France[1]	36.3	4.2	5.3
Germany	57.8	5.7	15.0
Greece	55.5	11.9	19.7
Hungary	36.1	1.4	9.4
Iceland	42.6	6.2	14.0
Ireland[1]	32.9	5.8	5.2
Italy	41.6	3.5	8.7
Luxembourg	41.1	4.7	8.9
Malta[1]	35.0	4.1	18.0
Netherlands	34.0	3.3	5.5
New Zealand	28.5	3.1	4.8
Norway	40.1	4.2	9.4
Slovakia	34.4	5.2	14.7
Slovenia	43.5	4.6	15.3
Spain[1]	36.0	4.1	4.3
Sweden	53.0	4.7	11.3
Switzerland	40.8	3.8	9.1
United Kingdom	36.2	4.5	5.1
United States	48.8	6.6	14.6

Table 3.4: Blood component usage per 1000 population for 2009/2010 (1 – Part or all from 2010 report; NA = not available)

A subset of these figures prompted a survey where respondents in 15 countries, all with higher Human Development Indices (HDI), were asked to fill out an in-depth questionnaire. It sought to explore whether differing features of the organisation of health care systems or even the blood supply system could be correlated in some way with the practice of blood banking and transfusion medicine (Aubuchon *et al.*, 2010). The authors concluded that there seemed to be no apparent relationship between the structures and organisations, or the financing arrangements and the propensity to implement new technologies, with the diversity of practice in transfusion

medicine evident across these same countries. They surveyed a number of qualitative issues, including the political system with respect to healthcare, hospital ownership, hospital governance and regulation, and the source of resource provision for blood collection. They additionally looked at control of new initiatives within the blood collection centres and medical indemnification for blood collectors, the structure of the blood collecting institutions, their independence, reporting relationships, and identity of decision makers. They also examined some quantitative data including Health Care Expenditure, HDI, number of blood components collected, the population of the surveyed countries, and the cost of the various products. The authors found no apparent correlation with the variation in practice but commented that they had not explored the effect of clinical demand on the collection rates and they speculated that this and other factors including the age distribution of the population may be important determinants.

3.2.2.2 Analysis

An initial analysis of the data collated in Table 3.4 was performed. The distributions of the three dependent variables, Red Cell, Platelet and Plasma Usage per 1000 population (Table 3.4), were analysed using the Kolmogorov-Smirnov test (Figure 3.2) using IBM® SPSS® Statistics Ver 20 to ensure that their distribution was normal (p-values = 0.584, 0.435 and 0.215 respectively). In order to explore the relationship between the three variables, 'Red Cell Usage per 1,000 Population', 'Platelet Usage per 1,000 Population' and 'Plasma Usage per 1,000 Population' were first plotted on a linear graph on Microsoft® Excel® for Mac 2011 (Figure 3.3). The data were also subjected to a Pearson Coefficient analysis using IBM® SPSS® Statistics Ver 20 using each variable as the dependent variable in turn to examine the relationship between the three variables (Table 3.5).

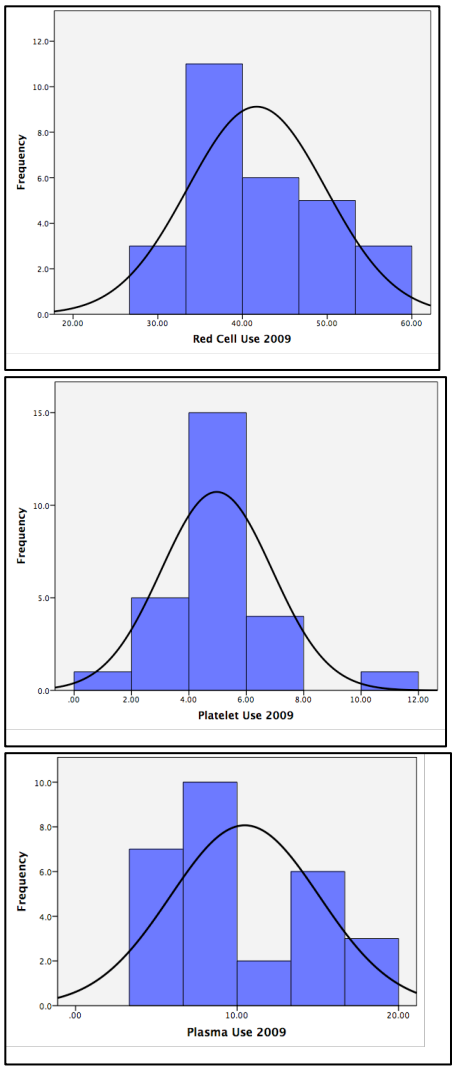

Figure 3.2: Distribution curves for the three dependent variables

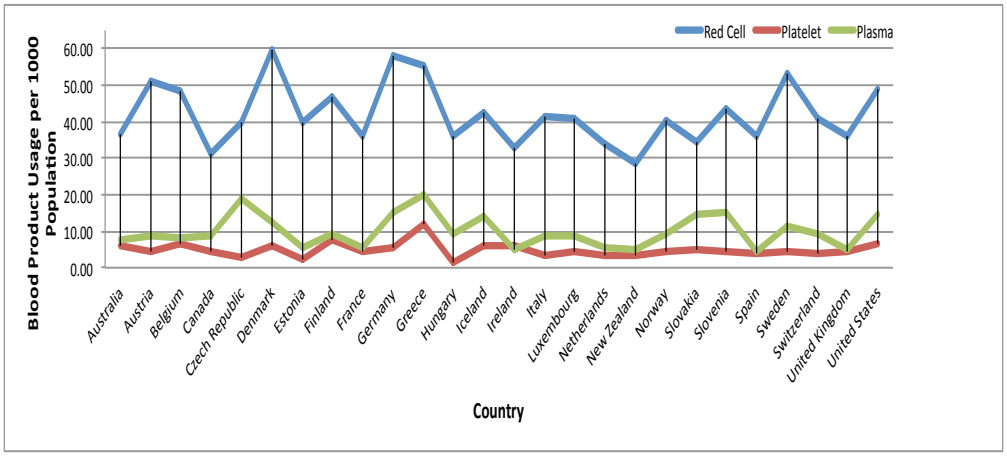

Figure 3.3: Plot of usage of red cells, platelets and plasma

Significant Relationships	Pearson Correlation	P-value
Red Cell Usage per 1,000 Population - Platelet Usage per 1,000 Population	0.538	**0.005**
Plasma Usage per 1,000 Population – Red Cell Usage per 1,000 Population	0.559	**0.003**
Platelet Usage per 1,000 Population – Plasma Usage per 1,000 Population	0.475	**0.014**

Table 3.5: Significant correlations between usage of red cells, platelets and plasma

The plot (Fig. 3.3) shows a significant correlation between the usages of the three blood products. This relationship is confirmed through the Pearson correlation shown in Table 3.5. It appears that, in general, countries that use higher amounts of red cells would also use higher amounts of plasma and platelets with the converse also being true.

3.2.3 Variation by geographical region

There are no compiled data available on regional usage of blood products based on discrete geographical regions across different countries. This is in contrast to the prevailing situation with regard to other therapeutic modalities (Public Health England, 2015). Such regional information would help continue to explore the extent of variation in blood product usage, and to determine whether the variation evident across countries on a national level, is also prevalent on a regional level within countries. Through the EBA network, correspondence was sent to the Chief Executives and the National Medical Directors of Transfusion Services (Blood Establishments) in Europe asking for regional data, if available, on blood component usage for a minimum of 3 consecutive years. The years were not specified so as not to limit the outcome of the request.

Data were received from a relatively small number of countries. In many countries, including the UK, the Netherlands, Estonia, Belgium, Hungary, and Slovakia, for example, this data is simply not available. The replies received

from Germany and Spain indicated that there was a possibility of perhaps retrieving the data from the Paul Elrich Institute in Germany and the Federal Department of Health in Spain. Communications with the individuals indicated in these two institutions did not yield any additional information. Data for regional usage in 2010/11, 2011/12, and 2012/13 in Australia were collated from the Australian Haemovigilance Report (National Blood Authority, 2015) and population data were collated from the Australian Bureau of Statistics (Australian Bureau of Statistics, 2015). Data for Denmark were collated from two sources; blood product data for 2007 and 2008 from the most recent Danish Transfusion Database Annual Report 2009 (Danish Transfusion Database, 2009) and population data were collated from Statistics Denmark (Statistics Denmark, 2009); data for 2015 were made available directly through the correspondence mentioned above. One year's worth of data each for Finland (2014) and Switzerland (2012) were received as a result of the above-mentioned correspondence. Correspondence with Austria, Italy and France yielded data across 3 years for each country. The data received for Austria were complete and included both the data on red cells and the population of each region for 2013, 2014 and 2015. The data for France for the years 2012, 2013 and 2014 were provided in the form of three reports in French (Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance, 2013; Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance, 2014; Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance, 2015) and population data extracted from the Institut Nationale de la Statistique et des Etudes Economiques (Institut Nationale de la Statistique et des Etudes Economiques, 2015). This data however encompassed all three products i.e. red cells + platelets + plasma. It was not possible to extract the data for red cells only. The data for Italy for the years 2013, 2014 and 2015 were presented in the form of three reports in Italian (Ministero della Salute, 2014; Ministero della Salute, 2015; Ministero della Salute, 2016) and population data extracted from I.Stat the Italian database for population statistics (I.Stat, 2016). The UK was only able to supply the data for the four countries i.e. England, Wales,

Scotland and Northern Ireland, for three consecutive years (2012, 2013 and 2014). Belgium supplied four years worth of data (2012, 2013, 2014 and 2015), split into two regions – Flanders and 'Other'. All the data collected were for red cells (apart from the composite data made available for France). There were no data on Platelet usage and Plasma usage on a regional basis. The data are displayed in Tables 3.6 – 3.14.

3.2.3.1 Data

	2012/2013			2011/2012			2010/2011		
Region	Units used	Population	Units per 1000 population	Units used	Population	Units per 1000 population	Units used	Population	Units per 1000 population
New South Wales	241982	7358791	32.9	256926	7262856	35.4	252792	7181410	35.2
Victoria	203374	5685931	35.8	207225	5585169	37.1	207828	5499459	37.8
Queensland	155301	4612504	33.7	166235	4522491	36.8	167051	4440761	37.6
West Australia	64064	2478657	25.8	65742	2395701	27.4	66012	2322127	28.4
South Australia	66311	1663431	39.9	69500	1647824	42.2	71782	1633468	43.9
Tasmania	14478	512632	28.2	15370	511794	30.0	15715	510165	30.8
Australian Capital Territory	12839	378335	33.9	13965	371584	37.6	13346	364875	36.6
Northern Territory	5194	238320	21.8	6333	233586	27.1	6047	230535	26.2
National	763542	22928602	33.3	801295	22531007	35.6	800571	22182801	36.1

Table 3.6: Regional data for Australia

	2013			2014			2015		
Region	Red Cells Distributed	Population	Units per 1000 population	Red Cells Distributed	Population	Units per 1000 population	Red Cells Distributed	Population	Units per 1000 population
Region 1	142297.0	3650000.0	39.0	138254.0	3680000.0	37.6	136075.0	3720000.0	36.6
Region 2	43902.0	1430000.0	30.7	40175.0	1430000.0	28.1	39582.0	1440000.0	27.5
Region 3	12802.0	370000.0	34.6	13320.0	380000.0	35.1	13065.0	380000.0	34.4
Region 4	22193.0	550000.0	40.4	22510.0	560000.0	40.2	21345.0	560000.0	38.1
National	221400	6000000.0	36.9	214170	6050000.0	35.4	209840	6100000.0	34.4

Table 3.7: Regional data for Austria

Region	2007			2008			2015		
	Red Cells Transfused	Population	Transfused per 1000 population	Red Cells Transfused	Population	Transfused per 1000 population	Red Cells Transfused	Population	Transfused per 1000 population
Hovedstaden	119192	1636744	72.8	112118	1645825	68.1	74046	1789174	41.4
Sjaelland	53425	816116	65.5	43063	819427	52.6	31254	827499	37.8
Syddanmark	76749	1189813	64.5	73842	1194659	61.8	47702	12111770	39.4
Midtylland	70128	1227424	57.1	63613	1237041	51.4	45307	1293309	35
Nordjylland	34575	576970	59.9	35400	578839	61.2	20825	585499	35.6
National	354069	5447067	65.0	328036	5475791	59.9	219134	5707251	38.4

Table 3.8: Regional data for Denmark

Region	2014		
	Units Used	Population	Units per 1000 population
Ahvenanmaa-Islands (South-West from Finland)	1260	28791	43.8
South Finland	68457	1895814	36.1
East Finland	29775	816786	36.5
North Finland	27677	741515	37.3
Middle Finland	41348	1110137	37.2
West Finland	34418	868470	39.6
National	202935	5461512	37.2

Table 3.9: Regional data for Finland

Region	2012			2013			2014		
	Products transfused	Population	Units per 1000 population	Products transfused	Population	Units per 1000 population	Products transfused	Population	Units per 1000 population
Alsace-Champagne-Ardenne-Lorraine	307493.0	5550672.0	55.4	306879.0	5554151.0	55.3	301078.0	5558160.0	54.2
Aquitaine-Limousin-Poitou-Charentes	288115.0	5826386.0	49.5	288017.0	5859024.0	49.2	273630.0	5889357.0	46.5
Auvergne-Rhones-Alpes	354944.0	7726430.0	45.9	351558.0	7768302.0	45.3	343466.0	7844798.0	43.8
Bourgogne-Franche-Comte	145954.0	2818299.0	51.8	146133.0	2820044.0	51.8	142873.0	2820673.0	50.7
Bretagne	153172.0	3247902.0	47.2	151945.0	3267551.0	46.5	149572.0	3285349.0	45.5
Centre	101623.0	2567067.0	39.6	103647.0	2573372.0	40.3	88278.0	2579285.0	34.2
Corse	15834.0	318233.0	49.8	11469.0	321865.0	35.6	10447.0	325210.0	32.1
Ile-de-France	601053.0	11929155.0	50.4	641893.0	11987311.0	53.5	583318.0	12044364.0	48.4
Languedoc-Roussillon-Midi-Pyrenees	286377.0	5655368.0	50.6	288610.0	5710759.0	50.5	282045.0	5764753.0	48.9
Nord-Pas-de-Calais-Picardie	268413.0	5980491.0	44.9	262168.0	5992338.0	43.8	260174.0	6001823.0	43.3
Normandie	150302.0	3325560.0	45.2	148342.0	3329982.0	44.5	137029.0	3333128.0	41.1
Pays de la Loire	163635.0	3646733.0	44.9	161658.0	3674627.0	44.0	158420.0	3702235.0	42.8
Provences-Alpes-Cote d Azur	236321.0	4944626.0	47.8	235891.0	4962649.0	47.5	234679.0	4980529.0	47.1
France Metropolitaine	3073236.0	63536918.0	48.4	3098210.0	63839972.0	48.5	2965009.0	64129660.0	46.2

Table 3.10: Regional data for France

	2013			2014			2015		
Region	Red Cells Distributed	Population	Units per 1000 population	Red Cells Distributed	Population	Units per 1000 population	Red Cells Distributed	Population	Units per 1000 population
Valle d'Aosta	4900.0	127844.0	38.3	4782.0	128591.0	37.2	4772.0	128298.0	37.2
Piemonte	197761.0	4374052.0	45.2	188917.0	4436798.0	42.6	187100.0	4424467.0	42.3
Liguria	73023.0	1565127.0	46.7	71000.0	1591939.0	44.6	72903.0	1583263.0	46.0
Lombardia	466480.0	9794525.0	47.6	457428.0	9973397.0	45.9	464078.0	10002615.0	46.4
PA di Trento	22098.0	530308.0	41.7	21314.0	536237.0	39.7	20605.0	537416.0	38.3
PA di Bolzano	22486.0	509626.0	44.1	21511.0	515714.0	41.7	20316.0	518518.0	39.2
Friuli Venezia Giulia	61398.0	1221860.0	50.2	56104.0	1229363.0	45.6	54757.0	1227122.0	44.6
Veneto	242254.0	4881756.0	49.6	239293.0	4926818.0	48.6	242527.0	4927596.0	49.2
Emilio Romagna	230128.0	4377487.0	52.6	217981.0	4446354.0	49.0	212905.0	4450508.0	47.8
Toscana	174643.0	3692828.0	47.3	169630.0	3750511.0	45.2	164153.0	3752654.0	43.7
Umbria	43520.0	886239.0	49.1	44046.0	896742.0	49.1	44099.0	894762.0	49.3
Marche	75003.0	1545155.0	48.5	74163.0	1553138.0	47.8	74499.0	1550796.0	48.0
Lazio	218856.0	5557276.0	39.4	213323.0	5870451.0	36.3	211633.0	5892425.0	35.9
Sardegna	114478.0	1640379.0	69.8	110805.0	1663859.0	66.6	111416.0	1663286.0	67.0
Abruzzo	54206.0	1312507.0	41.3	54726.0	1333939.0	41.0	54500.0	1331574.0	40.9
Campania	156111.0	5769750.0	27.1	158710.0	5869965.0	27.0	165633.0	5861529.0	28.3
Molise	15093.0	313341.0	48.2	16329.0	314725.0	51.9	15788.0	313348.0	50.4
Puglia	153566.0	4050803.0	37.9	152600.0	4090266.0	37.3	153969.0	4090105.0	37.6
Basilicata	24008.0	576194.0	41.7	25222.0	578391.0	43.6	24185.0	576619.0	41.9
Calabria	67442.0	1958238.0	34.4	66512.0	1980533.0	33.6	68089.0	1976631.0	34.4
Sicilia	202732.0	4999932.0	40.5	200177.0	5094937.0	39.3	200423.0	5092080.0	39.4
National	2621060.0	59685227.0	43.9	2565552.0	60782668.0	42.2	2568975.0	60795612.0	42.3

Table 3.11: Regional data for Italy

	2012		
region	**Units Distributed**	**Population**	**Units per 1,000 Population**
Aargau-Solothurn	20202	886623	22.8
Basel	24996	463962	53.9
Bern	49185	992617	49.6
Fribourg	8499	291395	29.2
Geneva	22174	463101	47.9
Grisons	6617	233289	28.4
Neuchâtel-Jura	6521	245496	26.6
Eastern Switzerland	19081	666310	28.6
Svizzera Italiana	12174	341652	35.6
Valais	13461	321732	41.8
Vaud	31179	734356	42.5
Central Switzerland	17910	690964	25.9
Zurich	65583	1707563	38.4
National	297582	8039060	37.0

Table 3.12: Regional data for Switzerland

Region	Year	Total Units	Population	Units per 1000 population
Flanders	2012	302544	6835577	44.26
Other	2012	206055	4200371	49.06
National	2012	508599	11035948	46.09
Flanders	2013	280727	6896445	40.71
Other	2013	195818	4235824	46.23
National	2013	476545	11132269	42.81
Flanders	2014	261561	6911226	37.85
Other	2014	190322	4244910	44.84
National	2014	451883	11156136	40.51
Flanders	2015	254839	6944003	36.7
Other	2015	186020	4265041	43.62
National	2015	440859	11209044	39.33

Table 3.13: Data for Belgium (split into Flanders and 'Other')

Country	Year	Population	Units per 1000 population
England	2012	53,493,729	32.86
Scotland	2012	5,313,600	34.9
Wales	2012	3,074,067	36.62
NI	2012	1,823,634	29.05
England	2013	53,865,800	31.63
Scotland	2013	5,327,700	33.85
Wales	2013	3,082,400	31.73
NI	2013	1,829,700	26.4
England	2014	54,316,600	30.62
Scotland	2014	5,347,600	31.55
Wales	2014	3,092,000	31.41
NI	2014	1,840,500	26

Table 3.14: Data for UK (Split by country; NI = Northern Ireland)

3.2.3.2 Analysis

The figures depict a wide range of variation with some countries having wider amplitudes. Using each country's average red cell usage as a reference (100%), it is possible to assess the variation across regions within the same country. The regions in Austria range between 81% and 111% (30 percentage points). Australian regions vary between 72% and 120% (48 percentage points). In Italy, the country with the highest variation, the range is between 64% and 158% (96 percentage points). French regions varied between 82% and 115% (33 percentage points). The regions in Denmark ranged between 87% and 113% (26 percentage points). In Finland, the country with the lowest variation, the range was between 97% and 118% (21 percentage points). Swiss regions also varied significantly demonstrating a range between 62% and 146% (84 percentage points). Figure 3.4 illustrates the distribution of variation in the different regions in the countries reviewed.

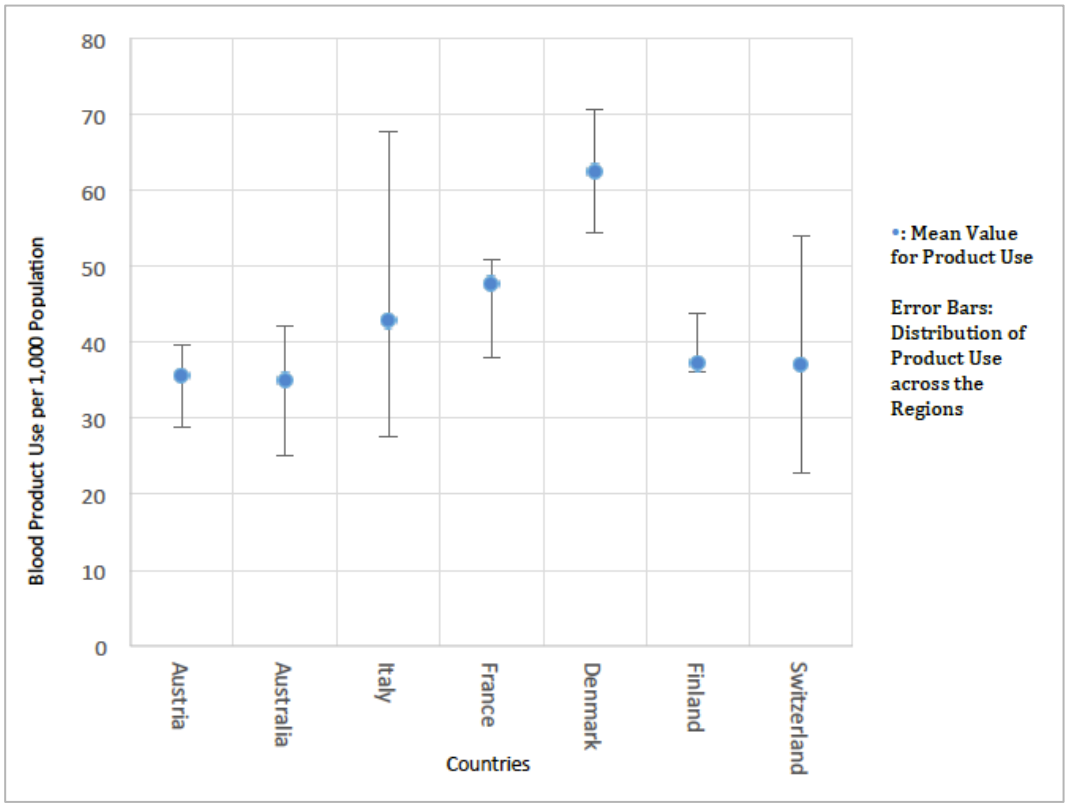

Figure 3.4: Distribution of blood product usage variation amongst the geographical regions in the different countries

Scatter plots performed using IBM® SPSS® Statistics Ver 20 with 'Population Size of Region' plotted on the X-axis and 'Red Cell Usage per 1,000 Population' plotted on the Y-axis were used to depict and analyse the regional data. The same data were subjected to a Pearson Correlation Coefficient analysis performed using IBM® SPSS® Statistics Ver 20 using 'Red Cell Usage per 1,000 Population' as the dependent variable and 'Population Size of Region' as the predictor.

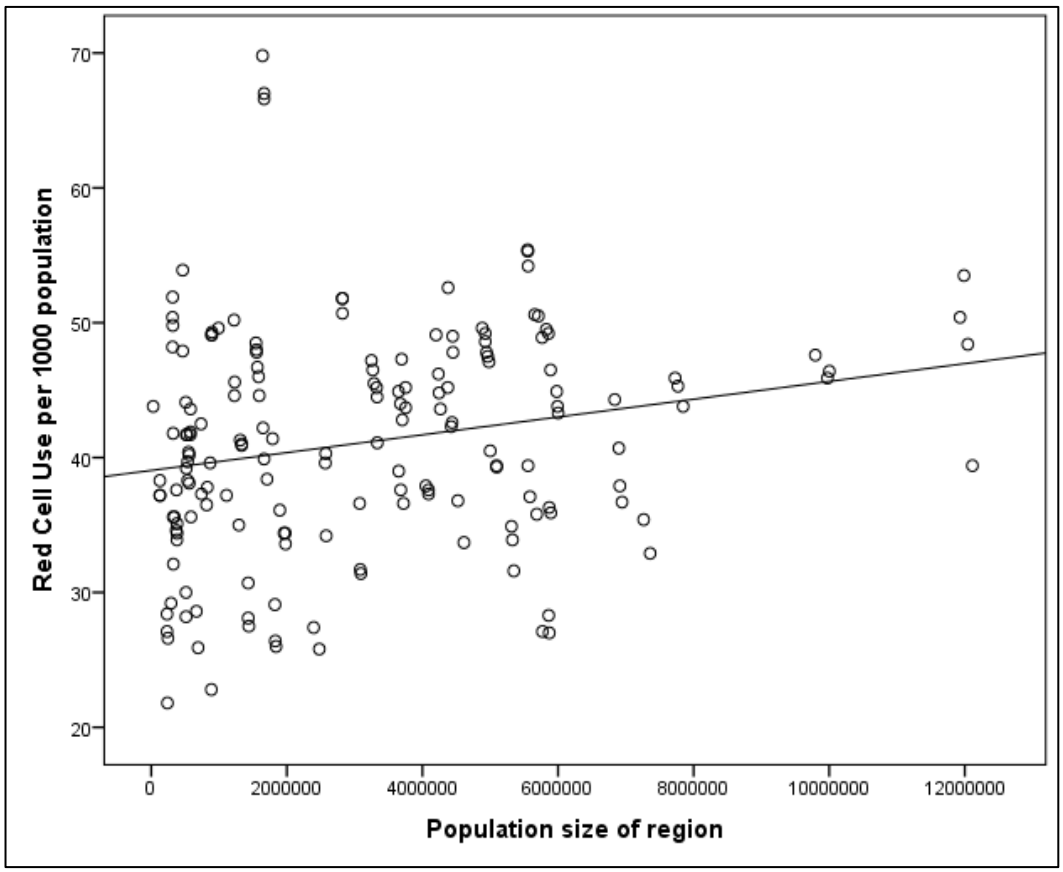

Figure 3.5: Scatterplot showing correlation of population size of region and regional red cell usage per 1,000 population

		Red Cell Use per 1000 population
Population size of region	Pearson Correlation	0.217
	P-value	**0.004**
	Sample Size	171

Table 3.15: Table showing Pearson correlation and P-value for the relationship between population size of region and regional red cell usage per 1,000 population.

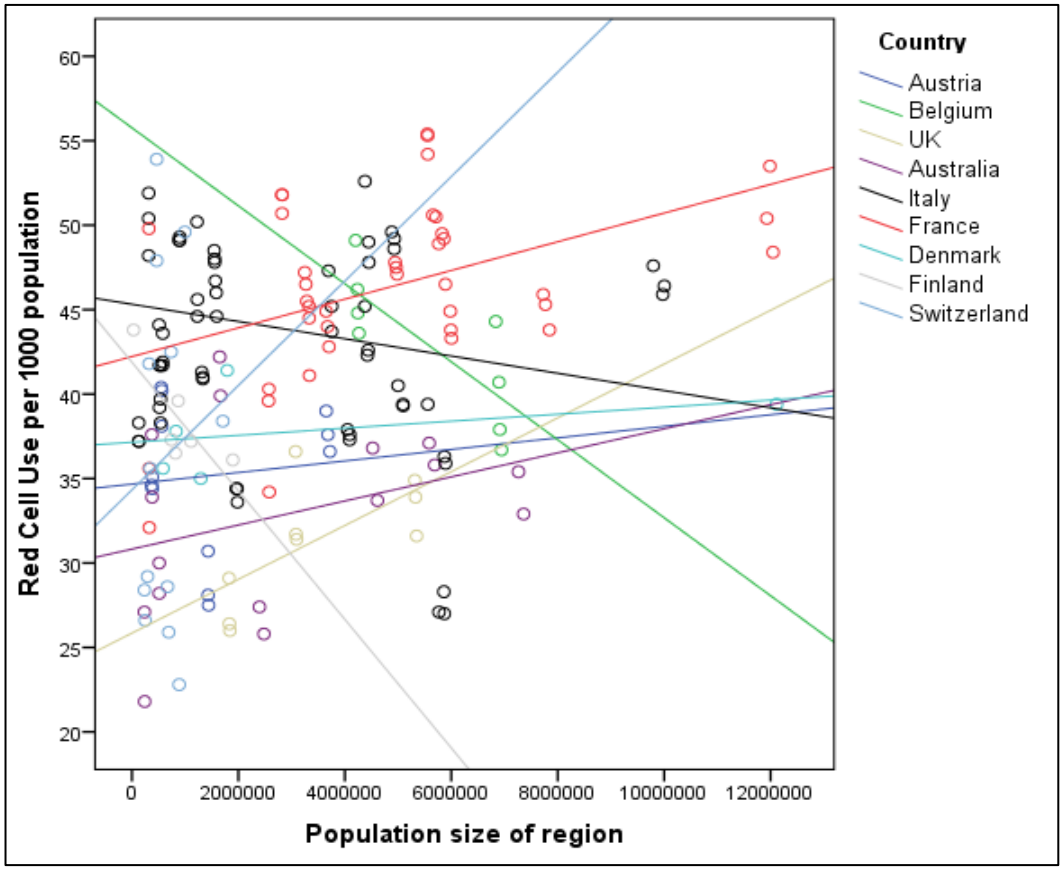

Figure 3.6: Scatter plot showing the relationship between regional red cell usage per 1,000 population and population size of region by individual country

Relationship between Regional 'Red Cell Use per 1000 Population' and Population Size of Region clustered by country	Pearson Correlation
Austria	0.107
Belgium	-0.781
UK	0.675
Australia	0.329
Italy	-0.160
France	0.446
Denmark	0.386
Finland	-0.792
Switzerland	0.124

Table 3.16: Correlation between regional red cell usage per 1,000 population and regional population, country by country

The scatter plot in Figure 3.5, depicting a plot of all regions from all countries pooled together, shows that regions with larger populations tend to have higher red cell usage than regions with lower populations. When plotted country by country however, the scatter plot (Figure 3.6) and the subsequent correlation (Table 3.16) tell a slightly different story. The relationship between 'Red Cell Usage per 1,000 Population' and 'Population Size of Region' is positive in the case of Australia, Austria, France, Denmark, and Switzerland i.e. the larger the population the larger the 'Red Cell Usage per 1,000 Population'. In the case of Italy and Finland, however, the relationship is negative i.e. the smaller the population, the larger the 'Red Cell Usage per 1,000 Population' tends to be.

region	cantons	University Hospital	Units Distributed	Units Distributed (corrected)	Population	Population > 65 Years	Units per 1000 Population	Units per 1000 Population (corrected)
Aargau-Solothurn	Aargau, Solothurn		20202	27891	886623	148501	22.8	31.5
Basel	Basel-Stadt, Basel-Land	yes	24996	21247	463962	95021	53.9	45.8
Bern	Bern	yes	49185	41807	992617	192915	49.6	42.1
Fribourg	Fribourg		8499	10674	291395	42007	29.2	36.6
Geneva	Geneva	yes	22174	18848	463101	75727	47.9	40.7
Grisons	Grisons, Glarus		6617	8871	233289	43531	28.4	38.0
Neuchâtel-Jura	Neuchâtel, Jura		6521	8859	245496	45156	26.6	36.1
Eastern Switzerland	St. Gall (70%), Thurgau, Appenzell Inner-/Ausserrhoden		19081	24774	666310	109950	28.6	37.2
Svizzera Italiana	Ticino		12174	12174	341652	71889	35.6	35.6
Valais	Valais		13461	16424	321732	57234	41.8	51.0
Vaud	Vaud	yes	31179	26502	734356	117744	42.5	36.1
Central Switzerland	Lucerne, Zug, Obwalden, Nidwalden, Uri, Schwyz (50%)		17910	23765	690964	113091	25.9	34.4
Zurich	Zurich, Schaffhausen, St. Gall (30%), Schwyz (50%)	yes	65583	55746	1707563	285852	38.4	32.6
National			297582	297582	8039060	1398618	37.0	37.0

Table 3.17: Corrected data for Switzerland

Regional variation was explored further in Switzerland with the help of Swiss colleagues who provided more detailed information (Table 3.17). Regional red cell usage was corrected for the presence of university hospitals in 5 regions. For the purposes of the analysis, it was assumed that 15% of blood used in a region with a university hospital was transfused to patients migrating into the region for medical specialist help. The blood usage for these regions was therefore revised downwards to 85% of the original figure. The residual 15% was then distributed across the regions without university hospitals according to a formula that took into consideration the individual regions' proportion of the population that was over 65 years. Despite these corrections there was still considerable variation across the regions. If the average use were to be taken as 100%, the variation ranged from 85% to

138% (53 percentage points) which is less than the variation using the crude unaltered data (84 percentage points) but still quite significant.

3.3 Discussion

The literature review examining blood product usage in CABG highlights an inconsistency in practice, that continues to be of concern (Magruder *et al.*, 2017). Significant variation in transfusion practice still exists across cardiac surgery centres even after adjustment of the data to correct for different variables. Additionally, it has been shown that hospitals that tend to use a lot of red cells also use more plasma and platelets (McQuilten *et al.*, 2014). Evidence-based assertions have been made to the effect that this inconsistency in transfusion practice may be due, at least partially, to institutional based protocols (Snyder-Ramos *et al.*, 2008). It has in fact been argued, in relation to transfusion of blood products, that in the absence of professional consensus, institutional culture assumes an important role (Jin *et al.*, 2013). An interesting suggestion made by Likosky et al is the possibility that geographical regions may have their own transfusion signature (Likosky *et al.*, 2014). They found that the rate of 1-unit as well as 2-unit transfusions varied more than 2-fold across regions.

Figure 3.1 on page 40 and Table 3.4 on page 42 give a very clear picture of the variation in red cell, plasma and platelet usage across a number of countries. It is worth noting that in countries with less developed health systems, inefficient practices and the lack of a modern transfusion service set-up contribute to a situation of chronic blood component shortages that lead to low levels of transfusion. Unlike the rest of the countries listed, which are ranked in the very high HDI group in the 2011 Human Development Ranking Report (United Nations Development Programme, 2011), Moldova and Romania are ranked in lower groups and they also have the lowest

figures for red cell use per 1000 population [13.4/1000 and 17.4/1000 respectively]. This is a reflection of the inadequacy of the local system which likely translates into under-transfusion (Murphy, 2012b). However, even if one were to disregard the countries with levels of use that hover around the 20-mark, there still is a 2-fold difference between the lowest using country – Ireland at 33 units per 1000 population and the highest using one – Denmark at 60 units per 1000 population. Attempts have been made to explain this difference by a demographic argument (Ali *et al.*, 2010; Seifried *et al.*, 2011), but the sheer difference prompts one to speculate that additional issues are at play.

The analysis performed comparing the three variables "Red Cell Usage per 1,000 Population', Platelet Usage per 1,000 Population' and 'Plasma Usage per 1,000 Population' (Figure 3.3; Table 3.5) on pages 44 and 45 showed that countries using high amounts of one product seem also to use higher amounts of the other products. It is certainly the case that in a few indications for blood product use e.g. haemhorrage and disseminated intravascular coagulation the concomitant transfusion of all three products occurs, and in haematological malignancies the use of both red cells and platelets is common. However, in many indications blood products are used individually and therefore, the correlation is surprising though similar to the reported finding that hospitals which use more of one tend to use more of the others (McQuilten *et al.*, 2014). This correlation is likely indicative of a pattern where low or high usage is also country specific.

Unlike in many other therapeutic modalities, there appears to be a dearth of information surrounding the use of blood products at a regional level. Though much evidence is found in the literature documenting the varying use of blood products in specific interventions across countries or institutions, as described, no publication has shown regional variation across different countries based on real regional data as has been shown in this

chapter. The figures acquired related only to red cell usage as unfortunately data were not forthcoming on plasma and platelet usage.

The anlaysis performed on the crude data acquired was actually quite revealing. It is clear that even at regional level the variation in red cell usage is quite significant, in Italy the highest-using region transfuses more than double the red cells transfused in the lowest-using region. The level of variation differs and there does not seem to be any association between the national average of red cell usage of a country and its range of regional variation. It may be argued that the variation may be due to the fact that some regions within a country, normally the ones with big urban centres and higher population sizes, would have large university hospitals with much higher clinical activity and therefore, of necessity, higher blood use. Though analysis of all the regions together did show an association between population size and 'Red Cell Usage per 1,000 Population', when the analysis was performed on a country by country basis, it was found that this association was reversed in Italy and Finland. Additionally, the more in-depth analysis of Switzerland showed that there was still considerable variation when corrections were made for medical migration into regions where university hospitals were situated, and allowance was made for demographic differences between regions.

3.4 Conclusion

1. A literature review exploring transfusion practices surrounding a sentinel surgical procedure in which a significant quantity of blood is transfused showed that the sheer inconsistency in practice could not be explained solely by clinical imperatives. Moreover there is evidence to suggest an effect of the individual institution (hospital) on the variation in blood usage, in other words local traditions appear to influence blood transfusion practice.

2. Multiple data sources including haemovigilance programmes and data collated from the Council of Europe and national blood transfusion reports show a consistent variation in blood usage across a number of countries.
3. Analysis of the usage figures for the three blood products shows that countries that use more of one tend to use more of another.
4. The sheer inconsistency of the variation found in red cell usage across regions within the same country, lack of association of the range of variation with the national average and the findings related to the inverse relationship between regional population size and red cell usage all militate in favour of the argument that a significant part of the variation in red cell usage seems to be without an as yet known basis. This continues to be confirmed by a more detailed analysis of variation in one specific country.

The literature reviewed and the data collated and analysed in this chapter therefore demonstrate very clearly that variation in blood product usage is a real phenomenon. At its widest range, when comparing usage both at a national level and at a regional level the higher-using regions / countries appear to use twice as much blood as the lowest-using regions / countries. This significant variation in practice in a therapeutic modality governed by very similar guidelines in all the countries reviewed deserves further exploration to tease out and to understand the contributing factors. Unless these are identified, one cannot start to address this seemingly inconsistent practice.

Chapter 4

Relationships between variation in blood product usage and other variables

4. Relationships between variation in blood product usage and other variables

Having both reviewed the literature and examined national figures for blood product usage, and compared regional data for a number of countries which were analysed here for the first time, it is opportune to look closer at what lies behind the variation. Though it is of concern, very little has been published to date on possible explanations. This chapter attempts an initial understanding of the reasons for this variation. It explores the potential relationships blood product variation may have with plausible predictors. It also probes the relationship between blood product usage and overall health system performance to identify any dependencies.

4.1 Plausible Predictors

4.1.1 Population demographics

As early as 1994 in the United States, a survey on blood transfusion had shown that 53.3% of red cells are transfused to patients who are more than 65years old (Vamvakas & Taswell, 1994). A more recent survey of the demographics of blood used in 2006 across four countries – USA, England, Austria and Denmark – showed that 50% of red cell units were transfused to patients over 65 years (Cobain *et al.*, 2006).

Comparing the figures provided by Eurostat, the European Commission's statistical database, on population age structure demonstrates significant

differences in the percentages of the population over 65 years of age among different countries (Eurostat, 2011). Since a relatively high proportion of blood used is transfused to the elderly it is plausible to assume that any major difference in the proportion of the population over 65 years among different countries will impact blood usage and will therefore give rise to variation. This association has already been examined. Ali et al reported that '*… the variation in RBC use per capita can be explained by the age distribution of the different populations and not by the different national and regional treatment policies and protocols used*' (Ali *et al.*, 2010).

4.1.2 Clinical drivers of blood product use

A small number of pathologies/procedures have been shown to consistently account for a significant proportion of blood component use. In Northern Ireland for example, a third of surgical patients receiving red cell transfusions would have had an orthopaedic procedure, and a further 12% undergo cardiac surgery. In the same country, of the transfused medical patients, 34% have an oncology-related condition, around a third of which are haematological (Barr *et al.*, 2010). This pattern is reflected in England and Wales where two of the top three Case-mix Groups receiving red cell transfusion are 'Musculoskeletal' and 'Haematology' (15% and 13% respectively) (Wells *et al.*, 2009). In addition, cardiac pathologies are responsible for 12% of plasma transfusion and haematological malignancies are responsible for 20% of platelet use while a further 11% of platelets are transfused to patients who undergo coronary artery bypass surgery. These patterns are also reflected in the States (Anderson *et al.*, 2007) and other countries (Cobain *et al.*, 2006). Plasma use is mostly associated with massive haemorrhage (Duguid *et al.*, 2004), including post-partum haemorrhage.

Thus cardiac surgery, hip replacement surgery (as a marker of orthopaedic surgery), maternal mortality (as a surrogate marker for severe post-partum haemorrhage), and malignancies more specifically haematological

malignancies would seem to be powerful drivers of blood component use in developed countries and significant differences in their prevalence may therefore also contribute partially to the difference in blood use across countries.

4.1.3 Other variables

4.1.3.1 Funding

It is plausible to examine whether a genuine interdependence exists between the degree of funding available to a health service and the amount of blood transfused in that service. This can be explored by determining the relationship between blood component use and health-related or development economic markers. Three commonly used markers would be:

a. *Health Care Expenditure per Capita* which reflects funding that countries make available for their populations' health
b. *Human Development Index* (HDI) which captures the level of development within a country. It is made up of a composite of 4 indicators within 3 dimensions – 'Life-expectancy at Birth' within the dimension of 'Health'; 'Mean Years of Schooling' and 'Expected Years of Schooling' within the dimension of 'Education'; and 'Gross National Income per Capita' within the dimension of 'Living Standards'.
c. *Gross Domestic Product* which reflects the economy of the country.

4.1.3.2 Population Density

Transfusion Services in countries that are more sparsely populated may have to carry a higher amount of red cells and platelets in stock in their remoter hubs in order to minimise the risk of supply failure to areas that are far from the large urban centres. This may to some degree impact the variation in the number of blood components issued by transfusion services, depending upon the remoteness of some areas that are serviced by the same Blood Centres.

As stated previously this value may be reported instead of the actual figure for blood component transfusion.

4.2 Overall Health Service Performance and Blood Product Variation

It would be interesting to see whether the level of blood product usage correlated in any way with the general performance of the health care systems in the individual countries.

Overall rankings for the delivery of health services in a country can be established through health service assessments. Various purposes have been attributed to the performance of health service assessments. The primary ones would include the motivation of health system reforms; the promotion of alignment and harmony amongst diverse players in individual health systems; the evaluation and tracking of system performance; and the facilitation of learning from comparisons across different countries (Bennett & Peters, 2015). There is a persistent interest particularly among international institutions in comparative analyses of health systems investigating the differences in delivery, governance and financing of health services across countries probing their relative effectiveness and equity. Two such institutions are the Organisation for Economic Cooperation and Development (OECD) and the World Health Organisation (WHO) who have led in this respect (Tchouaket *et al.*, 2012; World Health Organisation, 2016). This practice has not been without its controversy spanning from the whole philosophy of the idea, to the choice of indicators, to reliability of data (Coyne & Hilsenrath, 2002), (Navarro, 2002), (Musgrove, 2010).

There is no doubt that measurement of countries' status and progress towards meeting targets is a substantial task which would normally require action across a range of national and international organisations, both

governmental and non-governmental. The difficulties of measurement are also further compounded by persistent problems of data availability, quality and comparability across a host of indicators (World Health Organisation, 2016).

Having said that, a ranking of the health services of the different countries, whose variation of blood usage is being explored, has been computed using key performance indicators collated from the OECD database (Organisation for Economic Co-operation and Development, 2016b), and validated against the Health Sustainable Goal Index (GBD 2015 SDG Collaborators, 2016).

This ranking was used in the analysis performed in the next section

4.3 Analysis of the Effect of the Underpinning Contributors on the Variation in Blood Product Usage

Table 4.1 on page 69 lists the values for the factors identified as plausible predictors of the variation in blood component usage discussed in section 4.1 (page 61) for a number of developed countries for which red cell, platelet and plasma usage are available. 2009 was chosen as the index year as that seemed to be the year with the more complete data sets. The data are extracted from a number of online databases that are publically accessible including ones from the OECD, the World Bank Group, the Heal the World Foundation (Nation Master) and the United Nations Development Programme. The data retrieved relate to 2009 or the nearest available year. The individual factors identified are listed below with their relevant reference.

1. Per Cent Population above 65 years (Organisation for Economic Co-operation and Development, 2009b)
2. Human Development Index (HDI) (United Nations Development Programme, 2011)
3. Gross Domestic Product (GDP) per Capita US$ (World Bank, 2009c)
4. Health Care Expenditure per Capita US$ Purchasing Power Parity (World Bank, 2009b)
5. Population Density – Persons per Square Kilometre (Heal The World Foundation, 2012)
6. Prevalence of Coronary Artery Bypass Surgery per 100,000 Population (Organisation for Economic Co-operation and Development, 2009a)
7. Prevalence of Hip Replacement Surgery per 100,000 Population (Organisation for Economic Co-operation and Development, 2009a)
8. Age Standardised rate per 100,000 population for all cancers excluding non-melanoma skin cancers (International Agency for Research on Cancer, 2008)
9. Age Standardised rate per 100,000 population for HL, NHL, Leukaemia & MM (International Agency for Research on Cancer, 2008)
10. Maternal Mortality Ratio per 100,000 Live Births (World Bank, 2009a)

Table 4.2 on page 70 lists the values for the key performance indicators used in the country health service system ranking exercise discussed in Section 4.2 (page 64). The individual indicators were extracted from the OECD database (Organisation for Economic Co-operation and Development, 2016a) and are listed below. All indicators relate to 2009 or the nearest year and all have the specific web address indicated, or their digital object identifier (DOI) number, for ease of reference. Indicators 1 through to 7 were extracted from the *Health Care Quality Indicators* and indicators 8 to 10 were extracted from the *Cancer Care* sub-set of the *Health Care Quality Indicators*.

1. Asthma and Chronic Obstructive Pulmonary Disease hospital admissions in total population aged 15 years and over - Age-standardised rate per 100,000 population (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
2. Congestive Heart Failure and Hypertension hospital admissions in total population aged 15 years and over - Age-standardised rate per 100,000 population (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
3. Diabetes hospital admissions in total population aged 15 years and over - Age-standardised rate per 100,000 population (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
4. 30-day mortality after hospital admission for Myocardial Infarction in total population aged 45 years and over - Age and sex standardised rate per 100 patients (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
5. 30-day mortality after hospital admission for Haemorrhagic Stroke in total population aged 45 years and over - Age and sex standardised rate per 100 patients (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
6. 30-day mortality after hospital admission for Ischaemic Stroke in total population aged 45 years and over - Age and sex standardised rate per 100 patients (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
7. Hip fracture surgery initiated within 2 days after admission to hospital in total population aged 65 years and over - Crude rate per 100 patients (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
8. Breast cancer 5-year relative survival in the female population aged 15 years and over - Age standardised survival - % (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
9. Cervical cancer 5-year relative survival in the female population aged 15 years and over - Age standardised survival - % (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)

10. Colorectal cancer 5-year relative survival in the total population aged 15 years and over Age standardised survival - % (http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT)
11. Men – Life expectancy at 65 years – years (https//doi.org/10.1787/0e9a3f00-en)
12. Women - Life expectancy at 65 years – years (https//doi.org/10.1787/0e9a3f00)
13. Total life expectancy at birth – years (https//doi.org/10.1787/27e0fc9d-en)
14. Healthy life expectancy at birth – years (www.who.int/gho/mortality_burden_disease/life_tables/hale/en/)
15. Infant mortality rate per 1000 live births (https//doi.org/10.1787/83dea506-en)
16. Maternal mortality ratio per 100,000 live births (http://data.worldbank.org/indicator/SH.STA.MMRT.NE)
17. External causes of mortality - deaths per 100,000 population (http://stats.oecd.org/OECDStat_Metadata/ShowMetadata.ashx?Dataset=HEALTH_STAT&Coords=%5BVAR%5D.%5BCICDEXTC%5D&ShowOnWeb=true&Lang=en)
18. Potential years of life lost - years lost per 100,000 inhabitants aged between 0 – 69 years (https//doi.org/10.1787/193a2829-en)
19. Deaths from cancer per 100,000 inhabitants (https//doi.org/10.1787/8ea65c4b-en)
20. Child vaccination, Diphtheria, Tetanus & Pertussis - percent of children (https//doi.org/10.1787/b23c7d13-en)
21. Child vaccination, Measles - percent of children (https//doi.org/10.1787/b23c7d13-en)
22. Flu vaccination - percent of population aged 65 years and over (https//doi.org/10.1787/e452582e-en)

	Predictors									
Countries	Per Cent population over 65 Years	Human Development Index	Gross Domestic Product per Capita (current US$)	Health Care Expenditure per Capita US$	Population Density - Persons per Square Kilometre	Prevalence of Coronary Artery Bypass Surgery per 100,000 Population	Prevalence of Hip Replacement Surgery per 100,000 Population	Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers	Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM	Maternal Mortality Ratio per 100,000 Live Births
Australia	13.27	0.926	42131	3867	2.7818	69.9	154.3	314.1	28.2	8
Austria	17.50	0.879	45638	5037	99.3327	47.6	237.8	232.7	17.7	5
Belgium	17.12	0.883	43799	5104	349.4240	131.4	240.0	306.8	25.4	5
Canada	13.90	0.903	39644	4380	3.6981	63.4	122.5	296.6	28.5	12
Croatia	16.90	0.793	14323	1120	82.9100	NA	NA	263.1	18.0	14
Czech Republic	15.04	0.863	18137	1384	131.6290	56.2	166.4	295.0	18.1	8
Denmark	16.11	0.891	55933	6273	127.0535	78.6	235.7	326.1	21.2	5
Estonia	17.09	0.828	14375	1004	29.6091	53.3	87.6	230.4	18.6	12
Finland	16.88	0.877	45085	4310	15.6625	52.9	188.2	249.8	23.0	8
France	16.75	0.880	40663	4798	117.3332	30.2	223.8	300.4	23.9	8
Germany	20.53	0.900	40275	4629	230.2320	119.9	295.7	282.1	19.2	7
Greece	18.81	0.863	28521	3041	84.9806	NA	NA	160.0	13.3	2
Hungary	16.48	0.811	12635	938	107.9829	32.3	99.4	282.9	16.5	13
Iceland	11.77	0.897	38033	3130	3.1136	59.2	172.6	282.2	21.1	5
Ireland	11.10	0.905	49738	4952	63.0591	23.5	117.1	317.0	23.4	3
Italy	20.18	0.870	35073	3328	197.8498	32.0	150.0	274.3	26.5	5
Luxembourg	13.96	0.863	104354	8183	187.0839	54.4	221.6	284.0	22.4	17
Malta	14.00	0.827	19727	1446	1192.5100	NA	NA	211.4	19.5	8
Netherlands	15.15	0.905	47998	5164	395.0443	58.4	213.1	286.8	23.1	9
New Zealand	12.81	0.906	29352	2634	16.2073	77.0	148.5	309.2	30.7	14
Norway	14.78	0.941	76764	7662	14.7257	70.2	232.0	299.1	23.5	7
Slovakia	12.20	0.829	16126	1373	110.1458	24.9	78.1	260.6	19.7	6
Slovenia	16.19	0.876	24051	2175	99.9293	66.0	193.7	267.9	19.5	18
Spain	16.74	0.874	31891	3075	89.4949	17.6	92.6	241.4	20.8	6
Sweden	17.93	0.898	43472	4252	20.8066	45.0	214.0	252.1	20.4	5
Switzerland	17.24	0.899	63568	7141	183.9304	30.6	286.7	269.3	20.5	10
United Kingdom	15.81	0.860	35163	3285	250.8765	40.1	193.6	266.9	23.5	12
United States	12.95	0.906	45758	7410	33.1873	79.5	183.9	300.2	29.8	24

Table 4.1: Predictors used in correlation analyses (NA = not available; HL = Hodgkin's lymphoma; NHL = non-Hodgkin's lymphoma; MM = multiple myeloma)

Countries	Asthma & COPD Hosp adm in total pop aged 15 years and over (Age std rate per 100,000 population)	CHF & HT Hosp Adm in total pop 15y & over (Age std rate per 100,000 pop)	Diabetes hosp adm in tot pop 15 y and older (age std rate per 100,000 pop)	30 day mort after hosp adm for AMI in total pop 45y & over (age-sex std rate per 100 pts	30 day mort after hosp adm for hgic stroke in total pop 45y & over (age-sex std rate per 100 pts	30 day mort after hosp adm for isch stroke in total pop 45y & over (age-sex std rate per 100 pts	Hip Frac Surg init within 2 days after adm to hosp in total pop 65 y & over (crude rate per 100 pts)	Breast cancer 5y rel surv fem pop 15 y & over (age std surv % - 2008-2013 or nearest))	Cervical cancer 5y rel surv fem pop 15 y & over (age std surv % - 2008-2013 or nearest))	Colorectal cancer 5y rel surv tot pop 15 y & over (age std surv % - 2008-2013 or nearest))	Men - Life Expectancy at 65 Years (Years)	Women - Life Expectancy at 65 Years (Years)	Total Life Expectancy at Birth (Years)	Healthy Life Expectancy at Birth - HALE (Years)	Infant Mortality Rate (Per 1,000 Live Births)	Maternal Mortality Ratio (per 100,000 Live Births)	External Causes of Mortality (Deaths per 100,000 population)	Potential Years of Life Lost (Years Lost per 100,000 Inhabitants Aged 0-69)	Deaths from Cancer (Per 100,000 Inhabitants)	Child Vaccination - DTP (% of Children)	Child Vaccination - Measles (% of Children)	Flu Vaccination (% of Population Aged 65 Years and Over)
Australia	390.9	256.7	230.3	5.2	22.6	10.5	N/A	87.4	66.3	66.3	18.70	21.80	81.60	70.60	4.20	7.00	42.3	2930.80	200.80	92.00	94.00	74.60
Austria	385.2	663.7	369.8	12.3	20.4	7.3	82.4	80.8	62.8	62.9	17.60	21.20	80.40	70.50	3.80	4.00	46.9	3272.40	206.80	83.00	76.00	36.10
Belgium	258.1	192.8	176.5	7.6	30.5	9.2	82.9	85.1	65.3	64.3	17.50	21.10	80.10	69.55	3.50	8.00	57.5	3481.70	216.40	98.00	95.00	65.00
Canada	244.5	195.6	99.9	8	30	11.2	82.2	87.7	66	63.5	18.10	21.20	81.90	71.05	4.90	8.00	45.7	3199.80	214.60	95.00	95.00	66.50
Czech Republic	196.5	550.3	262.7	7.5	25.6	11	84.5	79.6	63.7	51.5	15.20	18.80	77.40	67.60	2.90	5.00	56	4053.30	253.10	99.00	98.00	22.10
Denmark	339.3	251.9	159.3	7.4	31.6	11.1	93.5	84.7	66.8	58.6	16.80	19.50	79.00	69.55	3.10	8.00	38.8	3385.90	248.90	89.00	84.00	48.50
Estonia	347.3	N/A	N/A	11.2	33.8	15.7	89.9	74.2	67.4	52.5	14.10	19.30	75.20	66.05	3.60	11.00	92.1	6219.30	237.40	95.00	95.00	1.40
Finland	235.9	409.9	162.3	8.4	13.3	5.5	80.8	86.9	65.5	63.4	17.30	21.50	80.10	69.45	2.60	3.00	72.4	3693.50	176.90	99.00	98.00	46.00
France	123.7	291.3	194.8	6.4	24.3	8.5	N/A	N/A	N/A	N/A	18.70	23.20	81.50	71.15	3.90	10.00	53.8	3508.70	212.00	98.00	89.00	63.90
Germany	233.7	630.2	219.2	10.3	17.7	7.8	85.2	84.6	64.9	63.6	17.60	20.80	80.30	70.00	3.50	7.00	33.5	3184.20	207.00	96.00	97.00	61.10
Greece	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	18.00	20.90	80.40	70.70	3.10	3.00	32.1	3278.50	203.30	99.00	99.00	41.40
Hungary	461	436	142.5	13.9	40.5	9.6	88.3	N/A	N/A	N/A	14.00	18.20	74.40	65.55	5.10	16.00	68.7	6286.50	295.50	99.00	99.00	31.60
Iceland	274.3	205.6	44.9	6.5	28.5	8.8	95.8	87.8	69.3	66	18.60	21.00	81.80	71.50	1.80	4.00	40.1	2415.20	209.30	96.00	92.00	N/A
Ireland	427.3	235.5	160.5	7.5	27.7	10.1	80.2	81	55.8	58	17.40	20.70	80.30	69.45	3.30	9.00	45.5	3404.70	242.50	94.00	90.00	53.80
Italy	134.9	342.5	62.6	6.1	19.9	6.8	28.8	N/A	N/A	N/A	18.10	21.80	81.70	71.40	3.20	4.00	33.7	2665.70	210.60	96.00	90.00	66.20
Luxembourg	205.2	N/A	181.5	7	22.4	8.9	N/A	N/A	N/A	N/A	17.60	21.40	80.70	70.15	2.50	11.00	47	2605.20	215.20	99.00	96.00	53.30
Netherlands	192	229.2	69	8.6	31.3	8.3	94.2	83.4	66.6	59.9	17.60	21.00	80.80	70.70	3.80	8.00	33.7	2812.10	239.30	97.00	96.00	74.00
New Zealand	420.4	250.2	169.3	6.2	29.6	8.4	82.2	84.5	68.1	62.1	18.40	20.90	80.70	70.35	5.20	12.00	46.5	3508.60	216.50	92.00	89.00	66.50
Norway	281.4	267.3	95.4	4.7	17.1	5.9	87.9	89.1	75.3	62.7	18.00	21.10	81.00	70.65	3.10	6.00	50.7	2917.30	208.50	94.00	93.00	43.90
Slovakia	374.2	810.2	224.8	9	31.7	12.1	N/A	N/A	N/A	N/A	14.10	18.00	75.30	66.50	5.70	6.00	55.8	5384.50	246.10	99.00	99.00	30.50
Slovenia	161.8	320.5	109.9	7.4	33	15.6	57	81	64.3	60.4	16.40	20.50	79.30	68.95	2.40	9.00	74.7	3554.40	258.20	96.00	95.00	22.00
Spain	276.1	206	64.4	8.8	27.5	10.6	38.1	N/A	N/A	N/A	18.30	22.50	81.90	70.80	3.20	5.00	28.8	2851.40	197.80	96.00	98.00	65.70
Sweden	207.5	363.9	133.8	4.7	15.1	6.8	92.3	86	68.1	60.7	18.20	21.20	81.50	70.85	2.50	5.00	44.4	2609.70	192.80	98.00	97.00	44.00
Switzerland	125.3	230.1	70	5.9	16.5	7	85.9	N/A	N/A	N/A	19.00	22.20	82.30	71.50	4.30	6.00	41.9	2658.40	183.20	95.00	92.00	46.00
United Kingdom	304.5	110.3	66.3	8.7	29.9	12.9	82.7	79.1	57.2	51.4	18.00	20.70	80.40	70.00	4.50	10.00	32.2	3377.80	228.50	93.00	86.00	72.30
United States	343.1	441.9	201.3	5.5	22.3	4.3	N/A	88.5	62.5	64.7	17.70	20.30	78.50	68.15	6.40	15.00	59.6	4778.60	199.50	95.00	90.00	66.80

Table 4.2: Clinical outcomes in OECD Countries (N/A = not available)

4.3.1 Analyses

Statistical analyses in this section were performed using IBM© SPSS© Statistics for Macintosh© Version 20.0.

4.3.1.1 Linear correlation

All the identified factors (predictors) were subjected to a Pearson Correlation Coefficient analysis using the Red Cell, Platelet and Plasma Usage per 1000 Population in turn as the dependent variables (Table 3.4, page 42) to measure the linear correlation between each dependent variable and each factor. Using this tool, 'Percent Population over 65 Years', 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population' and 'Prevalence of Hip Replacement Surgery per 100,000 Population' were individually found to be significantly positively correlated to 'Red Cell Usage per 1000 Population'. 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM' related negatively to the dependent variable and was only marginally above the 0.05 criterion for significance (Table 4.3).

Relationship	Pearson Correlation	P-value
Red Cell Usage per 1000 Population – Per Cent Population above 65 years	0.556	**0.002**
Red Cell Usage per 1000 Population – Human Development Index (HDI)	0.128	0.517
Red Cell Usage per 1000 Population – Gross Domestic Product (GDP) per Capita US$	0.194	0.324
Red Cell Usage per 1000 Population – Health Care Expenditure per Capita US$ Purchasing Power Parity	0.308	0.110
Red Cell Usage per 1000 Population – Population Density – Persons per Square Kilometre	-0.107	0.588
Red Cell Usage per 1000 Population – Prevalence of Coronary Artery Bypass Surgery per 100,000 Population	0.483	**0.014**
Red Cell Usage per 1000 Population – Prevalence of Hip Replacement Surgery per 100,000 Population	0.612	**0.001**
Red Cell Usage per 1000 Population – Age Standardised rate per 100,000 population for all cancers excluding non-melanoma skin cancers	-0.208	0.288
Red Cell Usage per 1000 Population – Age Standardised rate per 100,000 population for HL, NHL, Leukaemia & MM	-0.347	0.070
Red Cell Usage per 1000 Population – Maternal Mortality Ratio per 100,000 Live Births	-0.220	0.262

Table 4.3: Pearson correlation coefficient for variables in relation to red cell usage per 1000 population

In order to further tease out the relationship between 'Red Cell Usage per 1000 Population' and 'Health Care Expenditure per Capita US$ Purchasing Power Parity', a partial correlation was performed. This was corrected for the variation in 'Percent Population over 65 Years' since this latter factor has been shown to be one of the major determinants of the variation in international usage. Table 4.4 demonstrates clearly that once this factor is corrected for, there is a significant correlation between 'Red Cell Usage per 1000 Population' and 'Health Care Expenditure per Capita US$ Purchasing Power Parity' confirming the relationship between the dependent and the predictor.

Control Variables			Total Health Expenditure $ per Capita
Elderly population (over 65 y) as percent of population	Red Cell Usage per 1000 population	Correlation	0.430
		P-Value	**0.032**

Table 4.4: Partial correlation of red cell usage per 1000 population with total health expenditure per capita US$ purchasing power parity (corrected for percent population over 65 years')

A similar analysis using 'Platelet Usage per 1000 Population' as the dependent variable yielded a significant negative correlation with 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers' (Pearson Correlation = -0.471; P-value = 0.013). There also appears to be marginal correlation with 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population' (Pearson Correlation = 0.392; P-value = 0.052)

'Plasma Usage per 1000 Population' was significantly negatively correlated with 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM' (Pearson Correlation = -0.489; P-value = 0.008) and possibly marginally negatively correlated with 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers' (Pearson Correlation = -0.352; P-value = 0.066).

There was a significant amount of correlation amongst the predictors themselves. Most notably, 'Gross Domestic Product (GDP) per Capita (Current US$)' and 'Health Care Expenditure per Capita (current US$ purchasing power parity)' were very highly correlated almost reaching a level of 1 (Pearson Correlation = 0.922). It was subsequently decided to eliminate GDP from any further analyses.

Not unexpectedly, 'Health Care Spending per Capita (current US$ purchasing power parity)' was also correlated with 'Human Development Index'. Both these predictors also positively correlated with 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM' and with 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers', an understandable phenomenon in view of the fact that the diagnosed incidence of malignancy is higher in well-developed countries.

'Prevalence of Hip Replacement Surgery per 100,000 Population' was found to be significantly positively correlated with 6 out of the 9 predictors - 'Percent Population over 65 Years'; 'Human Development Index'; 'Gross Domestic Product per Capita (Current US$)'; 'Health Care Expenditure per Capita US$ Purchasing Power Parity'; 'Population Density – Persons per Square Kilometre'; and 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population'. Most of these correlations are intuitively explained. Hip replacement is a procedure that tends to be performed on the elderly, similarly to coronary artery bypass surgery, in countries with high levels of development that can afford to have it performed. The correlation with population density is likely explained by the positive correlation of population density with population over 65 years.

In order to continue to understand the relationship between blood product usage and cancer, a correlation was performed between data for cancer survival and mortality (extracted from Table 4.2, page 70) and red cell, platelet, and plasma use per 1,000 population. The data categories identified were the following:

1. Breast cancer 5-year relative survival in the female population aged 15 years and over (age standardised survival - %)
2. Cervical cancer 5-year relative survival in the female population aged 15 years and over (age standardised survival - %)

3. Colorectal cancer 5-year relative survival in the total population aged 15 years and over (age standardised survival - %)
4. Deaths from cancer (per 100,000 inhabitants)

The identified factors (predictors) were subjected to a Pearson Correlation Coefficient analysis using the Red Cell, Platelet and Plasma Usage per 1000 Population in turn as the dependent variables to measure the linear correlation between each dependent variable and each factor.

Relationship	Pearson Correlation	P-value
Platelet Usage per 1000 Population – Colorectal cancer 5-year relative survival in the total population aged 15 years and over (age standardised survival - %)	0.473	**0.047**
Platelet Usage per 1000 Population – Deaths from cancer (per 100,000 inhabitants)	-0.472	**0.020**

Table 4.5: Correlation between blood products and cancer survival and mortality

4.3.1.2 Regression analysis

The major limitation of the Pearson Correlation Coefficient Test is that it investigates solely the relationship between a dependent variable and a single predictor (explanatory variable). However, the goal of this exercise was to estimate collectively the quantitative effect of all the predictors upon the dependent variable that they influence. It is well known that a lone predictor could be rendered a very important contributor in explaining variations in the responses, but would be rendered unimportant in the presence of other predictors. In other words, the suitability of a predictor in a model fit often depends on what other predictors are included with it.

As pointed out previously, the Pearson correlation analysis showed significant correlation amongst the predictors themselves, a condition which is described as multicollinearity in regression analysis. This poses a problem because it prohibits precise statistical inference. In other words, small

changes in the data values may lead to large changes in the parameter estimates and this severely prohibits quality prediction therefore the results of the regression analyses were evaluated also in the light of the outcome from the Pearson Correlation.

A Regression Analysis using a backward procedure was used to identify the predictors that contribute significantly in explaining the variation in the responses (Red Cell / Platelet / Plasma Usage per 1000 Population).

The model used to analyse the data with 'Red Cell Usage per 1000 Population' as the dependent variable showed that the nine predictors together contributed to 73.5% of the variance.

The parsimonious regression model that related the dependent variable 'Red Cell Usage per 1000 Population' to the explanatory variables identified **5** significant predictors, 3 of them positively correlated and 2 of them negatively correlated: Per Cent Population over 65 Years; Health Care Expenditure per Capita US$ Purchasing Power Parity; Prevalence of Coronary Artery Bypass Surgery per 100,000 Population; Population Density – Persons per Square Kilometre; and Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM (Table 4.6). This five- predictor model explained 70.5% of the total variance (Table 4.7).

Model	Unstandardised Coefficients		Standardised Coefficients	t	P-value
	B	Std. Error	Beta		
(Constant)	28.979	11.047		2.623	0.017
Per Cent population over 65 Years	1.377	0.479	0.414	2.873	**0.010**
Health Care Expenditure per Capita US$ Purchasing Power Parity	0.002	0.001	0.410	3.031	**0.007**
Population Density - Persons per Square Kilometre	-0.022	0.010	-0.292	-2.098	**0.050**
Prevalence of Coronary Artery Bypass Surgery per 100,000 Population	0.151	0.040	0.515	3.755	**0.001**
Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM	-0.960	0.308	-0.458	-3.117	**0.006**

Table 4.6: Coefficients for red cell usage as dependent variable

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.840	0.705	0.627	4.91643

Table 4.7: Model summary – red cells

The parsimonious regression model that related the dependent variable 'Platelet Usage per 1000 Population' to the explanatory variables displayed one significant predictor – Prevalence of Coronary Artery Bypass Surgery per 100,000 Population and two marginally negatively correlated ones – 'Per Cent Population over 65 Years' and 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers' (Table 4.8). This model explained 31% of the total variance (Table 4.9).

Model	Unstandardised Coefficients		Standardised Coefficients	t	P-value
	B	Std. Error	Beta		
(Constant)	11.877	3.923		3.028	0.006
Per Cent Pop over 65	-0.201	0.110	-0.362	-1.832	0.081
Prev CABS per 100,000 Pop	0.026	0.009	0.527	2.743	**0.012**
All Cancers exc Non-melanoma Skin Cancers – Age Std Rate per 100,000 Pop	-0.017	0.010	-0.359	-1.777	0.090

Table 4.8: Coefficients for platelet usage as dependent variable

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.556	0.310	0.211	1.19381

Table 4.9: Model summary - platelets

The parsimonious regression model that related the dependent variable 'Plasma Usage per 1000 Population' to the explanatory variables identified 2 predictors using a backward procedure (Table 4.10). One of them is marginally positively correlated and the other is negatively correlated: 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population' (P-value = 0.053); and 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM' (P-value= 0.038). However, this two- predictor model explained only 24.7% of the total variance (Table 4.11).

Model	Unstandardised Coefficients		Standardised Coefficients	t	P-value
	B	Std. Error	Beta		
(Constant)	16.357	4.447		3.678	0.001
Prevalence of Coronary Artery Bypass Surgery per 100,000 Population	0.057	0.028	0.393	2.049	0.053
Age Standardised rate per 100,000 population for HL, NHL, Leukaemia & MM	-0.442	0.200	-0.423	-2.208	**0.038**

Table 4.10: Coefficients for plasma usage as dependent variable

R	R Square	Adjusted R Square	Std. Error of the Estimate
0.497	0.247	0.178	3.640

Table 4.11: Model summary – plasma

4.3.1.3 Country ranking

The 22 KPIs (predictors), in Table 4.2 page 70, for each country were combined together to rank the individual country's health system performance. Using IBM© SPSS© Statistics for Macintosh© Version 20.0 each variable was standardised to have a mean of 0 and a standard deviation of 1. The missing values were then replaced by 0. A number of clinical outcomes, more specifically 1 – 6 and 15 – 19, may be termed negative statements since larger values in the variable column signify poorer performance as opposed to the rest of the variables where larger values in the variable column correspond to better performance. In the case of the former variables, the standardised score obtained was multiplied by -1 such that the larger values in the variable column would have a negative score and the smaller values in the column would have a positive score. This computation was performed to correct for the directionality of the negative statements to enable a summation of the scores pertaining to each country with a view to ranking the health system performance of each country (Table 4.12).

Countries	Asthma & COPD Hosp adm in total pop aged 15 years and over (Age std rate per 100,000 population)	CHF & HT Hosp Adm in total pop 15y & over (Age std rate per 100,000 pop)	Diabetes hosp adm in tot pop 15 y and older (age std rate per 100,000 pop)	30 day mort after hosp adm for AMI in total pop 45y & over (age-sex std rate per 100 pts	30 day mort after hosp adm for hgic stroke in total pop 45y & over (age-sex std rate per 100 pts	30 day mort after hosp adm for isch stroke in total pop 45y & over (age-sex std rate per 100 pts	Hip Frac Surg init within 2 days after adm to hosp in total pop 65 y & over (crude rate per 100 pts)	Breast cancer 5y rel surv fem pop 15 y & over (age std surv % - 2008-2013 (or nearest))	Cervical cancer 5y rel surv fem pop 15 y & over (age std surv % - 2008-2013 (or nearest))	Colorectal cancer 5y rel surv tot pop 15 y & over (age std surv % - 2008-2013 (or nearest))	Men - Life Expectancy at 65 Years (Years)	Women - Life Expectancy at 65 Years (Years)	Total Life Expectancy at Birth (Years)	Healthy Life Expectancy at Birth - HALE (Years)	Infant Mortality Rate (Per 1,000 Live Births)	Maternal Mortality Ratio (per 100,000 Live Births)	External Causes of Mortality (Deaths per 100,000 population)	Potential Years of Life Lost (Years Lost per 100,000 Inhabitants Aged 0-69)	Deaths from Cancer (Per 100,000 Inhabitants)	Child Vaccination DTP (% of Children)	Child Vaccination Measles (% of Children)	Flu Vaccination (% of Population Aged 65 Years and Over)	Total Standardised Score
Iceland	0.07	0.80	1.38	0.57	-0.38	0.20	0.99	1.12	1.07	1.32	0.87	0.18	0.85	1.06	1.78	1.11	0.63	1.11	0.43	0.23	-0.15	0.00	15.24
Sweden	0.74	-0.12	0.23	1.35	1.55	0.89	0.78	0.59	0.75	0.00	0.60	0.34	0.72	0.71	1.15	0.82	0.35	0.93	1.03	0.78	0.77	-0.35	14.59
Norway	-0.01	0.44	0.73	1.35	1.26	1.20	0.50	1.50	2.69	0.50	0.46	0.26	0.50	0.59	0.61	0.52	-0.06	0.64	0.46	-0.32	0.04	-0.36	13.50
Switzerland	1.56	0.66	1.06	0.83	1.35	0.82	0.38	0.00	0.00	0.00	1.13	1.13	1.08	1.06	-0.48	0.52	0.51	0.88	1.39	-0.05	-0.15	-0.25	13.44
Italy	1.46	0.00	1.15	0.74	0.86	0.89	-3.15	0.00	0.00	0.00	0.53	0.81	0.81	1.00	0.52	1.11	1.04	0.87	0.38	0.23	-0.51	0.80	9.57
Finland	0.45	-0.39	-0.14	-0.25	1.81	1.34	0.07	0.86	0.05	0.67	-0.01	0.58	0.09	-0.11	1.06	1.41	-1.46	-0.10	1.62	1.06	0.96	-0.25	9.31
Spain	0.05	0.80	1.13	-0.42	-0.24	-0.42	-2.57	0.00	0.00	0.00	0.67	1.37	0.90	0.65	0.52	0.82	1.36	0.70	0.85	0.23	0.96	0.77	8.11
Australia	-1.11	0.50	-1.02	1.13	0.47	-0.39	0.00	1.00	0.26	1.39	0.93	0.81	0.76	0.53	-0.39	0.22	0.49	0.62	0.74	-0.87	0.22	1.24	7.57
Netherlands	0.89	0.66	1.07	-0.33	-0.79	0.37	0.89	-0.17	0.34	-0.20	0.20	0.18	0.41	0.59	-0.03	-0.07	1.04	0.74	-0.68	0.50	0.59	1.21	7.43
France	1.58	0.30	-0.56	0.61	0.22	0.30	0.00	0.00	0.00	0.00	0.93	1.92	0.72	0.88	-0.12	-0.67	-0.26	0.08	0.33	0.78	-0.70	0.68	7.04
Canada	0.36	0.86	0.67	-0.08	-0.60	-0.63	0.15	1.09	0.18	0.70	0.53	0.34	0.90	0.82	-1.02	-0.07	0.27	0.37	0.23	-0.05	0.40	0.82	6.25
Germany	0.47	-1.67	-0.87	-1.07	1.18	0.54	0.34	0.19	-0.12	0.72	0.20	0.02	0.18	0.18	0.24	0.22	1.06	0.38	0.51	0.23	0.77	0.54	4.25
Belgium	0.23	0.88	-0.32	0.10	-0.67	0.06	0.20	0.33	-0.01	0.89	0.13	0.26	0.09	-0.05	0.24	-0.07	-0.50	0.10	0.17	0.78	0.40	0.74	3.98
New Zealand	-1.40	0.54	-0.23	0.70	-0.54	0.34	0.15	0.16	0.75	0.35	0.73	0.10	0.36	0.42	-1.29	-1.26	0.21	0.08	0.16	-0.87	-0.70	0.82	-0.43
United States	-0.63	-0.58	-0.64	1.00	0.51	1.75	0.00	1.33	-0.76	0.99	0.26	-0.37	-0.62	-0.87	-2.37	-2.15	-0.63	-1.12	0.79	-0.05	-0.51	0.83	-3.85
Denmark	-0.59	0.53	-0.10	0.18	-0.83	-0.60	0.85	0.21	0.40	-0.52	-0.34	-1.01	-0.40	-0.05	0.61	-0.07	0.71	0.19	-1.03	-1.70	-1.61	-0.12	-5.27
United Kingdom	-0.24	1.36	1.11	-0.38	-0.58	-1.22	0.18	-1.42	-2.20	-2.31	0.46	-0.06	0.23	0.18	-0.66	-0.67	1.14	0.20	-0.28	-0.60	-1.25	1.12	-5.87
Ireland	-1.47	0.63	-0.11	0.14	-0.27	-0.25	0.03	-0.87	-2.57	-0.67	0.06	-0.06	0.18	-0.11	0.43	-0.37	0.28	0.18	-0.79	-0.32	-0.51	0.16	-6.30
Slovenia	1.19	0.13	0.54	0.18	-1.03	-2.15	-1.40	-0.87	-0.28	-0.07	-0.61	-0.21	-0.26	-0.40	1.24	-0.37	-1.61	0.03	-1.37	0.23	0.40	-1.50	-8.19
Austria	-1.05	-1.87	-2.82	-1.93	0.79	0.72	0.16	-0.93	-0.68	0.55	0.20	0.34	0.23	0.47	-0.03	1.11	0.19	0.30	0.52	-3.35	-3.08	-0.76	-10.92
Czech Republic	0.85	-1.21	-1.44	0.14	0.04	-0.56	0.29	-1.28	-0.44	-2.28	-1.41	-1.56	-1.11	-1.22	0.79	0.82	-0.40	-0.44	-1.18	1.06	0.96	-1.49	-11.10
Slovakia	-0.94	-2.72	-0.95	-0.51	-0.84	-0.94	0.00	0.00	0.00	0.00	-2.15	-2.19	-2.05	-1.86	-1.74	0.52	-0.39	-1.70	-0.93	1.06	1.14	-1.06	-18.25
Hungary	-1.81	-0.54	0.12	-2.62	-2.12	-0.08	0.53	0.00	0.00	0.00	-2.22	-2.03	-2.46	-2.38	-1.20	-2.45	-1.22	-2.55	-2.74	1.06	1.14	-1.00	-24.58
Estonia	-0.67	0.00	0.00	-1.45	-1.15	-2.19	0.63	-2.86	0.56	-2.03	-2.15	-1.16	-2.10	-2.09	0.15	-0.97	-2.74	-2.49	-0.61	-0.05	0.40	-2.57	-25.52

Table 4.12: Ranking of health system performance by country using standardised scores

In order to validate the ranking exercise, the scores obtained through this analyses were compared to the Health Related sustainable Development Goals Index published in the Lancet last year (GBD 2015 SDG Collaborators, 2016) (Table 4.13).

Countries	Total Score	Health Related Sustainable Development Goals Index (Lancet 2016)
Iceland	15.24	85
Sweden	14.59	85
Norway	13.50	81
Switzerland	13.44	78
Italy	9.57	78
Finland	9.31	82
Spain	8.11	82
Australia	7.57	81
Netherlands	7.43	82
France	7.04	77
Canada	6.25	81
Germany	4.25	80
Belgium	3.98	79
New Zealand	-0.43	74
United States	-3.85	75
Denmark	-5.27	79
United Kingdom	-5.87	82
Ireland	-6.30	81
Slovenia	-8.19	76
Austria	-10.92	74
Czech Republic	-11.10	74
Slovakia	-18.25	73
Hungary	-24.58	73
Estonia	-25.52	74

Table 4.13: Health system performance ranking: comparison between score based on clinical outcomes and the health related sustainable development goal index

The Pearson Correlation between the two groups of values showed quite significant correlation with a Pearson Correlation Coefficient of 0.756 with a

P-value of 0.000019. This demonstrated strong concordance between the two sets of values.

A Pearson Correlation was computed to measure the strength of the relationship between 'Red Cell Usage per 1,000 Population', 'Platelet Usage per 1,000 Population' and 'Plasma Usage per 1,000 Population' (Table 3.4, page 42) on the one hand and the standardised score (Table 4.12) obtained through the previous analysis (Table 4.14).

Pearson Correlation		Standardised Score
Red Cell Usage per 1000 population	Correlation Coefficient	0.107
	P-value	0.620
Platelet Usage per 1000 population	Correlation Coefficient	0.258
	P-value	0.223
Plasma Usage per 1000 population	Correlation Coefficient	-0.122
	P-value	0.569

Table 4.14: Correlation analysis between blood product usage and the standardised score

All Pearson correlations (0.107, 0.258 and -0.122) are close to 0 indicating that each relationship is rather weak. Moreover, the p-values (0.620, 0.223 and 0.569) all exceed the 0.05 level of significance indicating that each pairwise relationship is not significant.

4.4 Discussion

The analyses performed in the previous section suggests that for red cell transfusion rates per capita, most (70%) of the apparent variation in usage between countries can be explained by a number of underlying contributors that are peculiar to each country. The models for platelet use and plasma use, however, could explain a lesser amount of the variation.

4.4.1 Population demographics

Population demographics, more specifically the 'Per Cent Population over 65 Years' is clearly associated with the variation in usage at least for red cells. The extent of the correlation is substantial as demonstrated by the high Pearson Correlation figure of 0.556, the second highest in the analysis. This predictor is also the highest contributor in the regression model for red cells after the constant.

This is congruent with data found in the literature showing a disproportionate increase in blood usage in the elderly population as demonstrated in the following examples: A Belgian study published in 2007, reviewing the data for the year 2000, showed that patients over 65 years of age accounted for more than 66% of individuals receiving blood (Beguin *et al.*, 2007). Wells and co-workers, in a retrospective multi-centre epidemiological study in the UK showed that the median age for red cell recipients was 69 years and for FFP recipients it was 64 years while that for platelet recipients was 59 years (Wells *et al.*, 2009). Also, in Finland 70- to 80-year olds have been shown to have an 8-fold higher consumption than 20- to 40-year olds (Ali *et al.*, 2010).

The analyses presented above partially parallels modelling performed by Ali et al in their 2010 paper, where red cell usage according to Finnish practice was superimposed on to the population demographics of other countries (Ali *et al.*, 2010). One conclusion that this study makes, that the increasing population of elderly patients in most countries will have significant impact on the demand for red cells, is corroborated by the findings in this chapter. However, the authors went on to comment that the difference in usage observed between the lowest-using country and the highest-using country can be fully explained by the different national population pyramids, a position which was endorsed also by Seifried et al (Seifried *et al.*, 2011). This is in contrast with the current findings. Both the linear correlation process and the regression analysis have shown that population demographics, more specifically 'Per cent population over 65 Years', though certainly quite significant, is only one of a number of factors (some of which may not even have been addressed in this particular analysis) that partially explain the variance. Moreover, even all together, the predictors identified by the regression model were only capable of addressing 70% of the variation.

4.4.2 Clinical drivers of blood product use

4.4.2.1 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population'

This predictor was the most consistent across most analyses. Correlation was shown with red cell use in both the linear correlation and the regression analysis. The Pearson correlation in relation to platelet use demonstrated a marginally significant relationship, as did the regression analyses performed with platelet usage and plasma usage in turn as the dependent variables.

The association between cardiac surgery and high red cell use is not surprising and well known (Stover *et al.*, 1998) with 20% of all blood products transfused worldwide being attributed to coronary artery bypass graft procedures (Snyder-Ramos *et al.*, 2008). The US 2011 Nationwide

survey quotes a figure of 50% of all platelets transfused being used in cardiac surgery (Department of Health and Human Services, 2013). Fairly recent studies have continued to confirm this, including a review of data on 364,532 surgical in-hospital stays in Belgium which showed that 8% of the surgical transfusion costs were associated with coronary artery bypass surgery (Beguin *et al.*, 2007) and in Finland, of all blood components used, 16% were transfused for cardiac and circulatory disorders (Ali *et al.*, 2010). Similarly in Germany, cardiac surgery is responsible for almost 30% of red cell use, (Greinacher *et al.*, 2010). Increasingly, though, patients with coronary artery disease are undergoing medical interventions such as stenting rather than coronary artery bypass surgery (Fajadet & Chieffo, 2012). These non-surgical interventions are associated with less usage of blood products and therefore, in the future, transfusion in this category of patient can be expected to decrease.

4.4.2.2 'Prevalence of Hip Replacement Surgery per 100,000 Population'

The significantly positive correlations of 'Prevalence of Hip Replacement Surgery per 100,000 Population' with a high number of other predictors led to a dilution of its effect on 'Red Cell Usage per 1000 Population' when all the predictors were included in a Regression Model and it lost its initial significance as an independent predictor.

4.4.2.3 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM'; 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers'

Both these predictors were negatively correlated with blood product use. In the Pearson Correlation 'Age-standardised Rate per 100,000 Population for HL, NHL, Leukaemia & MM' correlated marginally with red cell use and

significantly with Plasma use. This correlation was confirmed in both corresponding regression models. 'Age-standardised Rate per 100,000 Population for All Cancers Excluding Non-melanoma Skin Cancers' was significantly negatively correlated with platelet use in the Pearson correlation, however the significance decreased to a marginal level in the corresponding regression model. This predictor was also marginally negatively correlated to plasma use in the Pearson correlation, a finding which was completely absent in the corresponding regression model.

A number of studies have shown that malignancies are associated with high blood use. A review of data on 589,936 medical in-hospital stays in Belgium, showed that oncological patients including individuals with haematological malignancies were responsible for around 40 % of transfusion costs (Beguin *et al.*, 2007). In Finland, haematological malignancies were responsible for 21% of transfusions (Ali *et al.*, 2010), and in Germany around 10% (Greinacher *et al.*, 2010).

The relationship between blood product use and a country's burden of malignancy is a complex relationship. Cancer incidence is known to increase with a country's wealth, while mortality from cancer has an inverse relation with markers of prosperity, as does the mortality/incidence ratio (Ades *et al.*, 2013). Predictors for cancer incidence include lifestyle, nutrition and infections (World Health Organisation, 2003), all effectors for other diseases which would themselves have an impact on blood product use.

Further analyses allowed some more insight into this relationship. Platelet usage was found to correlate significantly with 5-year survival in patients with colorectal cancer and was found to have an inverse relation with deaths from cancer. Or, patients with cancer fare better in countries where more platelets are used. In general, patients experience better survival within the context of health services which provide good access to care, more screening for cancer and better treatment for cancer. These conditions are commoner

in countries with better funded services. Platelets are the more expensive blood product amongst the three. In the United States, a platelet unit would cost 2.5 times the price of a red cell pack and 5 times a plasma pack (Toner *et al.*, 2011), and in the UK, the NHS blood component price list indicates prices of £120.00 for standard red cells, £193.15 for platelets and £28.46 for plasma (NHS Blood and Transplant, 2016). The point can perhaps be argued, therefore that platelets, being the more expensive product, are used more in countries with better funded health services.

4.4.3 Funding

4.4.3.1 'Health Care Expenditure per Capita (Current US$ Purchasing Power Parity)'; 'Gross Domestic Product per Capita (Current US$)'; 'Human Development Index'

Of these 3 predictors, the analysis draws attention to 'Health Care Expenditure per Capita (Current US$ Purchasing Power Parity)'. Initially there appeared to be no relationship between this predictor and 'Red Cell Usage per 1000 Population' in the Pearson correlation (Pearson Correlation = 0.308, p-value = 0.110). However, an additional analysis correlating red cell use with health spending while controlling for population over 65 showed a significant relationship (Pearson correlation = 0.430, p-value = 0.032). The regression analysis also portrayed a striking significance between this predictor and 'Red Cell Usage per 1000 Population' (p value = 0.007). A similar relationship was not present in the platelet and plasma analyses.

Funding of Blood Establishments is normally determined by the revenue made from the *sale* of blood products. Different mechanisms exist. The two main funding models are (1) actual revenue made from billing hospitals for the blood products provided, or (2) drawing down a budget from the national

health service with blood products being supplied to hospitals free of charge. The operating revenue of these not-for-profit institutions is quite substantial e.g.

- Finland – Finnish Red Cross Blood Service: >€74,000,000 (Finish Red Cross Blood Service, 2010)
- UK – NHS Blood and Transplant: >£550,000,000 (NHS Blood and Transplant, 2010)
- Netherlands – Sanquin: >€353,000,000 (Sanquin, 2010)
- Ireland – Irish Blood Transfusion Service: >€110,000,000 (Irish Blood Transfusion Service, 2010)

A case for supply-driven use may certainly be argued especially in countries where the distinction between the haematologists working within the Blood Establishments, who therefore manage blood collection, and the haematologists working on the hospital floor, and therefore requesting blood components for their patients, is blurred.

The correlation together with the point made in the previous section (4.4.2.3) suggests the very real possibility of a relationship with supply-sensitive care, a concept that is described by Wennberg in his book *Tracking Medicine* (Wennberg, 2010), and that contributes towards unwarranted variation. This is a phenomenon that was identified during the 1970's and 1980's in the USA when a number of studies showing geographic variation of care (Wennberg & Gittelsohn, 1973) concluded that patient care did not necessarily depend only on the severity of the condition or on patient choice of treatment but also on the ease of availability of materials and services to the caring physician. Significantly, in his treatise on the subject, Wennberg goes on to make the statement that more is not necessarily better. This premise adds credence to the fact that physicians' decisions on transfusion are not always based on evidence-based practice but are also influenced by increased availability of

blood components. This concept will be analysed in further depth in the next chapter.

4.4.4 Population density

The inverse relation to 'Population Density – Persons per Square Kilometre' may be a reflection of the higher stock of blood components remote hospitals, in countries with large areas which are sparsely populated, are forced to carry in order to ensure that they can cover for all eventualities. Remote hubs have to carry enough blood products to cope with emergencies and disasters, as one cannot always afford to wait long enough for supplies to reach these areas. On the other hand, hospitals in areas of countries where population density is higher, are more likely to be situated closer to each other and therefore may possibly rely on timely help from neighbouring depots. A point that lends some weight to this hypothesis is that when reporting blood component usage, as pointed out earlier in the chapter, some countries actually use a surrogate value – 'blood components distributed', which though close enough to the actual usage, may be slightly inflated by the extra components that are distributed to remote hubs, only to be discarded when not used.

4.4.5 Country ranking

The key performance indicators chosen for this analysis reflect the diversity of the processes occurring all along the pathway to health service delivery including funding, human resources, equipment, bed availability, ease of access, policy penetrance, etc. The ranking obtained using this analysis was validated by a comparison to the Health Sustainable Goal index (GBD 2015 SDG Collaborators, 2016), a tool based on the Global Burden of Diseases Project, designed to provide data to policymakers helping them to understand the nature of their individual country's health challenges, and allowing them therefore to implement strategies to improve their health

systems. It is based on premature death and disability data, by age and sex from 1990 to the present, for more than 300 diseases in almost 200 countries, as collected and analysed by more than 1800 collaborators in 124 countries (www.healthdata.org/gbd). A highly standardised approach is used to overcome issues of inconsistent coding and definitions and a number of mechanisms have been put in place to ensure independence, to review progress and to provide recommendations (Murray *et al.*, 2013). Very tight concordance was demonstrated between the two tools.

The analysis showed that blood product usage does not predict for overall health system performance and neither does better health system performance predict for any particular usage of any of the blood products.

4.5 Conclusion

Up to this point, the following has been established:

1. There is significant variation between the rates of usage of blood components across a number of countries though this does not correlate with overall health service performance. The variation therefore cannot be explained by different health system outcomes but must be related to other reasons.
2. The rate at which blood products are used, seems to be associated with a number of predictors which can contribute to a portion of the variation in blood product usage across different countries. These predictors include
    a) The percentage of the country population that is over 65 years of age
    b) The population density within the specific country
    c) Clinical activity as represented by CABG and the burden of cancer

d) Amount of funding within the individual country's health services

3. A certain amount of residual variation is unexplained by the predictors identified.

It is certainly clear that the variation in blood product usage across countries cannot all be explained away simply by invoking an argument centred around a different demographic, namely the percentage of the population over 65 years in the individual countries, as others have done (Ali *et al.*, 2010; Seifried *et al.*, 2011). Differences in clinical activity, and the variable scoping in health care funding, also demonstrably contribute to this variation. Out of all this arises an important question surrounding the relationship of these variables with blood product usage, i.e. whether the variation seen is representative purely of a different burden of disease in the different countries (and regions), and therefore constitutes effective care, or whether there may be an element of it that is supply-related and could therefore represent unwarranted variation. This query is the central topic dealt with in the next chapter.

Chapter 5

Effectors of Variation in Blood Transfusion Practices

5. Effectors of Variation in Blood Transfusion Practices

5.1 Unwarranted Variation in Health Care

In 2014 an OECD publication looking at variation in health care both across and within 13 countries, focusing on a selected set of high volume and high-cost health care activities, reported that there is substantial evidence to suggest that large geographic differences in health care provision are not consistent with disease burden or indeed, with patient preference. Rather it appears that in areas of high activity, unnecessary care is being provided. Differences in supply of services, and diversity in medical practices were cited as playing significant contributory roles towards creating this variation (Organisation for Economic Co-operation and Development, 2014). This forms part of a body of literature on unwarranted variation in healthcare reporting diagnostic and interventional practices that are dependent on geographic location on a country by country basis or on a region by region basis. In truth, the concept that a number of medical procedures may be unnecessary, and may result in harm to the patient rather than benefit, is an old one (Glover, 1938). Much of the published work on geographical variation in health care provision details the significant difference in practice across regions.

Considered a seminal paper, John Wennberg's original publication, in 1973, examined the extent to which bed and manpower use, expenditure and procedure utilization varied among hospital service areas in the state of Vermont (Wennberg & Gittelsohn, 1973). The authors found large differences in neighbouring communities a mere 20 miles apart which, they explained, were based more on behavioural and distributional differences than on

differences in illness patterns. Wennberg and his colleagues went on to establish the Dartmouth Atlas of Health Care through which much of the notional, methodological and illustrative work on variation in health care provision in the USA was performed (www.dartmouthatlas.org). Apart from consistently showing that the identified extensive small-area variations in care delivery cannot be explained by illness and patient behaviour, their work also highlights the fact that usage is influenced by attributes of the local physicians, and that physician opinion acts as a driver of demand for surgery. Patterns of practice variation were uncovered. In surgery, there was marked variation for specific procedures which were distinctive and persistent over time, for example the rate of tonsillectomy in the highest performing state was 10 times that of the lowest performing state. Hospitalisation rates for acute and chronic medical conditions were consistent from one cause of admission to another. However a region tended to have high rates or low rates in general. A few conditions stood out, in that variation was consistently low across the board. This happened with conditions such as myocardial infarctions, gastro-intestinal bleeds and strokes, and procedures like colectomy for colon cancer, herniorrhaphy, and hip repair.

All this was mirrored by similar work carried out in other countries where similar initiatives were taken and atlases documenting geographic variation were set up. These resources are now available in Canada (www.ices.on.ca) (Eskander *et al.*, 2015), England (www.fingertips.phe.org.uk) (Public Health England, 2015), Australia (www.safetyandquality.gov.au) (Australian Commission on Safety and Quality in Health Care, 2015), and Spain (www.atlasvpm.org) (Tebe *et al.*, 2013). ECHO, or the European Collaboration for Healthcare Optimisation is a recent initiative, funded through a European Framework 7 grant, led by a Spanish team from the Aragon Health Sciences Institute (IACS) in collaboration with partners from Denmark, Portugal, Austria, England and Slovenia (www.echo-health.eu). This group put together a number of atlases reporting unwarranted

differences in health systems performance across the various participating countries (Garcia Armesto *et al.*, 2014).

A recent systematic review of the literature on medical practice variations included 836 publications (between 2000 and 2011) that met the study criteria. All showed significant variation across regions, hospitals and physician practices in the treatment of many conditions and the supply of resources both between and within OECD countries. Many of the publications included in the review looked at specific clinical conditions mostly cancer, cardiovascular, gynaecological, musculoskeletal and respiratory diseases. Variation studies in immunization, screening and diagnostic testing were very prominent with the last category showing, for example, a 70-fold difference in the frequency of CT scans ordered for specific conditions and a 50-fold difference in diagnostic MRI scans ordered for breast cancer across hospitals in Ontario, Canada. Publications looking at medical admissions, elective surgical admissions, and the supply of health care resources per capita such as physician supply, bed supply and advanced technology (e.g. mammography units) were also well represented (Corallo *et al.*, 2014).

This variation in practice is echoed by the variation in blood product usage shown earlier on. A variation that also appears to follow higher levels of activity.

5.1.1 Sources of unwarranted variation

Based on this literature, a theoretical model (Figure 5.1) has been proposed mainly by the Dartmouth Atlas researchers identifying three categories of service (Table 5.1) that helps explain unwarranted variation, which is defined as medical practice variation across regions or provider groups that is not explained on the basis of illness or patient need.

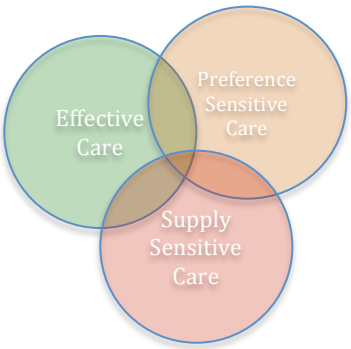

Figure 5.1: Service categories encapsulating unwarranted variation representing underuse of effective care, misuse of preference sensitive care and overuse of supply sensitive care (adapted from Dartmouth Atlas Project)

Effective Care[1]	Effective care refers to services that are of proven value and have no significant tradeoffs – i.e. the benefits of the services so far outweigh the risks that all patient with the specific medical need should receive them
Preference-sensitive Care[2]	Preference-sensitive care comprises treatments that involve significant tradeoffs affecting the patient's quality and/or length of life. Decisions about these interventions – whether to have them or not, which ones to have – ought to reflect the patients' personal values and preferences, and ought to be made only after patients have enough information to make an informed choice. Sometimes the scientific evidence on the main outcome is quite good; other times the evidence is weaker
Supply-sensitive Care[3]	Supply-sensitive care is care whose frequency of use is not determined by well-articulated medical theory, much less by scientific evidence. Supply-sensitive services include doctor visits, diagnostic tests and hospitalisations. The use of supply-sensitive care varies widely across regions within countries and across countries. Where there is greater capacity, more care is delivered – whether or not it is warranted

Table 5.1: Definitions of effective care; preference-sensitive care; supply-sensitive care [1 - (Dartmouth Atlas Project, 2007a); 2 - (Dartmouth Atlas Project, 2007b); 3 - (Dartmouth Atlas Project, 2007c)]

Part of this geographic variation has been attributed to over-utilisation (Emanuel & Fuchs, 2008). Over the years it has been robustly shown that due to a number of considerations, ranging across methods of physician remuneration, increased availability of resources, fear of litigation, and culture and physician attitudes, this variation in practice contributes to overdiagnosis and overtreatment which wastes resources and may even effectively lead to patient harm (Hicks, 2015; Ralston & Schroeder, 2015).

Though no formal definition exists for over-diagnosis (Carter *et al.*, 2015), it has come to represent a state of affairs where, as a consequence of a number of issues, individuals are diagnosed with conditions that would never cause symptoms or morbidity had they remained un-diagnosed (Malhotra *et al.*, 2015). This can then lead to over-treatment a term that includes (i) treatment of these over-diagnosed conditions and (ii) also encompasses treatment that has minimal evidence of benefit or is excessive relative to alternative accepted standards (Malhotra *et al.*, 2015). A classic example of this is transfusing blood products to patients whose clinical circumstances do not require them, a common enough situation in many hospitals. Both types of over-treatment have the potential of causing patient harm. In the cases brought about by over-diagnosis harm can happen either directly e.g. radiation from unnecessary imaging, or indirectly when it leads to unnecessary downstream treatment. Unnecessary treatment also has the potential for both anticipated and unanticipated negative consequences a significant possibility also associated with blood transfusion as evidenced by the haemovigilance data highlighted in Chapter Three.

Over-diagnosis and over-treatment have been grouped together under the term 'Over-use', a phenomenon that has been recognized to contribute to the projected unsustainability of quality health care worldwide. In the USA it is estimated that around a third of medical practice may qualify as 'Over-use' (Institute of Medicine, 2012). Similar findings, though perhaps not to as large

an order, are also found in other countries (Malhotra *et al.*, 2015; Vogel, 2015).

5.1.2 Supply sensitive care as a source of unwarranted variation

Supply sensitive care, a term coined by Wennberg in the seventies, and later incorporated into the model of service proposed by the Dartmouth Atlas refers to the influence supply of resources has on utilisation rates (Wennberg & Gittelsohn, 1973). Within this concept, the level of utilisation of beds, tests and procedures is therefore not dependent on any specific medical evidence but is a consequence of local capacity. Therefore in regions where more hospital beds per capita are available, hospital admissions rates are higher; in areas with more doctors per capita, more specialist visits occur; and where more CT scanners are available, more CT scans are performed on patients (Wennberg, 2010). These relationships have been demonstrated quite consistently (www.dartmouthatlas.org). The converse is also true in that where there are fewer medical resources less utilisation occurs, and therefore patients receive less care. These latter patients, though, do not experience any less survival or poorer quality of life when compared to their counterparts in other geographic locations that have more resources and consequent higher health care spending (Rothberg *et al.*, 2010).

The analysis in the previous chapter showed a correlation between the availability of resources, in the form of funding, and increased transfusion of blood products. It also showed a relationship between high clinical activity and higher blood product usage. It is therefore very plausible to extrapolate that the same factors also influence the way doctors practice transfusion medicine. Over-diagnosis and over-treatment will have an effect on blood product usage, since blood transfusion is used in various surgical procedures, in various medical conditions including anaemia and thrombocytopaenia, in hereditary and acquired coagulation disorders and in haematology / oncology patients.

One driver for supply sensitive care is thought to be *Fee for Service*, a re-imbursement model where services provided are un-bundled and paid for separately. This has been blamed for contributing to over-use as it is implicated in incentivising quantity rather than quality. Much has been made of this, especially in the USA, and recent legislation has attempted to re-engineer re-imbursement processes into associating payment with quality or value (McMahon & Chopra, 2012). This is by no means a problem restricted to the United States. A recent broadly inclusive longitudinal study showed that higher reported achievement incentivised under the *Quality and Outcome Framework* (QOF – a pay for performance instrument) in the UK has not reduced premature deaths in the population (Kontopantelis *et al.*, 2015). To date no link has been reported between supply-sensitive care, or the effect of *fee for service* re-imbursement models, and Transfusion Medicine (Aubuchon *et al.*, 2010). Whether this link exists, and therefore blood product use is also a victim of supply sensitive care, is discussed below.

5.1.3 Predictors of supply sensitive care

In general terms supply sensitive care constitutes the additional frequency of clinical activities such as doctors' visits, diagnostic tests and hospital admissions related to the capacity of the local health care system (Wallace *et al.*, 2012). As far as diagnostic tests are concerned, it is well known that medical imaging such as computerized tomography (CT), mammography and magnetic resonance imaging (MRI), is one of the areas where over-use is common. It is estimated that 10 – 30% of imaging is performed for inappropriate indications (Rubin *et al.*, 2015). CT has been promoted incorrectly for tumour detection (Djulbegovic & Paul, 2011), for example. Though mammography does have some benefit in screening for breast cancer, analyses have shown that a very small percentage of women are actually helped by the test (Welch & Frankel, 2011). In one study over half the requests for a MRI test were found to be inappropriate or of uncertain

value (Emery *et al.*, 2013). Table 5.3, (page 108), lists the identified predictors for supply sensitive care.

5.1.4 Professional uncertainty and difficulty with change as effectors of unwarranted variation

Within the context of unwarranted variation, the professional uncertainty hypothesis as defined by Wennberg and Gittelsohn, in 1982, (Wennberg *et al.*, 1982) takes into account the degree of uncertainty physicians face in making decisions. The authors linked the diversity in surgical practice to differences in beliefs among doctors when it came to considering the indication and efficacy of a procedure when faced with circumstances in which clinical science was inadequate. This hypothesis became one of the central themes employed to rationalise unwarranted variation.

It was proposed that in general, procedures with low variation such as colectomy for colon cancer, hernia or hip repair, or treatment for myocardial infarction or gastrointestinal bleeds were ones where the condition to be treated could be reliably diagnosed, and where there was significant consensus on the value of the procedure. On the other hand, high variation procedures like cardiac surgery would have the converse characteristics bringing professional uncertainty to the fore. This theory has been expounded upon by a number of authors and has been central to the explanations given for variation both on a regional level and across countries (Birkmeyer *et al.*, 2013; Weeks *et al.*, 2014) and has been used also to explain away variation in other circumstances, for example variation in primary health care services (Grytten & Sorensen, 2003).

Evidence shows that clinicians tend to regret the consequences of unnecessary treatments, less than the consequences of not administering treatment, especially when they perceive that treatment may have led to

some benefit (Djulbegovic & Paul, 2011). Therefore they tend towards giving the treatment to avoid uncertainty. The medical culture of shame and blame has been a fundamental of Western medical training for generations. Universal trust in the limitless capacity of medicine is ingrained in modern Western medical culture (Hoffman & Kanzaria, 2014). This phenomenon predicates an insistence on perfect results and a consequent lack of tolerance for what in fact is inevitable morbidity and mortality. An outcome that is less than ideal therefore becomes reflective of a perceived bad process. This inevitably puts huge pressure on doctors to try to be perfect and to strive for 'certainty' (Kassirer, 1989), one consequence being that uncertainty should be avoided at all costs and that one should therefore err in favour of 'doing more'.

Lack or delay in take-up of new evidence by doctors as it becomes available has also been identified as an issue in the context of misuse or over-use in health care services (Institute of Medicine, 2001). Despite the wealth of evidence, its systematic and consistent application still defies most institutions (Oxman *et al.*, 1995). Though a number of strategies have been employed to alter this state of affairs, there seems to be a lack of effectiveness in translating research into practice (Bero *et al.*, 1998). The report of the Institute of Medicine, Crossing the Quality Chasm, indicates an average lag of 17 years for new evidence to be introduced into daily practice (Institute of Medicine, 2001). Research that could have made a difference has often been ignored for a long time e.g. using crystalloid instead of colloid for volume replacement in shock (Perel *et al.*, 2013). The social context within which implementation of change, on foot of new evidence, occurs is of course a determining factor and the culture of each organisation plays a significant role (Stetler, 2003). Its capacity to identify, interpret, share and put new evidence in use is critical (Wensing *et al.*, 2006). The promotion of a learning culture within the organisation and proactive leadership are also very important for the implementation of change (Nelson *et al.*, 2002).

It is plausible to speculate that professional uncertainty and difficulty with change also hold true in the practice of blood transfusion. As highlighted in Chapter Three, it was less than 20 years ago that the first seminal double blind randomised trial looking at transfusion triggers (Hebert *et al.*, 1999) was performed. Prior to that practice was based mostly on tradition and anecdotal experience. Guidelines have incorporated this new evidence but it is probably reasonable to assume that there is a delay in putting this evidence into use.

5.2 Cultural Constructs and Health Care

Notions such as avoiding uncertainty and openness to change form part of organisational culture. Geert Hofstede devised a model through which he measured the strength of country-specific cultural dimensions within an organisation (Hofstede, 2001). This model is one of the most frequently cited in publications looking at behavioural differences across different countries (Kirkman *et al.*, 2006). Hofstede in his model defines culture as "the collective programming of the mind that distinguishes the members of one group or category of people from another" (Hofstede *et al.*, 2010). The model is based on systematic analysis of detailed survey data about the values of employees working in local subsidiaries of a large multi-national corporation: IBM. This revealed common problems but with solutions differing from country to country in specific dimensions:

1. Social inequality, including the relationship with authority
2. The relationship between the individual and the group
3. Concepts of masculinity and femininity
4. Ways of dealing with uncertainty and ambiguity

The culture dimensions were named 'Power Distance', 'Collectivism vs Individualism', 'Masculinity vs Femininity' and 'Uncertainty Avoidance'. Later

in collaboration with other individuals an additional two dimensions were described: ‘Long vs Short Term Orientation’ and ‘Indulgence vs Restraint’ (Table 5.2).

Power Distance (pdi)	The extent to which the less powerful members of institutions and organisations within a country expect and accept that power is distributed unequally
Collectivism vs Individualism (idv)	Individualism pertains to societies in which the ties between individuals are loose: everyone is expected to look after him/herself and his and her immediate family. Collectivism pertains to societies in which people from birth onward are integrated into strong, cohesive in-groups, which throughout people's lifetime continue to protect them in exchange for unquestioning loyalty
Masculinity vs Femininity (mas)	A society is termed masculine when emotional gender roles are clearly distinct: men are supposed to be assertive, tough and focussed on material success, whereas women are supposed to be more modest, tender and concerned with quality of life. A society is termed feminine when emotional genders overlap: both men and women are supposed to be modest, tender and concerned with the quality of life.
Uncertainty Avoidance (uai)	The extent to which the members of a culture feel threatened by ambiguous or unknown situations.
Long vs Short Term Orientation (ltowvs)	Long term orientation stands for the fostering of virtues oriented toward future rewards – in particular perseverance and thrift. Short term orientation stands for the fostering of virtues related to the past and present – in particular, respect for tradition, preservation of face, and fulfilling social obligations.
Indulgence vs Restraint (ivr)	Indulgence stands for a tendency to allow relatively free gratification of basic natural human desires related to enjoying life and having fun. Restraint reflects a conviction that such gratification needs to be curbed and regulated by strict norms.

Table 5.2: Geert Hofstede's culture dimension definitions adapted from *Culture and Organisations: Software of the Mind: Intercultural Cooperation and its Importance for Survival. 3rd Edition*

Professional uncertainty and difficulty with change are best represented by 3 of the dimensions; the Uncertainty Avoidance Index (UAI), the Power

Distance Index (PDI), and the Individualism vs Collectivism construct, since they capture notions such as the ability to cope with new situations, conformity with the status quo, and dealing with uncertainty. In this culture model, for every country, each dimension is assigned a discrete value depending on the positioning of the particular country within the spectrum of the individual cultural dimension.

These constructs are used below to explore the extent blood transfusion practice is influenced by professional uncertainty and difficulty with change.

5.3 Analyses

5.3.1 Supply sensitive care

A representative dataset (Table 5.3) comprising markers whose variation is associated with supply sensitive care has been compiled using information from the OECD database (Organisation for Economic Co-operation and Development, 2016a). The table was populated with data for 2009/2010 or the nearest year. Data that were missing were tabled as N/A or *not available.* The markers are listed below together with their unique digital object identifier (DOI) numbers for ease of reference.

'Hospital Beds Per 1,000 Inhabitants' (https//doi.org/10.1787/0191328e-en) and 'Hospital Discharges Per 100,000 Inhabitants' (https//doi.org/10.1787/5880c955-en) are included as markers for hospital activity. The markers representing diagnostic tests and hospital equipment include 'CT Scanners Per 1,000,000 Inhabitants' (https//doi.org/10.1787/bedece12-en), 'MRI Units Per 1,000,000 Inhabitants' (https//doi.org/10.1787/1a72e7d1-en), Mammography Machines Per 1,000,000 Inhabitants' (https//doi.org/10.1787/685c9c5e-en), 'Radiotherapy Equipment Per 1,000,000 Inhabitants' (https//doi.org/10.1787/47a5492f-en), 'CT Exams Per 1,000 Inhabitants' (https//doi.org/10.1787/3c994537-en) and 'MRI Exams Per 1,000 Inhabitants' (https//doi.org/10.1787/1d89353f-en). 'Doctors Consultations Per Capita' (https//doi.org/10.1787/173dcf26-en), 'Medical Doctors Per 1,000 Inhabitants' (https//doi.org/10.1787/4355e1ec-en), 'Nurses Per 1,000 Inhabitants' (https//doi.org/10.1787/283e64de-en), 'Medical Graduates Per 100,000 Inhabitants' (https//doi.org/10.1787/ac5bd5d3-en) and 'Nurse Graduates Per 100,000 Inhabitants' (https//doi.org/10.1787/c54611e3-en) represent professional staffing and clinical activity.

Statistical analysis was performed using IBM® SPSS® Statistics for Mackintosh Ver 20. The data in Table 5 were used as predictors in this analysis and the data in Table 3.4 (page 42) for blood product usage were used as the independent variables.

	Health Activity and Resource Predictors												
Countries	Hospital Beds (Per 1,000 Inhabitants)	CT Scanners (Per 1,000,000 Inhabitants)	MRI Units (Per 1,000,000 Inhabitants)	Mammography Machines (Per 1,000,000 Inhabitants)	Radiotherapy Equipment (Per 1,000,000 Inhabitants)	Doctor Consultations (Per Capita)	Hospital Discharges (Per 100,000 Inhabitants)	CT Exams (Per 1,000 Inhabitants)	MRI Exams (Per 1,000 Inhabitants)	Medical Doctors (Per 1,000 Inhabitants)	Nurses (Per 1,000 Inhabitants)	Medical Graduates (Per 100,000 Inhabitants)	Nurse Graduates (Per 100,000 Inhabitants)
Australia	3.77	39.14	5.72	24.62	8.90	6.60	16593.90	92.60	21.20	3.12	10.18	10.88	63.54
Austria	7.68	29.36	18.46	22.29	5.03	6.90	27912.90	NA	NA	4.69	7.63	20.69	48.01
Belgium	6.51	NA	NA	NA	NA	7.60	17057.90	187.10	65.30	2.92	9.42	7.88	37.25
Canada	2.80	13.80	7.91	16.23	NA	7.60	8282.90	122.60	42.70	2.34	9.32	6.95	45.26
Czech Republic	7.14	14.17	5.74	12.73	8.52	11.20	20899.60	87.90	32.30	3.58	8.09	12.63	13.95
Denmark	3.49	23.72	15.39	17.02	12.67	4.60	16031.00	95.90	53.50	3.54	15.61	21.80	83.23
Estonia	5.37	14.99	7.49	9.86	2.25	6.30	17566.80	153.40	37.40	3.28	6.16	8.99	35.37
Finland	6.25	20.42	15.73	31.65	8.80	4.20	18441.10	23.80	34.70	3.09	13.56	9.37	57.62
France	6.66	11.08	6.43	NA	NA	6.70	17036.70	138.40	55.10	3.27	8.19	6.87	34.30
Germany	8.24	31.24	25.15	NA	NA	9.20	23670.30	114.10	96.40	3.62	11.95	12.29	45.14
Greece	4.93	34.30	22.06	49.88	5.76	4.00	20636.40	325.00	99.30	NA	NA	11.57	25.78
Hungary	7.14	7.18	2.79	14.57	4.09	11.90	21189.90	74.90	31.50	3.02	6.21	9.21	33.61
Iceland	3.72	34.54	21.98	15.70	12.56	6.40	13936.00	156.50	75.70	3.65	15.29	11.62	64.68
Ireland	2.83	14.99	11.69	13.89	8.38	3.80	13024.20	NA	NA	3.01	12.50	15.92	31.75
Italy	3.69	31.85	21.59	32.02	6.33	6.80	14238.30	NA	NA	4.17	6.48	11.31	18.31
Luxembourg	5.47	26.12	14.06	20.09	6.03	6.10	16081.20	194.30	75.50	2.70	11.12	NA	17.88
Netherlands	4.66	11.25	10.95	NA	NA	5.70	11583.80	65.20	43.60	2.92	11.66	12.55	38.24
New Zealand	2.41	14.64	9.76	25.28	8.37	4.10	14555.70	NA	NA	2.58	9.73	7.83	31.21
Norway	4.52	NA	NA	NA	NA	4.00	17721.10	NA	NA	4.05	15.93	10.69	72.23
Slovakia	6.54	13.37	6.13	14.48	10.77	11.60	18851.70	85.90	29.90	3.30	6.07	7.82	56.83
Slovenia	4.60	11.77	6.86	17.16	5.88	6.60	17365.40	42.60	20.70	2.41	8.03	7.94	80.45
Spain	3.16	16.04	12.41	14.58	4.49	7.50	10314.00	85.70	59.60	3.60	4.95	8.37	20.43
Sweden	2.76	NA	NA	NA	NA	2.90	16245.40	NA	NA	3.82	11.03	10.68	NA
Switzerland	5.10	32.80	NA	33.19	16.92	4.00	16873.00	NA	NA	3.83	15.20	9.41	74.10
United Kingdom	3.26	6.68	5.51	8.80	5.10	5.00	13231.70	NA	NA	2.65	9.75	13.18	29.41
United States	3.08	40.87	31.52	41.77	11.30	4.10	13090.70	252.60	95.80	2.44	10.80	6.70	63.43

Table 5.3: Predictors used in analyses (NA = not available)

5.3.1.1 Linear correlation

All the markers were subjected to a Pearson Correlation Coefficient analysis using red cell, platelet and plasma usage per 1000 population in turn as the dependent variables to measure the linear correlation between each dependent variable and each supply sensitive care indicator identified. Using this tool a number of health resources, hospital activity, and diagnostic test markers were found to correlate significantly with each of the 3 dependent variables as tabulated in Tables 5.4, 5.5 and 5.6 respectively.

Significant Relationships	Pearson Correlation	P-value
Red Cell Usage per 1,000 Population - CT Scanners (Per 1,000,000 Inhabitants)	0.561	**0.005**
Red Cell Usage per 1,000 Population - MRI Units (Per 1,000,000 Inhabitants)	0.665	**0.001**
Red Cell Usage per 1,000 Population - Mammography Machines (Per 1,000,000 Inhabitants)	0.476	**0.034**
Red Cell Usage per 1,000 Population - Hospital Discharges (Per 100,000 Inhabitants)	0.491	**0.011**
Red Cell Usage per 1,000 Population - MRI Exams (Per 1,000 Inhabitants)	0.593	**0.009**
Red Cell Usage per 1,000 Population - Medical Doctors (Per 1,000 Inhabitants)	0.386	*0.057*
Red Cell Usage per 1,000 Population - Medical Graduates (Per 100,000 Inhabitants)	0.425	**0.034**

Table 5.4: Significant correlations between red cell use and supply sensitive care predictors

Significant Relationships	Pearson Correlation	P-value
Platelet Usage per 1,000 Population - CT Scanners (Per 1,000,000 Inhabitants)	0.524	**0.010**
Platelet Usage per 1,000 Population - MRI Units (Per 1,000,000 Inhabitants)	0.537	**0.010**
Platelet Usage per 1,000 Population - Mammography Machines (Per 1,000,000 Inhabitants)	0.633	**0.003**
Platelet Usage per 1,000 Population - CT Exams (Per 1,000 Inhabitants)	0.570	**0.013**
Platelet Usage per 1,000 Population - MRI Exams (Per 1,000 Inhabitants)	0.556	**0.017**
Platelet Usage per 1,000 Population - Nurses (Per 1,000 Inhabitants)	0.486	**0.014**

Table 5.5: Significant correlations between platelet use and supply sensitive care predictors

Significant Relationships	Pearson Correlation	P-value
Plasma Usage per 1,000 Population - Hospital Discharges (Per 100,000 Inhabitants)	0.418	**0.034**
Plasma Usage per 1,000 Population – CT Scanners (Per 1,000,000 Inhabitants)	0.361	*0.091*
Plasma Usage per 1,000 Population – MRI Units (Per 1,000,000 Inhabitants)	0.372	*0.088*

Table 5.6: Significant correlations between plasma use and supply sensitive care predictors

Supply sensitive care markers for diagnostic tests were correlated with the usage of all three blood products, albeit marginally so with Plasma.

'CT Scanners (Per 1,000,000 Inhabitants)' and 'MRI Units (Per 1,000,000 Inhabitants)' correlated with all three dependent variables. P-values were <

0.05 level of significance with ‘Red Cell Usage per 1000 population’ and ‘Platelet usage per 1000 population’ and >0.05 <0.1for ‘Plasma usage per 1000 population’. ‘Mammography Machines (Per 1,000,000 Inhabitants)’ correlated both with ‘Red Cell usage per 1000 population’ and with ‘Platelet usage per 1000 population’ as did ‘MRI Exams (Per 1,000 Inhabitants). ‘CT Exams (Per 1,000 Inhabitants)’ correlated with ‘Platelet Usage per 1000 population’.

‘Hospital Discharges (Per 100,000 Inhabitants)’, a marker of hospital activity, correlated significantly with both ‘Red Cell Usage per 1000 population’ and with ‘Plasma Usage per 1000 population’.

Markers for professional staffing also correlated with blood product usage: ‘Medical Doctors (Per 1,000 Inhabitants)’ and ‘Medical Graduates (Per 100,000 Inhabitants)’ with ‘Red Cell Usage per 1000 population’; and ‘Nurses (Per 1,000 Inhabitants)’ with ‘Platelet Usage per 1000 population’.

There was also correlation amongst the diagnostic test predictors themselves. The equipment markers ‘CT Scanners (Per 1,000,000 Inhabitants)’, ‘MRI Units (Per 1,000,000 Inhabitants)’ and ‘Mammography Machines (Per 1,000,000 Inhabitants)’ correlated significantly with one another as they also did with ‘CT Exams (Per 1,000 Inhabitants)’ and ‘MRI Exams (Per 1,000 Inhabitants)’. There was no significant correlation, however, between the latter two predictors.

‘Hospital Discharges (Per 100,000 Inhabitants)’ was significantly associated with ‘Medical Doctors (Per 1,000 Inhabitants).

The markers for professional staffing also correlated amongst themselves: ‘Medical Doctors (Per 1,000 Inhabitants)’ with Medical Graduates (Per 100,000 Inhabitants)’ and ‘Nurses (Per 1,000 Inhabitants)’ with ‘Nurse Graduates (Per 100,000 Inhabitants)’.

5.3.2 Professional uncertainty and difficulty with change

Table 5.7 represents the values assigned to each cultural construct in Hofstede's cultural dimensions model for the countries used in the analysis (Hofstede *et al.*, 2010). Croatia and Iceland were omitted because of missing values.

Country	pdi	idv	mas	uai	ltowvs	ivr
Australia	36	90	61	51	21	71
Austria	11	55	79	70	60	63
Belgium	65	75	54	94	82	57
Canada	39	80	52	48	36	68
Czech Republic	57	58	57	74	70	29
Denmark	18	74	16	23	35	70
Estonia	40	60	30	60	82	16
Finland	33	63	26	59	38	57
France	68	71	43	86	63	48
Germany	35	67	66	65	83	40
Greece	60	35	57	112	45	50
Hungary	46	80	88	82	58	31
Ireland	28	70	68	35	24	65
Italy	50	76	70	75	61	30
Luxembourg	40	60	50	70	64	56
Malta	56	59	47	96	47	66
Netherlands	38	80	14	53	67	68
New Zealand	22	79	58	49	33	75
Norway	31	69	8	50	35	55
Slovakia	104	52	110	51	77	28
Slovenia	71	27	19	88	49	48
Spain	57	51	42	86	48	44
Sweden	31	71	5	29	53	78
Switzerland	34	68	70	58	74	66
United Kingdom	35	89	66	35	51	69
United States	40	91	62	46	26	68

Table 5.7: Values for Hofstede's cultural dimensions

5.3.2.1 Linear Correlation

The values assigned to Hofstede's cultural dimensions were subjected to a Pearson Correlation Coefficient analysis using the Red Cell, Platelet and Plasma Usage per 1000 population in turn as the dependent variables to measure the linear correlation between each dependent variable and each dimension.

Statistical analysis was performed using IBM® SPSS® Statistics for Mackintosh Ver 20. The data in Table 5.7 were used as predictors in this analysis and the data in Table 3.4 (page 42) for blood product usage were used as the independent variables.

This analysis yielded significant results with the dependent variable 'Plasma Usage per 1000 Population'. There appears to be a significant negative correlation with IDV – Collectivism vs Individualism. There is also a marginal correlation with PDI – Power Distance Index (Table 4.8).

Significant Relationships	Pearson Correlation	P-value
Plasma Usage per 1,000 Population – PDI (Power Distance Index)	0.347	*0.082*
Plasma Usage per 1,000 Population – IDV (Individualism vs Collectivism)	-0.467	**0.016**
Plasma Usage per 1,000 Population – UAI (Uncertainty Avoidance Index)	0.320	0.111

Table 5.8: Correlation between plasma usage and Hofstede's cultural dimensions

The analyses performed with 'Red Cell Usage per 1000 Population' and 'Platelet Usage per 1000 Population' as dependent variables did not yield any significant correlations.

The analysis was also performed while omitting the Scandinavian countries. The results were not markedly different, in that the dependent variable 'Plasma Usage per 1,000 Population' showed a similar correlation, though in this analysis UAI – Uncertainty Avoidance Index also correlates significantly (Table 5.9). There was a difference in the result of the analysis with 'Red Cell Usage per 1,000 Population' as the dependent variable. This analysis yielded a marginal correlation of the variable with UAI - Uncertainty Avoidance Index (Table 5.10). There were still no correlations in the analysis performed with 'Platelet Usage per 1,000 Population'.

Significant Relationships	Pearson Correlation	P-value
Plasma Usage per 1,000 Population – PDI (Power Distance Index)	0.409	*0.053*
Plasma Usage per 1,000 Population – IDV (Individualism vs Collectivism)	-0.485	**0.019**
Plasma Usage per 1,000 Population – UAI (Uncertainty Avoidance Index)	0.440	**0.036**

Table 5.9: Correlation between plasma usage and power distance index (PDI), collectivism vs individualism (IDV), and uncertainty avoidance index (UAI)

Significant Relationships	Pearson Correlation	P-value
Red Cell Usage per 1,000 Population – UAI (Uncertainty Avoidance Index)	0.392	*0.064*

Table 5.10: Correlation between red cell usage and uncertainty avoidance index

5.4 Discussion

5.4.1 Unwarranted variation

The representative markers listed in Table 5.3 were identified on the basis of the frequency with which they have been associated with unwarranted variation or supply sensitive care (Emery *et al.*, 2013; Rubin *et al.*, 2015; Tasian *et al.*, 2014; Wennberg *et al.*, 2015; Westert *et al.*, 1993). The predictors in the table in fact correlate among themselves. Countries with a larger number of CT Scanners per capita also have a larger amount of MRIs per capita and mammography machines per capita. In countries with higher numbers of doctors, more hospital discharges happen signifying a higher level of hospital activity. This variation occurs in countries with health services of a similar level. In effect, this finding validates the markers identified as being representative of unwarranted variation.

5.4.2 Unwarranted variation in blood product usage

Various publications examining blood product usage in specific circumstances have shown variation in use (Gombotz *et al.*, 2014; Mitra *et al.*, 2015). Hospitals using high volumes of one product also use high volumes of the other two products (McQuilten *et al.*, 2014) and a review of use of blood products among older adults in the United States showed that one is more likely to receive blood if one lives in the Southern region of the USA as opposed to individuals living in the West (Rogers *et al.*, 2009). The authors of one publication have gone so far as to claim that geographic regions have their own transfusion signature (Likosky *et al.*, 2014). Now, in this thesis, for the first time, this variation in blood products has been linked to unwarranted variation.

In Chapter Three, it was clearly shown that regional variation, mirroring the geographic variation shown in unwarranted variation, also occurs in blood product usage. Additionally, the analysis performed above clearly shows that blood product usage has a significant relationship with markers of supply sensitive care. All three products show a relationship to a greater or lesser degree with the diagnostic test markers, the health resource markers, and the hospital activity markers. More blood products are used in countries with higher levels of markers associated with supply sensitive care confirming the fact that blood product usage is also a victim of unwarranted variation.

5.4.3 Professional uncertainty and difficulty with change

There appears to be some correlation between blood product usage and Hofstede's culture dimensions. A number of interesting points may be made possibly giving further insight into attitudes surrounding the practice of blood transfusion.

The strongest correlation appears to be between 'Plasma Usage per 1,000 Population' and the 'Individualism vs Collectivism Index (IDV)'. The relationship is an inverse one, i.e. in countries scoring higher on the individualism side of the spectrum, less blood is used and in countries tending towards Collectivsm, more blood products are transfused. A number of observations can be made. According to Hofstede's dimensions of national cultures, there is a positive attitude towards what is new in countries stronger on the individualism construct. The education process within these countries tends to prepare the individual to cope with new, unknown and unforeseen situations, and the purpose of learning is to 'know how to learn'. Families within that culture encourage children to develop their own opinions thereby fostering a more discerning attitude. Individualist cultures also encourage the seeking out of more knowledge and cultivate an independent self (Hofstede *et al.*, 2010). It is therefore easy to conceive that in these countries new evidence tends to be accepted faster. The new

evidence in blood transfusion practice mainly surrounds a more conservative attitude recommending lower transfusion triggers and therefore less blood use. Additionally, within individualistic cultures, the patient is much more involved in the decision making shifting the focus from Supply Sensitive Care to Preference Sensitive Care and doctors are more willing to adopt a 'wait and see' attitude rather than rushing in with some form of therapy (Meeuwesen *et al.*, 2009). On the other hand in countries tending towards the Collectivism side of the spectrum, conformity tends to be a valued quality, where the group predetermines opinions. When new issues crop up, there needs to be collective discussion and change occurs only when the collective is satisfied that it is the right way forward. The institution plays a very strong part in determining behaviour (Hofstede *et al.*, 2010). In these countries there is therefore procrastination in the adoption of new evidence. Practitioners would also tend to conform to the traditions within the individual institution, which itself appears to be a variable affecting transfusion practice (Surgenor *et al.*, 1998).

Another correlation that appears valid is the one between 'Plasma Usage per 1,000 Population' and the 'Uncertainty Avoidance Index (UAI)'. This relationship does not hold for all countries. The analysis which included the Scandinavian countries showed a lower Pearson correlation and a P-value >0.1. However when the Scandinavian countries were omitted from the analysis, the correlation became much stronger with a p-value of 0.036. Additionally within these parameters, there also appears to be some relationship, albeit marginal, between 'Red Cell Usage per 1,000 Population' and UAI. Within the model, Hofstede also included a dimension he termed Uncertainty Avoidance Index (UAI). He borrowed the term from American organisation sociology. Modern societies differ on the way they cope with uncertainty and this in turn brings about a different approach to practice in healthcare in the different societies. In uncertainty avoiding cultures doctors are prone to a higher level of drug prescription, an attitude that their patients expect of them (Hofstede *et al.*, 2010). It has been shown, for example, that

doctors practicing within this culture feel uncomfortable with the diagnostic difficulty raised in relation to viral and bacterial infections and tend to use more antibiotics unnecessarily (Borg, 2012). It is therefore likely that the same doctors would be uncomfortable tolerating mild deficiencies in haemoglobin or raised PTs and APTTs and would tend to transfuse plasma and possibly red cells earlier. On the other hand in uncertainty tolerant countries, there is stronger patient engagement and doctors tend not to prescribe medication unnecessarily. Additionally, physicians in countries with a high UAI are tolerant of familiar risk (as opposed to unfamiliar risk which generates uncertainty) (Borg *et al.*, 2012), and are therefore more likely to underestimate the potential complications of blood products, a therapy they prescribe several times a day. This would tend to encourage a more liberal attitude in relation to their use.

'Power Distance Index (PDI)' was the third dimension highlighted by the analysis albeit in a marginal fashion. 'Plasma usage per 1,000 Population' was marginally correlated (p-value = 0.53) with 'Power Distance Index (PDI)'. The lower the PDI, the lower the 'Plasma Usage per 1,000 Population with the converse also being true. Individuals in countries scoring low on PDI tend to be more adaptable, empowered and less dependent (Hofstede *et al.*, 2010), therefore favouring their adoption of evidence. The tendency towards dependency and faithfulness towards institutional norms and directions is stronger in countries with larger power distance cultures making it less easy for individuals to subscribe to newly emerging evidence as it becomes available. Additionally, instruments of accountability, such as audits, are unpopular in countries with a high PDI as they are perceived to target the less powerful (Borg, 2014). It is therefore difficult to establish baselines and perform gap analyses through which one may identify reasons for change. Power-holders in these cultures (senior doctors) are often subject to less accountability, a situation in turn used by the less powerful (junior doctors) as justification to ignore guidelines (Borg, 2014). A further point that may contribute to the issue is that in countries with low PDI patients are

empowered and participate in treatment decisions shifting the focus towards Preference Sensitive Care. It is worth noting that in a previous publication an inverse relationship was shown between PDI and blood donation, where the authors postulated that in high power distance cultures, people may be more inclined to donate blood only when told to do so explicitly by power-holders (de Kort *et al.*, 2010).

5.5 Conclusions

A number of conclusions that contribute new information to the area may be drawn from this chapter:

Analysis of supply sensitive care predictor data shows that high activity markers tend to occur together i.e. countries with higher activity in one marker seem to have higher activities in many other markers. This phenomenon occurs on a background of well-developed health services of very similar levels.

Blood product usage shows significant geographical variation (Chapter Three) mirroring geographic variation in other modalities. Furthermore blood product usage is significantly related with markers of supply sensitive care making a very strong case for unwarranted variation in blood transfusion practice

Increased blood product usage seems to occur in countries with low scores for individualism, higher Uncertainty Avoidance Indices, and possibly high Power Distance Indices, dimensional constructs that encapsulate the notions of professional uncertainty and difficulty with change.

Chapter 6

Conclusions, Limitations and the Future

6. Conclusions, Limitations and the Future

6.1 Introduction

Blood transfusion is one of the most common patient treatment procedures in clinical practice in hospitals in the developed world (Pfunter & Stocks, 2010). It is complicated by a number of well known, and less well known associated hazards. Judicious use based on evidence is therefore a highly sensible approach. Unnecessary transfusions, carrying risk without benefit, should be avoided. Ensuring that patients are only transfused the blood products they really require is the most effective way of providing optimal treatment while safeguarding the patient from unnecessary risk associated with unwarranted use, and at the same time guaranteeing equity of access to what is essentially a limited resource (Murphy *et al.*, 2011; Seifried *et al.*, 2011).

An examination of the national figures for blood product usage shows extensive variation with the highest users transfusing twice as much blood products as the lower users. Apart from demonstrating an association with population demographics, more specifically with the percent of population over 65 years of age (Ali *et al.*, 2010), the reasons for this variation are unknown (Aubuchon *et al.*, 2010).

This thesis set about examining the variation that was apparent on a nation-by-nation basis. Regional data on blood product usage was collated and examined. The relationship between blood product usage data and other variables including measures of healthcare was explored and the impact of a number of potential effectors identified. In this way, the thesis sought to unravel the reasons behind the variation in blood product usage – a

necessary prelude to making recommendations or taking initiatives to ensure the achievement of appropriate blood use. It also sought to define a potential tool that could be used to assess the impact of measures introduced to effect change.

6.2 Summary of Key Findings

6.2.1 Confirmation of variation and its extent

A literature review exploring transfusion practices associated with coronary artery bypass surgery, a procedure that is responsible for approximately 20% of all products transfused worldwide (Snyder-Ramos *et al.*, 2008) showed an extensive inconsistency in blood use that goes much beyond that related to clinical issues. Moreover there appears to be evidence to suggest an effect of the individual institution (hospital) on the variation in blood usage.

For the first time, regional data for a number of countries were compared. The variation was considerable and its extent does not seem to relate to the countries' national averages. It was also discovered that though in general the number of red cells used was related to the size of the population in the region, this did not hold true for all countries. Correction for the percent of the population over 65 years and for migration to large urban areas for specialty care in one country did not eliminate the variation. Additionally, an analysis of the national usage figures for red cells, platelets and plasma shows that countries that use more of one product tend to use more of the other products. Clearly variation in blood product usage in countries with relatively similar health systems, and across regions within the same country is a real phenomenon, mirroring geographic variation seen in other areas of health care.

6.2.2 Relation of variation with overall health system performance

The variation in blood product usage does not correlate with overall health performance. There is no simple linear relationship between blood use and health system performance indices. Countries with health care systems that perform better do not seem to cluster at either end of the blood product usage scale. This was shown for the first time by correlating blood usage with a standardised score based on a number of markers reflecting overall performance of the health systems of a number of countries. This is in keeping with findings that variation in other areas of healthcare are not necessarily related to overall outcomes (Heijink *et al.*, 2015).

6.2.3 Correlation of blood usage variation to a number of predictors

Up to now the only correlation that had been associated with the variation in blood usage has been the percentage of the population above 65 years. This finding has been confirmed in this thesis, but is by no means the sole predictor of the variation. Additional new predictors were discovered namely:

1. The population density within the specific country
2. Clinical activity as represented by (a) CABG and (b) the burden of cancer
3. Amount of funding within the individual country's health services

Together these predictors explained approximately 70% of the variation in red cell usage, 31% of the variation in platelet usage and 25% of the variation in plasma usage.

The percentage of the population over 65 years cannot, on its own, explain away all the variation in blood product usage, as some authors have claimed (Ali *et al.*, 2010; Seifried *et al.*, 2011). This thesis has shown that differences

in clinical activity, and issues related to health care funding, also contribute to the explanation.

6.2.4 Potential effectors of the variation

A number of new findings in this regard were made:

Analysis of supply sensitive care predictor data shows extensive variation in activity levels in a number of specific markers, and shows that in general a country would have markers with similar levels of activity, i.e the level of activity is country-dependent. This parallels the finding mentioned earlier where countries tending to use more of one blood product use more of the others. Furthermore blood product usage is significantly related with markers of supply sensitive care, and since this occurs on a background of well-developed health services of similar levels with broadly similar outcomes, a strong case for unwarranted variation in blood transfusion practice can be made.

Using Hofstede's culture model, it was discovered that increased plasma usage mostly seems to occur in countries with low scores for individualism, higher Uncertainty Avoidance Indices, and possibly high Power Distance Indices, and for red cells possibly in countries with higher Uncertainty Avoidance. These dimensional constructs encapsulate the notions of professional uncertainty and difficulty with adopting change. A case can certainly be made for difficulty with adoption of available evidence-based guidelines as a reason for the unwarranted variation. Additionally there also appears to be a degree of professional uncertainty contributing to the unwarranted variation, in that physicians tend to 'err on the side of caution' and transfuse blood products even when this is not strictly necessary.

6.3 Blood Product Usage as a Quality Indicator

Quality indicators (QIs) are measures that have been developed by Health Services to assess quality in healthcare. Many examples of quality indicators exist and various agencies in different countries make use of a selection to measure the status of their health system including the Agency for Healthcare Research and Quality, The Joint Commission (and Joint Commission International), Canadian Institute for Health Information, (https://www.ahrq.gov, https://www.jointcommission.org, https://www.chi.ca/en). Potential QIs should be assessed for feasibility depending on their practical application in health service studies and on the quality and availability of data; for reliability and reproducibility; for acceptability both to assessors and institutions being scrutinised; for sensitivity to change; and for validity (Otsubo *et al.*, 2016).

Blood product usage is ideally placed to be used as a quality indicator:

Feasibility:
Blood product usage data can be very practically applied in healthcare services research. It is a measure that encapsulates appropriateness of practice in several clinical sectors simultaneously, health service funding, penetrance of policy and guidelines, the degree of unwarranted variation, and medical and nurse training. The data are readily available and are collected and published regularly conferring a huge advantage when compared to other indices. The quality of data is high and relatively easily retrieved from hospital and Blood Establishment databases.

Reliability:
Traceability of blood products has become a cornerstone of practice over the years. Legislation within the European Union for example has made traceability of every blood product mandatory. The fate of almost every

blood unit is accurately recorded allowing for extraction of very precise and reliable data.

Acceptability:

There appear to be no issues with acceptability. The values for national blood product usage are already published in Council of Europe reports and in various national reports and are freely available. Many hospitals voluntarily participate in international quality initiatives that include collection of data on blood usage e.g. the Performance Assessment Tool for Quality Improvement in Hospitals (PATH) (www.pathqualityproject.eu). This is a system designed by the WHO to support hospitals defining strategies for improvement in quality (Groene *et al.*, 2008).

Sensitivity to change:

Blood product usage is very sensitive to change. The financial crisis occurring in 2008 was followed by a significant downturn in the world economy. This had an extensive impact on most countries with health spending bearing its own share of cutbacks. Additionally the last few years have seen an emphasis on Patient Blood Management (PBM) programmes. PBM is a programme of initiatives some countries have adopted or are in the process of adopting to deal with optimising patient care in relation to blood transfusion. It aims for a multidisciplinary approach that encompasses measures to avoid unnecessary transfusions and to ensure that patients receive optimal treatment. Both these initiatives and the financial crisis have had an impact on blood usage. It is immediately clear from the data in Tables 3.6 – 3.14 that in most countries red cell usage decreased on a national basis when compared to the index value used throughout this thesis (Table 3.4).

Validity:

Blood product usage, as an index measuring quality performance, has been validated by the analysis performed in this thesis. It was clearly shown that blood product usage does not relate to the overall performance of health care

systems. An index that moves with overall performance would not necessarily be sensitive to change in the degree of unwarranted variation. Blood product usage however has been shown to move with markers that are directly related to supply sensitive care. Moreover, usage seems to be related also to cultural differences that may affect the extent of unwarranted variation.

This thesis is therefore a powerful demonstration using very potent clinical totems – the widespread use of blood, the problems associated with it, the costs, the prevalence of guidelines, the existence of high grade studies in high grade journals – that irrational and evidence-denying variation in clinical practice exists and can be measured relatively easily, and that comparison of clinical use of blood in health care in discrete geographical regions may be used as a general measure of the effectiveness of different tools to improve practice over time and space, not just within the context of blood product use, but possibly in clinical practice in general.

Blood product usage is a valid measure of variation in practice within health care regions that do not have a reason for variation from other regions with similar economics and politics other than failure to implement good practice for whatever reason or reasons. It is therefore possible to envisage that variation in blood product usage can be used as a quality performance indicator to see whether direct interventions have an effect on this poor penetration of emerging evidence or to study the time to adoption of emerging evidence, and how that might be improved upon.

Variation in blood product usage would be an ideal candidate to measure changes brought about by the initiatives associated with transfusion which have been incorporated in the *Choosing Wisely* campaign. This started as an initiative of the American Board of Internal Medicine Foundation in the United States in 2012 aiming at helping physicians identify tests and interventions that were often unnecessary and therefore potentially harmful

(Hurley, 2014). Since then this initiative has gone global: Canada, New Zealand, Australia, Japan, and a number of European countries, Germany, the Netherlands, Italy, Switzerland and England and Wales, have launched similar campaigns (Vogel, 2015). Overuse of blood transfusion is listed as a *Choosing Wisely* recommendation in the US. Similarly blood transfusion recommendations have been made with regards to the UK *Choosing Wisely* campaign (Murphy, 2015). Blood product usage would be the ideal indicator to use to measure interventions within this campaign such as the one being suggested by Malhotra et al, where guideline committees are being encouraged to produce tools to help doctors understand and share decisions with their patients based on best evidence (Malhotra *et al.*, 2015).

6.4 Limitations

There are a number of limitations with regards to the work within this thesis. The analyses are limited to one defined period – 2009/2010. This specific period was chosen because of availability of a majority of the data used. Confirming the analyses for different sets of years would have made the conclusions more robust. However, though the data for blood product usage are available for other years, some of the other data used, especially that extracted from the OECD database for particular markers is only available for specific years and is often not available for subsequent years. Re-attempting the analyses in this way was not possible during the time-frame of the thesis.

It may have been useful to age adjust the national figures on blood product usage to eliminate the bias in favour of populations with a higher percentage of people over 65 years. This was not possible as the figures for blood usage for different age groups for each country are not available. This was mitigated for by adding in 'Percent Population Above 65 Years' as a variable within the analysis.

Lack of regional data for platelet and plasma usage precluded a regional analysis of their use. Such an analysis would have given further insight into the extent of regional variation in blood product usage.

Though, as pointed out on page 102, Hofstede's theory of cultural dimensions is one of the most frequently cited models in terms of cultural theories, it is not without its critics and of course has limitations. The main limitation stems from the fact that the original study was performed in the international subsidiaries of one company, and the number of respondents may not have been large enough to make it completely representative and generalizable for all the nations studied.

The main statistical tools used within this thesis are the Pearson correlation and regression analysis. It is well known that when testing multiple relationships using these methods, strong relationships between the variables being examined could occasionally also arise from the influence of other unmeasured variables and the results do not guarantee causal relationships between the independent and dependent variables.

A further limitation was the issue of missing data in the databases from which data for this thesis was extracted. Though countries participate in the various initiatives for data collection, some do not provide all the data requested. Countries with multiple missing data points were, in some analysis, left out altogether. Pairwise deletion was used in the Pearson correlation analysis rather than listwise deletion to maintain as many datapoints as possible for the analysis.

6.5 Future Work

There is scope for continuing to validate the blood product usage as a tool for measurement of change by re-analysing the data when the figures for markers in different years become available in the specific databases.

There is also scope for further collaboration with colleagues to identify ways of collecting regional data for usage of blood products - in the case of red cells, in countries where this is not yet available, and in the case of platelets and plasma, in most countries. This would provide an additional tool, this time to measure change in regions.

Similarly collaborative studies on using blood product usage as a quality performance indicator to measure the effect of interventions applied to reduce unwarranted variation in standards of health care will be an ongoing project.

References

Abraham, I. & Sun, D. (2012) The cost of blood transfusion in Western Europe as estimated from six studies. *Transfusion*, 52 (9): 1983-1988.

Ades, F., Senterre, C., de Azambuja, E., Sullivan, R., Popescu, R., Parent, F. & Piccart, M. (2013) Discrepancies in cancer incidence and mortality and its relationship to health expenditure in the 27 European Union member states. *Annals of Oncology*, 24 (11): 2897-2902.

Agencia Nacional de Vigilancia Sanitaria (2010) *Relatorio de Hemovigilancia 2007-2008*. Available from: http://portal.anvisa.gov.br/documents/33868/405222/Relat%C3%B3rio+de+Hemovigil%C3%A2ncia+-+2007+e+2008/68356d60-a415-44ec-a528-53e9f6d3123c

Ali, A., Auvinen, M. K. & Rautonen, J. (2010) The aging population poses a global challenge for blood services. *Transfusion*, 50 584-588.

Anderson, S. A., Menis, M., O'Connell, K. & Burwen, D. R. (2007) Blood use by inpatient elderly population in the United States. *Transfusion*, 47 582-592.

Andreasen, J. J., Westen, M., Pallesen, P. A., Jensen, S., Gorst-Rasmussen, A. & Johnsen, S. P. (2007) Transfusion practice in coronary artery bypass surgery in Denmark: a multicenter audit. *Interactive CardioVascular and Thoracic Surgery*, 6 623-627.

Andreu, G. (2002) Haemovigilance network in France: organisation and analysis of immediate transfusion incident reports from 1994 to 1998. *Transfusion*, 42 1356-1364.

Aubuchon, J. P., Custer, B. & Cher, G. (2010) A comparison of healthcare and blood supply system structures. *Vox Sanguinis*, 100 22-35.

Australasian Society of Blood Transfusion (2001) *Clinical practice guidelines on the use of blood components (red blood cells, platelets, fresh frozen plasma, cryoprecipitate)*. Available from: https://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/cp78_cp_blood_components.pdf

Australian Bureau of Statistics (2015) *3218.0 regional population growth, Australia. Table 10: estimated resident population, States and territory summary*. [online] Available from: http://www.abs.gov.au/ausstats/subscriber.nsf/log?openagent&32180ds0001_2005-15.xls&3218.0&DataCubes&69EA5EDF01684278CA257F8500171164&0&2014-15&30.03.2016&Latest (Accessed 8 Sep 2016).

Australian Commission on Safety and Quality in Health Care (2015) *Australian atlas of healthcare variation*. Available from: http://www.safetyandquality.gov.au

Barr, P. J., Donnelly, M., Morris, K., Parker, M., Cardwell, C. & Bailie, K. E. M. (2010) The epidemiology of red cell transfusion. *Vox Sanguinis*, 99 239-250.

Beguin, C., Closon, M. C., Vandekerckhove, P. & Baele, P. (2007) Concentration of transfusion resources on a few pathologies and a few patients: analysis of the comprehensive in-hospital patient database. *Transfusion*, 47 217-227.

Benjamin, R. J. & Whitaker, B. I. (2011) Boom or bust? Estimating blood demand and supply as the baby boomers age. *Transfusion*, 51 670-673.

Bennett, S. & Peters, D. H. (2015) Assessing National Health Systems: Why and How. *Health Systems & Reform*, 1 (1): 9-17.

Bennett-Guerrero, E., Zhao, Y., O'Brien, S. M., Ferguson, T. B., Peterson, E. D., Gammie, J. S. & Song, H. K. (2010) Variation in use of blood transfusion in coronary artery bypass graft surgery. *Journal of the American Medical Association*, 304 (14): 1568-1575.

Bero, L. A., Grilli, R., Grimshaw, J. M., Harvey, E., D, O. A. & Thomson, M. A. (1998) Closing the gap between researching practice: an overview of systematic reviews of interventions to promote the implementation of research findings. *British Medical Journal*, 317 465-468.

Birkmeyer, J. D., Reames, B. N., McCulloch, P., Carr, A. J., Campbell, W. B. & Wennberg, J. E. (2013) Variation in Surgery 1: understanding of regional variation in the use of surgery. *Lancet*, 382 1121-1129.

Borg, M. A. (2012) National cultural dimensions as drivers of inappropriate ambulatory care consumption of antibiotics in Europe and their relevance to awareness campaigns. *Journal of Antimicrobial Chemotherapy*, 67 763-767.

Borg, M. A. (2014) Cultural determinants of infection control behaviour: understanding drivers and implementing effective change. *Journal of Hospital Infection*, 86 161-168.

Borg, M. A., Camilleri, L. & Waisfisz, B. (2012) Understanding the epidemiology of MRSA in Europe: do we need to think outside the box? *Journal of Hospital Infection*, 81 251-256.

Borkent-Raven, B. A., Janssen, M. P. & van der Poel, C. L. (2010) Demographic changes and predicting blood supply and demand in the Netherlands. *Transfusion*, 50 2455-2460.

Bracey, A. W. (2008) Blood Transfusion in cardiac surgery: a highly varied practice. *Transfusion*, 48 1271-1273.

Brinkhous, K. M., Shanbrom, E., Roberts, H. R., Webster, W. P., Fekete, L. & Wagner, R. H. (1968) A new high-potency glycine-precipitated antihemophilic factor (AHF) concentrate: treatment of classical hemophilia and hemophilia with inhibitors. *Journal of the American Medical Association*, 205 613-617.

Brown, J. R., Birkmeyer, N. J. & O'Connor, G. T. (2007) Meta-analysis comparing the effectiveness and adverse outcomes of anti-fibrinolytic agents in cardiac surgery. *Circulation*, 115 2801-2813.

Canadian Blood Services (2010) *Annual Checkup: A report to Canadians 2009/2010*. Available from: http://itsinyoutogive.ca/Annual/2010/pdfs/cbsltc_report_en.pdf Ontario, Canada

Carson, J. L., Terrin, M. L., Noveck, H., Sanders, D. W., Chairman, B. R., Rhoads, g. g., Nemo, G., Dragert, K., Beaupre, L., Hildebrand, K., Macaulay, W., Lewis, C., Cook, D. R., Dobbin, G., Zakriya, K. J., Apple, F. S., Horney, R. A. & Magaziner, J. (2011) Liberal or restrictive transfusion in high-risk patients after hip surgery. *New England Journal of Medicine*, 365 2453-2462.

Carter, S. M., Rogers, W., Heath, I., Degeling, C., Doust, J. & Barratt, A. (2015) The challenge of overdiagnosis begins with its definition. *British Medical Journal*, 350 h869.

Centers for Disease Control and Prevention (1982) *Epidemiologic notes and reports Pneumocystis carinii pneumonia among persons with hemophilia A*. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001126.htm

Centers for Disease Control and Prevention (1983) *Current trends prevention of acquired immune deficiency syndrome (AIDS): Report of inter-agency recommendations*. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00001257.htm

Centers for Disease Control and Prevention (1986) *Current trends Human T-Lymphotrophic Virus type III / Lymphadenopathy-Associated Virus antibody testing at alternate sites*. Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/00000728.htm

Centers for Medicare and Medicaid Services (2009) *National Health Expenditure Projections 2010-2020*. Available from: https://www.cms.gov/NationalHealthExpendData/downloads/proj2010.pdf

Cobain, T. J., Vamvakas, E. C., Wells, A. & Titlestad, K. (2006) A survey of the demographics of blood use. *Transfusion Medicine*, 17 1-15.

Comer, P. J. & Huntly, P. J. (2003) TSE risk assessment: a decision support tool. *Statistical Methods in Medical research*, 12 279-291.

Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance (2013) *Rapport d'hemovigilance des coordonateurs régionaux d'hemovigilance et de sécurité transfusionnelle. Année 2012*. Available from: http://www.hemovigilance-cncrh.fr/www2/lu_pour_vous/rapports_hemovigilance.html

Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance (2014) *Rapport d'hemovigilance des coordonnateur régionaux d'hemovigilance et du sécurité transfusionnelle. Année 2013*. Available from: http://www.hemovigilance-cncrh.fr/www2/lu_pour_vous/rapports_hemovigilance.html

Conference Nationale des Co-ordonnateurs Régionaux d'Hemovigilance (2015) *Rapport d'hemovigilance des coordonnateurs régionaux d'hemovigilance et de sécurité transfusionnelle. Année 2014*. Available from: http://www.hemovigilance-cncrh.fr/www2/lu_pour_vous/rapports_hemovigilance.html

Cooper, H. A., Rao, S. V., Greenberg, M. D., Ramsey, M. P., McKenzie, M., Alcorn, K. W. & Panza, J. A. (2011) Conservative versus liberal red cell transfusion in acute myocardial infarction (the CRIT Randomised Pilot Study). *American Journal of Cardiology*, 108 1108-1111.

Corallo, A. N., Croxford, R., Goodman, D. C., Bryan, E. L., Srivastava, D. & Stukel, T. A. (2014) A systematic review of medical practice variation in OECD countries. *Health Policy*, 114 5-14.

Coyne, J. S. & Hilsenrath, P. (2002) The World Health Report 2000: can health care systems be compared using a single measure of performance? *American Journal of Public Health*, 92 (1): 30-33.

Crosby, E., Ferguson, D., Hume, H. A., Kronick, J. B., Larke, B., LeBlond, P., McLellan, B. & Warkentin, T. E. (1997) Guidelines for red blood cell and plasma transfusion for adults and children. *Canadian Medical Association Journal*, 156 (11 suppl): S1-S24.

Currie, C. J., Patel, T. C., McEwan, P. & Dixon, S. (2004) Evaluation of the future supply and demand for blood products in the United Kingdom National Health Service. *Transfusion Medicine*, 14 19-24.

Danish Transfusion Database (2009) *Danish Transfusion Database. Annual Report 2009. The most blood consuming diagnoses and surgical procedures: using red cells*. Available from: http://www.dtdb.dk/download/DTDB_Rapport_2009_43.pdf

Dartmouth Atlas Project (2007a) *A Dartmouth atlas project brief: effective care*. Available from: http://www.dartmouthatlas.org/downloads/reports/effective_care.pdf

Dartmouth Atlas Project (2007b) *A Dartmouth atlas project topic brief: preference-sensitive care*. Available from: http://www.dartmouthatlas.org/downloads/reports/preference_sensitive.pdf

Dartmouth Atlas Project (2007c) *A Dartmouth atlas project topic brief: supply-sensitive care*. Available from: http://www.dartmouthatlas.org/downloads/reports/supply_sensitive.pdf

Davidson, T., Ekermo, B., Gaines, H., Lesko, B. & Akerlind, B. (2011) The cost effectiveness of introducing nucleic acid testing to test for hepatitis B, hepatitis C and human immunodeficiency virus among blood donors in Sweden. *Transfusion*, 51 421-429.

de Kort, W., Wagenmans, E., van Dongen, A., Slotboom, Y., Hofstede, G. & Veldhuizen, I. (2010) Blood product collection and supply: a matter of money? *Vox Sanguinis*, 98 201-208.

Department of Health and Human Services (2011) *The 2009 National Blood Collection and Utilization Survey Report*. Available from: https://wayback.archive-it.org/3919/20140402175927/https:/www.hhs.gov/ash/bloodsafety/2009nbcus.pdf Washington, DC

Department of Health and Human Services (2013) *The 2011 Nationwide Blood Collection and Utilization survey Report*. Available from: https://www.hhs.gov/sites/default/files/ash/bloodsafety/2011-nbcus.pdf Washington, DC

Djulbegovic, B. & Paul, A. (2011) From efficacy to effectiveness in the face of uncertainty: indication creep and prevention creep. *Journal of the American Medical Association*, 305 (19): 2005-2006.

Duguid, J., O'Shaughnessy, D. F., Atterbury, C., Bolton Maggs, P., Murphy, M., Thomas, D., Yates, S. & Williamson, L. M. (2004) Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *British Journal of Haematology*, 126 11-28.

Emanuel, E. J. & Fuchs, V. R. (2008) The perfect storm of overutilization. *Journal of the American Medical Association*, 299 (23): 2789-2791.

Emery, D. J., Shojania, K. G., Forster, A. J., Mojaverian, N. & Feasby, T. E. (2013) Overuse of magnetic resonance imaging. *Journal of the American Medical Association*, 173 (9): 823-825.

Eskander, A., Irish, J. C., Urbach, D. R. & Goldstein, D. P. (2015) *Head and neck cancer surgery in Ontario, 2003 - 2010*. Available from: http://www.ices.on.ca/~/media/Files/Atlases-Reports/2015/Head-Neck-Cancer-Surgery-Atlas/Full-Report.ashx Toronto, ON

European Union (2003) *Directive 2002/98/EC of the European Parliament and the Council as regards setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC*. Available from: http://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/dir_2002_98/dir_2002_98_en.pdf Official Journal of the EU

European Union (2004) *Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004484.pdf Official Journal of the EU

European Union (2005a) *Directive 2005/61/EC implementing Directive 2002/98/EC of the European Parliament and of the Council as regards traceability requirements and notification of serious adverse reactions and events*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004485.pdf Official Journal of the EU

European Union (2005b) *Commission Directive 2005/62/EC of 30 September 2005 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards community standards and specifications relating to a quality system for blood establishments*. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32005L0062&from=EN Official Journal of the EU

Eurostat (2011) *Proportion of population aged 65 and over (% of total population)*. Available from: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&init=1&language=en&pcode=tps00028&plugin=1 Eurostat Website

Evatt, B. L. (2006) The tragic history of AIDS in the hemophilia population, 1982-1984. *Journal of Thrombosis and Hemostasis*, 4 2295-2301.

Faber, J. C. (2002) Haemovigilance around the world. *Vox Sanguinis*, 83 (S1): 71-76.

Fajadet, J. & Chieffo, A. (2012) Current management of left main coronary artery disease. *European Heart Journal*, 33 36-50.

Finish Red Cross Blood Service (2010) *Finnish Red Cross Blood Service in 2009; Living life together every day*. Available from: https://www.redcross.fi/materiaali/finnish-red-cross-annual-reports

Freedman, J., Luke, K., Escobar, M., Veronica, L. & Chiavetta, J. A. (2008) Experience of a network of transfusion coordinators for blood conservation (Ontario Transfusion Coordinators [ONTraC]). *Transfusion*, 48 237-250.

Garcia Armesto, S., Martinez Lizaga, N., Angulo Pueyo, E., Bloor, K. & Cookson, R. (2014) *ECHO atlas on lower value care in England*. Available from: http://echo-health.eu/wp-content/uploads/2015/03/report_LVC_ENG_final_owen_logos_5.pdf

GBD 2015 SDG Collaborators (2016) Measuring the health-related sustainable development goals in 188 countries: a baseline analysis from the Global Burden of Disease Study 2015. *Lancet*, 388 (10053): 1813-1850.

Ghani, A. C., Ferguson, N. M., Donnelly, C. A. & Anderson, R. M. (2000) Predicted vCJD mortality in Great Britain. *Nature*, 406 583-584.

Glover, J. A. (1938) The incidence of tonsillectomy in school children. *Proceedings of the Royal Society of Medicine*, 31 1219-1236.

Gombotz, H., Rehab, P. H., Shander, A. & Hofmann, A. (2014) The second Austrian benchmark study for blood use in elective surgery: results and practice change. *Transfusion*, 54 2646-2657.

Gombotz, H., Rehak, P. H., Shander, A. & Hofmann, A. (2007) Blood use in elective surgery: the Austrian benchmark study. *Transfusion*, 47 1468-1479.

Goodnough, L. T., Johnston, M. F. M. & Toy, P. T. C. Y. (1991) The variability of transfusion practice in coronary artery bypass surgery. *Journal of the American Medical Association*, 265 86-90.

Greenwalt, T. J. (1997) A short history of transfusion medicine. *Transfusion*, 37 (5): 550-563.

Greinacher, A., Fendrich, K., Alpen, U. & Hoffmann, W. (2007) Impact of demographic changes on the blood supply: Mecklenburg West Pomerania as a model region for Europe. *Transfusion*, 47 395-401.

Greinacher, A., Fendrich, K. & Hoffmann, W. (2010) Demographic change: the impact on safe blood supply. *ISBT Science Series*, 5 239-243.

Greinacher, A., Weitmann, K., Lebsa, A., Gloger, D., Stangenberg, W., Kiefel, V. & Hoffmann, W. (2016) A population-based longitudinal study on the implications of demographics on future blood supply. *Transfusion*, 56 2986-2994.

Groene, O., Klazinga, N., Kazandjian, V., Lombrail, P. & Bartels, P. (2008) The World Health Organisation performance assessment tool for quality improvement in hospitals (PATH): an analysis of the pilot implementation in 37 hospitals. *International Journal of Quality in Health Care*, 20 (3): 155-161.

Grytten, J. & Sorensen, R. (2003) Practice variation and physician-specific effects. *Journal of Health Economics*, 22 403-418.

Hajjar, L. A., Vinvent, J. L., Galas, F. R., Nakamura, R. E., Silva, C. M., Santos, M. H., Fukushima, J., Kalil Filho, R., Sierra, D. B., Lopes, N. H., Mauad, T., Roquim, A. C., Sundin, M. R., Leao, W. C., Almeida, J. P., Pomerantzeff, P. M., Dallan, L. O., Jatene, F. B., Stolf, N. A. & Auler, J. O. J. (2010) Transfusion requirements after cardiac surgery. The TRACS randomised controlled trial. *Journal of the American Medical association*, 304 1559-1567.

Ham, C. (2010) The coalition government's plans for the NHS in England: Much more work is needed to ensure they can deliver improvements in care. *British Medical Journal*, 341 c3790.

Heal The World Foundation (2012) *Population density per square kilometre by country*. [online] Available from: http://www.nationmaster.com/graph/geo_pop_den-geography-population-density (Accessed 12 April 2012).

Hebert, P. C., Wells, G., Blajchman, M. A., Marshall, J., Martin, C., Pagliarello, G., Tweeddale, M., Schweitzer, I. & Yetisir, E. (1999) A multi-center randomized controlled clinical trial of transfusion requirements in critical care. *New England Journal of Medicine*, 340 409-417.

Heijink, R., Engelfriet, P., Rehnberg, C., Kittelsen, S. A. C. & Hakkinen, U. (2015) A window on geographic variation in health care: insights from Europe. *Health Economics*, 24 164-177.

Hema-Quebec (2010) *Annual Report 2009-2010*. Available from: https://www.hema-

quebec.qc.ca/userfiles/file/media/anglais/publications/RA2010_HemaQuebec_ang_web.pdf Quebec, Canada:

Hicks, L. K. (2015) Reframing overuse in health care: Time to focus on the harms. *Journal of Oncology Practice*, 11 (3): 168-170.

Hoffman, J. R. & Kanzaria, H. K. (2014) Intolerance of error and culture of blame driven medical excess. *British Medical Journal*, 349 g5702.

Hofstede, G. (2001) *Culture's consequences: comparing values, behaviours, institutions, and organisations across nations.* Thousand Oaks, CA: Sage Publications.

Hofstede, G., Hofstede, G. J. & Minkov, M. (2010) *Cultures and organisations: software of the mind: intercultural cooperation and its importance for survival*. 3rd edn. McGraw-Hill.

Hurley, R. (2014) Can doctors reduce harmful medical overuse worldwide. *British Medical Journal*, 349 g4289.

I.Stat (2016) *Popolazione residente al 1 gennaio I.Stat export*. [online] Available from: http://dati5b.istat.it/OECDstat_Metadata/ShowMetadata.ashx?Dataset=DCIS_POPRES1&ShowOnWeb=true&Lang=fr (Accessed 12 Sep 2016).

Institut Nationale de la Statistique et des Etudes Economiques (2015) *Estimations de population au 1er janvier, par region, sexe et grande class d'ageEstimations de population au 1er janvier, par region, sexe et grande class d'age*. [online] Available from: http://www.insee.fr (Accessed 20 Sep 2016).

Institute of Medicine (2001) *Crossing the quality chasm: a new health system for the 21st century*. Available from: http://www.nationalacademies.org/hmd/~/media/Files/Report Files/2001/Crossing-the-Quality-Chasm/Quality Chasm 2001 report brief.pdf Washington

Institute of Medicine (2012) *Best care at lower cost: the path to continuously learning health care in America*. Available from: http://www.nationalacademies.org/hmd/~/media/Files/Report Files/2012/Best-Care/BestCareReportBrief.pdf

International Agency for Research on Cancer (2008) *Cancer - crude and age standardized rates per 100,000*. [online] Available from: http://globocan.iarc.fr/Pages/summary_table_pop_sel.aspx (Accessed 28 Feb 2012).

Irish Blood Transfusion Service (2010) *Irish Blood Transfusion Service Annual Report 2009*. Available from: http://www.giveblood.ie/About_Us/Publications_Guidelines/Annual_Reports/2000-to-2010/

Janssen, M. P., van der Poel, C. & Behr-Gross, M. E. (2011) *The collection testing and use of blood and blood products in Europe 2009*. Available from: https://www.edqm.eu/medias/fichiers/the_collection_testing_and_use_of_blood_and_blood_components_in_europe_2009_report.pdf

Janssen, M. P., van der Poel, C. & Behr-Gross, M. E. (2014) *The collection, testing and use of blood and blood components in Europe 2010 Report*. Available from: https://www.edqm.eu/medias/fichiers/the_collection_testing_and_use_of_blood_and_blood_components_in_europe_2010_report.pdf

Japanese Red Cross Society (2010) *Haemovigilance by JRCS 2008*. Available from: http://www.jrc.or.jp/vcms_lf/anzen_HVreport2008_en.pdf

Jin, R., Zelinka, E. S., McDonald, J., Byrnes, T., Grunkemeier, G. L. & Brevig, J. (2013) Effect of hospital culture on blood transfusion in cardiac procedures. *Annals of Thoracic Surgery*, 95 1269-1275.

Kassirer, J. P. (1989) Our stubborn quest for diagnostic certainty. A cause of excessive testing. *New England Journal of Medicine*, 320 1489-1491.

Kendrick, D. B. (1964) *Blood program in world war II*. Office of the Surgeon General, Dept of the Army.

Kirkman, B. L., Lowe, K. B. & Gibson, C. B. (2006) A quarter century of *Culture's Consequences*: a review of empirical research incorporating Hofstede's cultural values framework. *Journal of International Business Studies*, 37 285-320.

Kontopantelis, E., Springate, D. A., Ashworth, M., Webb, R. T., Buchan, I. E. & Doran, T. (2015) Investigating the relationship between quality of primary care and premature mortality in England: a spatial whole-population study. *British Medical Journal*, 350 h904.

Lafortune, G. & de Looper, M. (2011) *Health at a Glance*. Available from: https://www.oecd.org/els/health-systems/49105858.pdf

Landsteiner, K. & van der Scheer, J. (1924) On the specificity of agglutinins and precipitins. *The Journal of Experimental Medicine*, 40 (1): 91-107.

Lasmezas, C. I., Deslys, J. P., Demaimay, R., Adjou, K. T., Lamoury, F., Dormont, D., Robain, O., Ironside, J. & Hauw, J. J. (1996) BSE transmission to macaques. *Nature*, 381 743-744.

Lewisohn, R. (1916) The importance of the proper dosage of sodium citrate in blood transfusion. *Annals of Surgery*, 64 (5): 618-623.

Likosky, D. S., Al-Attar, P. M., Malenka, D. J., Furnary, A. P., Lehr, E. J., Paone, G., Kommareddi, M., Helm, R., Jin, R., Maynaud, C., Hanson, E. C., Olmstead, E. M., Mackenzie, T. A., Ross, C. S. & Zhang, M. (2014) Geographic variability in potentially discretionary red blood cell transfusions after coronary artery bypass graft surgery. *The Journal of Thoracic and Cardiovascular Surgery*, 148 3084-3089.

Llewellyn, C. A., Hewitt, P. A., Knight, R. S. G., Amar, K., Cousens, S., Mackenzie, J. & Will, R. G. (2004) Possible transmission of variant Creudzfeldt-Jakob disease by blood transfusion. *Lancet*, 363 417-421.

Ludlam, C. A. & Turner, M. L. (2005) Managing the risk of transmission of variant Creutzfeldt-Jakob disease by blood products. *British Journal of Haematology*, 132 13-24.

Maddux, F. W., Dickinson, T. A., Rilla, D., Kamienski, R. W., Saha, S. P., Eales, F., Rego, A., Donias, H. W., Crutchfield, S. L. & Hardin, R. A. (2009) Institutional variability of intraoperative red blood cell utilization in coronary artery bypass graft surgery. *American Journal of Medical Quality*, 24 403-411.

Magruder, J. T., Blasco-Colmenares, E., Crawford, T., Alejo, D., Conte, J. V., Selenger, R., Fonner, C. E., Kwon, C. C., Bobbitt, J., Brown, J. M., Nelson, M. G., Horvath, K. A. & Whitman, G. R. (2017) Variation in red blood cell transfusion practices during cardiac operations among centres in Maryland: Results from a state quality-improvement collaborative. *Annals of Thoracic Surgery*, 103 152-161.

Malhotra, A., Maughan, D., Ansell, J., Lehman, R., Henderson, A., Gray, M., Stephenson, T. & Bailey, S. (2015) Choosing wisely in the UK: the Academy of Medical Colleges' initiative to reduce the harms of too much medicine. *British Medical Journal*, 350 h2308.

Marshall, D. A., Kleinman, S. H., Wong, J. B., AuBuchon, J. P., Grima, D. T., Kulin, N. A. & Weinstein, M. C. (2004) Cost effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. *Vox Sanguinis*, 86 28-40.

Maycock, W. d'A. (1940) Blood Transfusion in the B.E.F. *British Medical Journal*, 2 467.

McClelland, D. B. L., Pirie, E. & Franklin, I. M. (2010) *Manual of optimal blood use*. Available from: http://www.optimalblooduse.eu

McHenry, L. & Khoshnood, M. (2014) Blood money:Bayer's inventory of HIV-contaminated blood products and third world haemophiliacs. *Accountability in Research*, 21 (6): 389-400.

McMahon, L. F. & Chopra, V. (2012) Health care cost and value: the way forward. *Journal of the American Medical Association*, 307 (7): 671-672.

McQuilten, Z. K., Andrianopoulos, N., Wood, E. M., Cole-Sinclair, M. F., McNeil, J. J., Cameron, P. A., Reid, C. M., Newcomb, A. E., Smith, J. A. & Phillips, L. E. (2014) Transfusion practice varies widely in cardiac surgery: results from a national registry. *The Journal of Thoracic and Cardiovascular Surgery*, 147 1684-1690.

Meeuwesen, L., van den Brink-Muinen, A. & Hofstede, G. (2009) Can dimensions of national culture predict cross-national differences in medical communication? *Patient and Education and Counseling*, 75 58-66.

Ministero della Salute (2014) *Programma di autosufficienza nazionale del sangue e dei suoi prodotti Anno 2014*. Available from: http://www.gazzettaufficiale.it/gazzetta/serie_generale/caricaDettaglio?dataPubblicazioneGazzetta=2014-11-14&numeroGazzetta=265 Roma, Italia

Ministero della Salute (2015) *Programma di autosufficienza nazionale del sangue e i suoi prodotti Anno 2015*. Available from: http://www.centronazionalesangue.it/MC-API/Risorse/StreamAttributoMediaOriginale.aspx?guid=2C82EE43-290E-462F-BEC0-FCF5391568BD Roma, Italia

Ministero della Salute (2016) *Programma nazionale del autosufficienza del sangue e dei suoi prodotti Anno 2016*. Available from: http://www.centronazionalesangue.it/MC-API/Risorse/StreamAttributoMediaOriginale.aspx?guid=A72AF36D-FDE3-417A-9C0B-B119F52FF9CD Roma, Italia

Mitra, B., Nash, J. L., Cameron, P. A., Fitzgerald, M. C., Moloney, J. & Velmahos, G. C. (2015) Potentially avoidable blood transfusion during trauma resuscitation. *Injury International Journal of the Care of the Injured*, 46 10-14.

Murphy, M. F. (2012a) End-to-end electronic transfusion management in hospital practice. *ISBT Science Series*, 7 192-196.

Murphy, M. F. (2015) The Choosing Wisely campaign to reduce harmful medical overuse: its close association with Patient Blood Management initiatives. *Transfusion Medicine*, 25 287-292.

Murphy, M. F., Stanworth, S. J. & Yazer, M. (2011) Transfusion practice and safety: current status and possibilities for improvement. *Vox Sanguinis*, 100 46-59.

Murphy, M. F., Wallington, T. B., Kelsey, P., Boulton, F., Bruce, M., Cohen, H., Duguid, J., Knowles, S. M., Poole, G. & Williamson, L. M. (2001) British Committee for Standards in Haematology guidelines for the clinical use of red cell transfusions. *British Journal of Haematology*, 113 24-31.

Murphy, W. G., (2012b) Personal communication.

Murphy, W. G. (2012c) Of mad cows and bolted horses: the economics of blood safety. *Transfusion*, 52 (11): 2278-2281.

Murphy, W. G. (2013) Lessons from the response to the threat of transfusion-transmitted vCJD in Ireland. *Transfusion Clinique et Biologique*, 20 416-421.

Murray, C. J. L., Frenk, J., Piot, P. & Mundel, T. (2013) GBD 2.0: a continuously updated global resource. *Lancet*, 382 9-11.

Musgrove, P. (2010) Health care systems ranking. *New England Journal of Medicine*, 362 (16): 1546-1547.

Myers, R. W. (1945) *Life-saving blood flows on Iwo, thanks to last month's donors*. Available from: http://spiderbites.nytimes.com/pay_1945/articles_1945_03_00002.html

National Blood Authority (2011) *Australian Haemovigilance Report 2010*. Available from: https://www.blood.gov.au/system/files/documents/australian-haemovigilance-report-2010_0.pdf

National Blood Authority (2015) *The Australian Haemvigilance Report 2015*. Available from: https://www.blood.gov.au/pubs/2015-haemovigilance/index/part-05-fresh-blood-product-use-and-haemovigilance-systems.html

Navarro, V. (2002) Can health care systems be compared using a single measure of performance? *American Journal of Public Health*, 92 (1): 31-34.

Nelson, E. C., Batalden, P. B., Huber, T. P., Mohr, J. J., Godfrey, M. M., Headrick, L. A. & Wasson, J. H. (2002) Microsystems in health care: Part 1. Learning from high performing front-line clinical units. *The Joint Commission Journal on Quality Improvement*, 28 (9): 472-493.

NHS Blood and Transplant (2010) *NHS Blood and Transplant Annual Report and Accounts 2009/10*. Available from: http://www.nhsbt.nhs.uk/download/trust_fund_accounts_2010.pdf

NHS Blood and Transplant (2016) *NHS Blood and Components Price List 2016/17*. Available from: http://hospital.blood.co.uk/media/28230/component-price-list-2016-2017.pdf

Niranjan, G., Asimakopoulos, G., Karagounis, A., Cockerill, G., Thompson, M. & Chandrasekaran, V. (2006) Effects of cell-saver autologous blood transfusion blood loss and homologous blood transfusion requirements in patients undergoing cardiac surgery on- versus off-cardiopulmonary bypass: a randomised trial. *European Journal of Cardiothoracic Surgery*, 30 271-277.

Norgaard, A., de Lichtenberg, T. H., Nielsen, J. & Johansson, P. I. (2014) Monitoring compliance with transfusion guidelines in hospital departments by electronic data capture. *Blood Transfusion*, 12 509-519.

NZBLOOD (2010) *National Haemovigilance Programme: Annual Report 2009*. Available from: http://www.nzblood.co.nz/assets/Haemovigilance/Haemovigilance-Annual-Report-2009.pdf

Organisation for Economic Co-operation and Development (2009a) *Data set: Health care utilisation; surgical procedure by ICD-9-CM per 100,000 population: coronary bypass, hip replacement*. [online] Available from: http://stats.oecd.org/ (Accessed 10 April 2012).

Organisation for Economic Co-operation and Development (2009b) *Annual Labour Force Statistics: Population over 65 as a percent of population*. [online] Available from: http://stats.oecd.org/ (Accessed 15 Jun 2012).

Organisation for Economic Co-operation and Development (2014) *Geographic variations in health care: what do we know and what can be done to improve health system performance?* Available from: http://www.oecd.org/health/geographic-variations-in-health-care-9789264216594-en.htm OECD publishing

Organisation for Economic Co-operation and Development (2016a) *OECD Data - Health*. Available from: https://data.oecd.org/health.htm

Organisation for Economic Co-operation and Development (2016b) *"Health Status", OECD Health Statistics (database)*. Available from: http://stats.oecd.org/Index.aspx?DataSetCode=HEALTH_STAT

Otsubo, T., Imanaka, Y., Morishima, T., Sasaki, N., Park, S. & Lee, J. (2016) Variations in healthcare spending and quality among institutions. In: Johnson, A. & Stukel, T. A., eds. *Medical Practice Variations*. 1 edn. New York: Springer US: 383-406.

Oxman, A. D., Thomson, M. A., Davis, D. A. & Haynes, R. B. (1995) No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *Canadian Medical Association Journal*, 153 (10): 1423-1431.

Pair, C. Q. (1929) Intravenous Therapy. *Journal of the National Medical Association*, 22 (1): 21-24.

Pena, J. R. A. & Dzik, W. (2014) Utilization management in the blood transfusion service. *Clinica Chimica Acta*, 427 178-182.

Perel, P., Roberts, I. & Ker, K. (2013) Colloids vs crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews*, (2): CD000567.

Pfunter, A. W. L. & Stocks, C. (2010) *Most frequent procedures performed in US hospitals*. Available from: http://hcup-us.ahrq.gov/reports/statbriefs/sb149.pdf

Picker, S. M., Kaleta, T., Hekmat, K., S, K. & Gathof, B. S. (2007) Anti-platelet therapy preceding coronary artery surgery: implications for bleeding, transfusion requirements and outcome. *European Journal of Anaesthesiology*, 24 332-339.

Pool, J. G. & Shannon, A. E. (1965) Production of high-potency concentrates of antihemophilic globulin in a closed-bag system — assay in vitro and in vivo. *New England Journal of Medicine*, 273 1443-1447.

Public Health England (2015) *The NHS atlas of variation in healthcare: reducing unwarranted variation to increase value and improve quality*. Available from: https://www.england.nhs.uk/rightcare/intel/cfv/atlas/ London, UK

Ralston, S. L. & Schroeder, A. R. (2015) Doing more vs doing good:Aligning our ethical principles from the personal to the societal. *JAMA Pediatrics*, 169 (12): 1085-1086.

Rehm, J. P., Otto, P. S., West, W. W., Grange, J. J., Halloran, B. G., Lynch, T. G. & Baxter, B. T. (1998) Hospital-wide education program decreases red blood cell transfusions. *Journal of Surgical Research*, 75 183-186.

Rogers, M. A. M., Blumberg, N., Saint, S., Langa, K. M. & Nallamothu, B. K. (2009) Hospital variation in transfusion and infection after cardiac surgery: a cohort study. *BMC Medicine*, 7 37-45.

Rothberg, M. B., Cohen, J., Lindenauer, P., Maselli, J. & Auerbach, A. (2010) Little evidence of correlation between growth in health care spending and reduced mortality. *Health Affairs*, 29 (8): 1523-1531.

Rubin, B. B., Drenth, B. & Beanlands, R. S. B. (2015) Appropriate quality imaging tests through linkage of payment to guidelines, accreditation and training. *Canadian Medical Association Journal*, 187 (4): E126-E127.

Sanquin (2010) *Sanquin Annual Report; Close to '09*. Available from: http://www.sanquin.nl/repository/documenten/en/about-sanquin/sanquin/45297/45308/ENG_Sanquin_jaarverslag_2009_binnenwerk_def.pdf

Seeff, L. B. (1988) Transfusion-associated hepatitis B: past and present. *Transfusion Medicine Reviews*, 2 (4): 201-214.

Seifried, E., Klueter, H. & Weidmann, C. (2011) How much blood is needed? *Vox Sanguinis*, 100 10-21.

Shander, A., Hofmann, S., Ozawa, S. & Javidroozi, M. (2009) The true cost of red blood cell transfusion in the surgical patient. *Blood*, 112 1147.

Slichter, S. J., Kaufman, R. M., Assmann, S. F., McCullough, J., Triulzi, D. J., Strauss, R. G., Gemsheimer, T. B., Ness, P. M., Brecher, M. E., Josephson, C. D., Konkle, B. A., Woodson, R. D., Ortel, T. L., Hilyer, C. D., Skerrett, D. L., McCrae, K. R., Sloan, S. R., Uhl, L., George, J. N., Aquino, V. M., Manno, C. S., McFarland, J. G., Hess, J. R., Lessinger, C. & Granger, S. (2010) Dose of prophylactic platelet transfusions and prevention of hemorrhage. *New England Journal of Medicine*, 362 600-613.

Slight, R. D., Alston, R. P., McClelland, D. B. & Mankad, P. S. (2009) What factors should we consider in deciding when to transfuse patients undergoing elective cardiac surgery? *Transfusion Medicine Reviews*, 23 42-54.

Slight, R. D., Bappu, N. J., Nzewi, O. C., B, M. D. & Mankad, P. S. (2006) Perioperative red cell, plasma and blood volume change in patients undergoing cardiac surgery. *Transfusion*, 46 392-397.

Snyder-Ramos, S. A., Mohnle, P., Weng, Y. S., Bottiger, B. W., Kulier, A., Levin, J. & Mangano, D. T. (2008) The on-going variability in blood transfusion practices in cardiac surgery. *Transfusion*, 48 1284-1299.

Starr, D. (1998) *Blood: An epic history of medicine and commerce*. New York, USA: Alfred A Knopf.

Statistics Denmark (2009) *RASU11: Population by region, education, socioeconomic status, age and sex*. [online] Available from: http://www.statistikbanken.dk/statbank55/SelectVarVal/define.asp?MainTable=RASU11&PLanguage=1&Tabstrip=&PXSId=0&SessID=182700766&FF=20&grouping5=20061114954292221859 2&tfrequency=1 (Accessed 14 Dec 2016).

Stetler, C. B. (2003) Role of the organisation in translating research into evidence-based practice. *Outcomes Management*, 7 (3): 97-103.

Stover, E. P., Siegel, L. C., Parks, R., Levin, J., Body, S. C., Maddi, R., D'Ambra, M. N., Mangano, D. T. & Spiess, B. D. (1998) Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines. *Anesthesiology*, 88 327-333.

Surgenor, D. M., Churchill, W. H., Wallace, E. L., Rizzo, R. J., McGurk, S., Goodnough, L. T., Kao, K. J., Koerner, T. A. W., Olson, J. D. & Woodson, R. D. (1998) The specific hospital significantly affects red cell and component transfusion practice in coronary artery bypass graft surgery: a study of five hospitals. *Transfusion*, 38 122-134.

Tasian, G. E., Pulido, J. E., Keren, R., Dick, A. W., Setodji, C. M., Hanley, J. M., Madison, R. & Saigal, C. S. (2014) Use of regional variation in initial CT imaging for kidney stones. *Pediatrics*, 134 (5): 909-915.

Tchouaket, E. N., Lamarche, P. A., Goulet, L. & Contandriopoulos, A. P. (2012) Health care system performance of 27 OECD countries. *The International Journal of Health Planning and Management*, 27 (2): 104-129.

Tebe, C., Abilleira, S., Ridao, M., Espallargues, M., Salas, T. & Bernal-Delgado, E. (2013) *VPM Atlas de variaciones en la pratica medica en el sistema nacional de salud: atlas de variaciones en el manejo de la enfermedad cerebrovascular isquemica*. Available from: http://www.atlasvpm.org

The National CJD Research & Surveillance Unit (2017) *Variant CJD cases worldwide*. [online] Available from: http://www.cjd.ed.ac.uk/sites/default/files/worldfigs_1.pdf (Accessed 23 February 2017).

Thomas, S., Turner, M. L. & Williamson, L. (2013) UK approach to assessing assays and filters designed to reduce the risk of transfusion-transmitted vCJD. *Transfusion Clinique et Biologique*, 20 405-411.

Toner, R. W., Pizzi, L., Leas, B., Ballas, S. K., Quigley, A. & Goldfarb, N. I. (2011) Costs to hospitals of acquiring and processing blood in the US: a survey of hospital-based blood banks and transfusion services. *Applied Health Economics and Health Policy*, 9 (1): 29-37.

UK Department of Health (2007) *Better blood transfusion - safe and appropriate use of blood*. Available from: http://www.transfusionguidelines.org/document-library/documents/hsc-2007-001-better-blood-transfusion-safe-and-appropriate-use-of-blood London, UK

United Nations Development Programme (2011) *Human Development Report 2011 Statistical Tables*. [online] Available from: http://hdr.undp.org/en/statistics/hdi/ (Accessed 22 March 2012).

Vamvakas, E. C. & Taswell, H. F. (1994) Epidemiology of Blood Transfusion. *Transfusion*, 34 464-470.

Vogel, L. (2015) Choosing wisely around the world. *Canadian Medical Association Journal*, 187 (11): E341-E342.

Wallace, E., Smith, S. M. & Fahey, T. (2012) Variation in medical practice: getting the balance right. *Family Practice*, 29 501-502.

Weeks, W. B., Paraponaris, A. & Ventelou, B. (2014) Geographic variation in rates of common surgical procedures in France in 2008-2010, and comparison to the US and Britain. *Health Policy*, 118 215-221.

Welch, H. G. & Frankel, B. A. (2011) Likelihood that a woman with screen-detected breast cancer has had her "life saved" by that screening. *Archives of Internal Medicine*, 171 (22): 2043-2046.

Wells, A. W., Llewelyn, C. A., Casbard, A., Johnson, A. J., Amin, M., Ballard, S., Buck, J., Malfroy, M., Murphy, M. F. & Williamson, L. M. (2009) The EASTR Study: Indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfusion Medicine*, 19 315-328.

Wennberg, J. & Gittelsohn, A. (1973) Small area variations in health care delivery: A population-based health information system can guide planning and regulatory decision-making. *Science*, 182 1102-1108.

Wennberg, J., McPherson, K. & Goodman, D. (2015) Small area analysis and the challenge of practice variation. In: Johnson, A. & Stukel, T., eds. *Medical Practice Variations*. New York, USA: Springer Science & Business Media:

Wennberg, J. E. (2010) *Tracking Medicine; A researcher's quest to understand health care*. Oxford University Press, Inc.

Wennberg, J. E., Barnes, B. A. & Zubkoff, M. (1982) Professional uncertainty and the problem of supplier induced demand. *Social Science & Medicine*, 16 811-824.

Wensing, M., Wollersheim, H. & Grol, R. (2006) Organisational interventions to implement improvements in patient care: a structured review of reviews. *Implementation Science*, 1 2.

Westert, G. P., Nieboer, A. P. & Groenewegen, P. P. (1993) Variation in duration of hospital stay between hospitals and between doctors within hospitals. *Social Science and Medicine*, 37 (6): 833-839.

Will, R. G., Ironside, J. W., Ziedler, M., Estibeiro, K., Cousens, S. N., Smith, P. G., Alperovitch, A., Poser, S., Pocchiari, M. & Hofman, A. (1996) A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet*, 347 921-925.

Williamson, L. M. (1998) *Serious hazards of transfusion annual report 1996-1997*. Available from: https://www.shotuk.org/wp-content/uploads/2010/03/SHOT-Report-96-97.pdf

Williamson, L. M., Llewelyn, C. A., F, F. N., Allain, J.-P., Bellamy, M. C., Ballin, T. P., Freeman, J., Klinck, J. K., Ala, F. A., Smith, N., Neuberger, J. & Wreghitt, T. (1999) A randomised trial of solvent/detergent and standard fresh frozen plasma in the coagulopathy of liver disease and transplantation. *Transfusion*, 39 1227-1234.

World Bank (2009a) *Maternal mortality ratio per 100,000 population*. [online] Available from: http://data.worldbank.org/indicator/SH.STA.MMRT (Accessed 11 April 2012).

World Bank (2009b) *Health care expenditure per capita (current US$ purchasing power parity)*. [online] Available from: http://data.worldbank.org/indicator/SH.XPD.PCAP?view=chart (Accessed 10 April 2012).

World Bank (2009c) *Gross domestic product per capita (current US$)*. [online] Available from: http://data.worldbank.org/indicator/NY.GDP.PCAP.CD?year_high_desc=true (Accessed 15 June 2012).

World Health Organisation (2003) *World Cancer Report*. Available from: http://www.iarc.fr/en/publications/pdfs-online/wcr/2003/WorldCancerReport.pdf Geneva, Switzerland

World Health Organisation (2010) *Clinical transfusion process and patient safety - Aide memoire for national health authorities and hospital management*. Available from: http://www.who.int/bloodsafety/clinical_use/who_eht_10_05_en.pdf?ua=1

World Health Organisation (2016) *World health statistics 2016: monitoring health for the SDGs.* Available from: http://www.who.int/gho/publications/world_health_statistics/2016/en/ Geneva, Switzerland

Appendices

Correspondence to individual medical directors of national transfusion services in Europe

Dear XXXXXXX,

I hope you are keeping well. I would be grateful if you could have a look at the attachment to this mail. As I explained, I have put together a model that shows correlation of the variation in red cell use with a number of factors. However, I am also interested in looking at the regional differences within individual countries. My theory is that the variation in red cell use, though trackable to some national demographic differences, is also a result of practice differences within institutions. I also believe that demonstration of variation in red cell use across regions within the same country will continue to strengthen this hypothesis. The ultimate aim is to make the case that one requires local leadership to implement appropriate red cell use and just writing national guidelines and leaving it up to the individual medics to follow them does not work in the same way across different countries. Additionally I think it is important to highlight that the implementation of PBM cannot be a case of one-size fits all - it really depends upon the culture of the organisation and the tools to put PBM in place should be adapted to the specific institution.

I am writing to you in the hope that you may be able to supply me with the data for your country or to put me in contact with anyone within your organization who may have access to these figures. Of course, I would gladly share what I've done to date and what I hope to continue to do, and would be only too happy to collaborate on this with individuals who may be interested.

I look forward to your thoughts and comments.

Warm regards,

Dr Stefan Laspina
Consultant, Transfusion Medicine
Mater Dei Hospital Blood Bank
Clinical Chairperson, Haematology & Oncology
Mater Dei Hospital
Malta

Attachment to correspondence

Subsequent Council of Europe documents have shown that blood usage across different countries varies. It has been posited that this variance may be a result of demographic differences rather than an actual difference in specific medical practice. A performance of statistical correlations does indicate that this variance may indeed be partially explained by demographics. But not all of it is. I have attempted to build a model showing the association of the variance with a number of factors. It appears that as one would intuitively expect, the variance is associated with indices such as 'Per Cent Population over 65 Years' (as has been shown in a couple of publications) and the 'Prevalence of Coronary Artery Bypass Surgery per 100,000 Population'. It does however also seem likely that blood use varies with the 'Health Care Expenditure per Capita US$ Purchasing Power Parity', and also that part of the variance cannot be explained except perhaps by real differences in practice. This latter point is also evident from the publications showing differences in practice across countries and even across institutions within the same country with regards to the use of red cells in specific procedures such as hip replacement and cardiac surgery.

Up until now, I have used only National statistics available from various public reports and various publically available databases. At this stage I would like to look at the differences across regions within the same country. I would like to examine the hypothesis that the patterns of usage are consistent across the country (i.e. very similar in a majority of regions) as opposed to the hypothesis that every region has a different pattern of usage and the national figure is only a composite of what occurs in the regions.

I would be sincerely grateful if you could help me out with this. In order to examine the hypothesis, I would need figures for red cell use (or red cell distribution) in the regions and, if available, the population of the individual regions. If possible, the data should be for **either of** 2012, 2013 or 2014.

I am attaching a template for ease of compilation:

Country:	XXXXXXXXXXX (Insert Name of Country)		
	Region Name	Red Cells Used Within Region 2012 / 2013 / 2014 (Circle as appropriate)	Population of Region
Region 1			
Region 2			
Region 3			
Region 4			
Region 5			
Etc…			