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Cost of allogeneic blood management in Germany: A literature and expert interview - based investigation

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by

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Dear people,

I must honestly to tell you that, I am under pressure when writing this acceptance speech. Tomorrow it must go to the printing, I just moved and started a new thing in life and completing the thesis equally between. I shake it so quick from my sleeve and it may be that I forget someone, but do not fret personally. The person which I forget unintentionally, shall we meet for dinner?

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Kishankumar R. Vaghasiya, in March 2017.

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List of Abbreviations

ABC	Activity Based Cost
ABT	Allogeneic Blood Transfusion
AT	Austria
BTS	Blood Transfusion Safety
CAPA	Corrective and Preventive Action
CDC	Centre for Disease Control
CH	Switzerland
CoE	Council of Europe
CPI	Consumer Price Index
CTD	Chronic Transfusion Dependency
EC	Erythrocytes
EDQM	European Directorate for the Quality of Medicines and HealthCare
ESAs	Erythropoietic Stimulating Agents
EU	European Union
FFP	Fresh Frozen Plasma
GDP	Gross Domestic Product
HBC	Hepatitis B Core Antigen
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
MDS	Myelodysplastic Syndromes
NAT	Nucleic Acid Amplification Techniques
OECD	Organisation for Economic Co-operation and Development
PBM	Patient Blood Management
PC	Platelets Consumption
PEI	Paul Ehrlich Institute
RBC	Red Blood Cell
TACO	Transfusion Associated Circulatory Overload
TC	Thrombocytes
TFG	Transfusionsgesetz (Transfusion Act)
WBD	Whole Blood Donation
WHA	World Health Assembly
WHO	World Health Organisation
WNV	West Nile Virus

Abstract

Background: Transfusion of allogeneic blood are widely utilized in the management of medical and surgical procedures; these is sometimes underestimated in prospect of the cost and overestimated in terms of its effectiveness. Incomplete accounting for blood costs has the potential to misdirect programmatic decision making by health care systems. Hence, the aim of this study was to an in-depth examination of allogeneic blood transfusion costs and evaluation of finite resources consumption for quality treatment in Germany.

Methods: In this prospective study, literature search aims to understand the current cost of allogeneic blood transfusion. Secondary data source information is a comprehensive practical analysis, which helps to understand the current supply of blood products to complement the theoretical knowledge. Semi-structured experts´ interview strives to integrate the expertise in the current practice of blood transfusion management and their resources used on the ground level with possible solutions for the future. Meanwhile, all methods give us an insight into the costs and resources used in allogeneic blood transfusions past, present and future in Germany.

Results: The present analysis captures direct and indirect cost of a single unit of blood transfused in Germany and cost of single & double unit of blood transfused in Europe. The mean cost per two unit of transfused blood in Europe is €888.56. In Germany, the mean direct allogeneic blood unit cost was estimated at €272.71 and the mean indirect cost and opportunity cost per unit of blood transfusion was estimated at €33.20 and €62.00 respectively. Finally, the total cost of the whole blood transfusion process in terms of government perspectives was estimated around €1.18 billion in 2011, but it decreased to €0.98 billion in 2015.

Conclusion: Findings of this study confirms that blood transfusion costs have been undervalued and demonstrates best practice of allogeneic blood management that appears strongly aligned to cost savings and quality treatment which may further assist the decision makers like legislators, policy makers, and other healthcare professionals. Eventually, the chosen research design and methods can be drawn out further to improve the results with more detailed analysis.

Key words: Allogeneic blood transfusion, Activity based cost, Direct cost, Indirect cost, Resource allocation, Blood product supply.

1. Background

In modern medical practice, blood plays a pivotal role. However, vital health care commodities made from blood are on the verge of scarcity (Mo Amin et al., 2004)(Williamson & Devine, 2013). Around the world, the need for blood and its products is rapidly increasing. Health care systems are advancing and providing improved health coverage. In middle and high socio-economic status countries, medical and surgical procedures are continuously improving; being conducted in increasingly efficient ways (‘World Health Organisation’, 2016).

Health care expenditure growth is continuously stepping up of the gross domestic product (GDP) in most of the European countries. In Germany, the health spending GDP ratio has increased from 9.8% to 11.1% from 2000 to 2016 and health spending per capita in real terms has also increased by approximately 2% annually from 2009 until 2013, respectively (OECD, 2017).

In 2011, the World Health Organization´s (WHO) Global Database on Blood Safety (GDBS) reported that, globally 112.5 million units of blood was donated (‘World Health Organisation’, 2016). From the collected blood units, separation of blood components allows a single unit of blood to benefit several patients. The blood and its components is prepared, sold & delivered to the hospital blood depots and laboratories for further procedure and/or transfusion (‘World Health Organisation’, 2016). Half of its volume was collected, processed and paid for by high-income countries with the largest proportion consumed in the European Union and USA, that is 19% of the world’s population (‘World Health Organisation’, 2016). In high income countries, this is commonly used for supportive care in cardiovascular surgery, transplant surgery, massive trauma and therapy for solid & haematological malignancies.

From an economic point of view, blood transfusion services are mainly funded by sickness funds and German state government and, its main benefit to the users is that it is totally free of cost (‘Transfusionsgesetz - TFG’, 2016). These services completely rely on the regular, unpaid and voluntary donation of whole blood donors as well as apheresis donors, which are conducted by the following organisations as shown in the Table 1.1 (PEI, 2017).

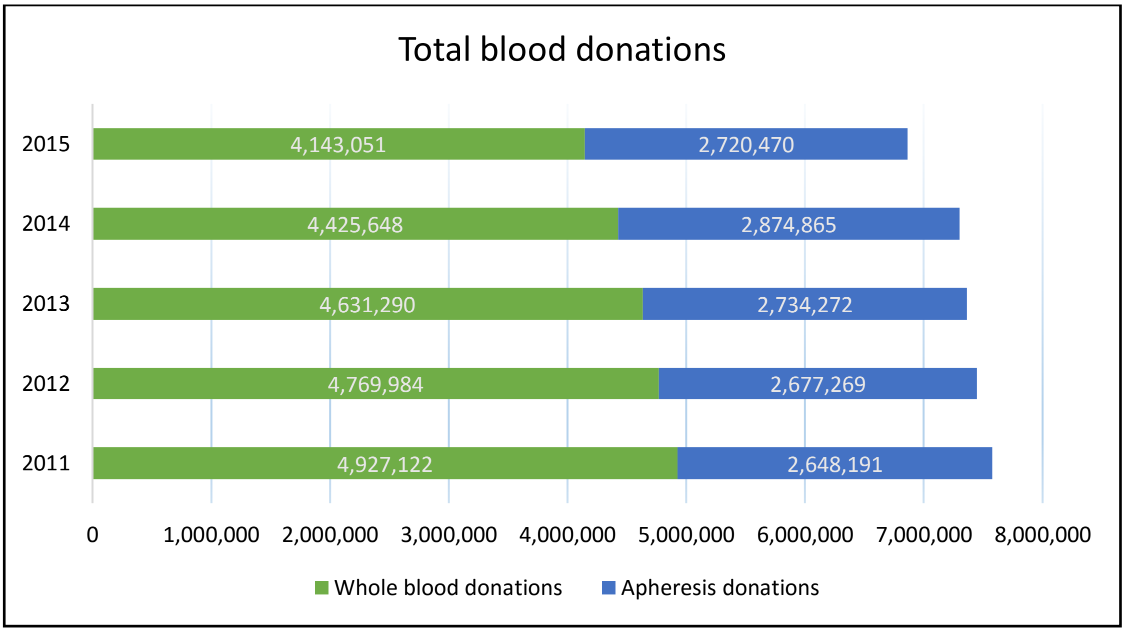
Table 1.1: Blood manufacturers (collection, production, import, and export) – 2015 (PEI, 2017)

Type of organisation	Number of manufacturers
State-run, municipal or private hospitals, non-profit limited liability company	69
German Red Cross	12
Plasma processing industry	19
Private donation centre	27
Bundeswehr (German army)	1
Facilities collecting autologous blood, manufacturing blood components from directed donations or hematopoietic stem cell preparations	112
Total	**240**

The challenging task about health care is to deliver it at an affordable cost with improved quality of care every time because the cost of a donated unit is preferably high around the world (Fragoulakis, Stamoulis, Grouzi, & Maniadakis, 2014).

In the year 2011, the total number of blood donations from all over Germany were 4,827,122 and apheresis donations were 2,648,191 but these donations have gradually declined by the year 2015. This drop took place because of the shrinkage in the pool of blood donors as shown in Figure 1.1 (PEI, 2017).

Figure 1.1: Whole and apheresis blood donations – 2011 to 2015 (PEI, 2017)



Since the discovery of blood types and their advancements, transfusions can be either a life-saving or life threatening intervention ('World Health Organisation', 2016). Transfusions of allogeneic blood are widely utilized in the management of medical and surgical procedures. The transfusion rate in Germany is 57.3 units per 1000 population, in Denmark 60.2, in United Kingdom (UK) 36.1 and in France 35.4 respectively. These countries have similar demographics with almost the same type of health system and distribution of disposable income. The range per capita of blood transfusion however differs variably, which is approximately 1:2 but in benchmarking blood utilisation between hospitals and matched patient groups, the variability of range is far greater (L.R. van Hoeven, M.P. Janssen, & G. Rautmann, 2011) (WHO, 2011).

In this modern era, several predicaments to humanity have exposed people to acquire different medical conditions and emergencies of which one such need has come out to be blood transfusion (Matowa & Ndwabe, 2016) (Abraham & Sun, 2012).

1.1. Introduction to blood transfusion

Transfusion is a kind of liquid organ transplantation and blood transfusion is a procedure in which blood is given through an intravenous (IV) line into the blood vessels of the body (National Heart Lung and Blood Institute, 2017). In the treatment of many diseases, blood transfusion is required in patients having both medical and surgical complications, like acute blood loss, haemorrhagic shock that can either be after accidents or during surgical procedures and anaemic patients with cancer. It is also necessary and helpful for patients requiring RBCs, platelets and plasma derived products as it helps in maintaining an adequate RBC and plasma volume (Kaur, Basu, Kaur, & Kaur, 2011) (EDQM, 2017).

There are two main types of blood transfusion, allogeneic blood transfusion and autologous blood transfusion. Cellular blood components like erythrocytes (EC), thrombocytes (TC) and blood plasma, cannot be synthesized. Therefore, blood transfusion is being considered a special alternative to eradicate this difficulty (Rottenkolber, Schmiedl, Rottenkolber, Thuermann, & Hasford, 2012). In the human body, erythrocytes or red blood cells have an important role to play in many patho-physiological functions. RBC transfusion helps to treat the complications of haemorrhage and improves oxygen supply to the tissues and vital organs. Thrombocytes or platelet transfusion is indicated in preventing haemorrhage in the patients with thrombocytopenia or platelet malfunction. Plasma transfusion is utilized for the reversal of anticoagulant effects (Sharma, Sharma, & Tyler, 2011). The transfusion of allogeneic blood products, especially of red blood cells (RBCs), is one of the most prevalent interventions in clinical practice (Lelubre & Vincent, 2011). In 2011 and 2012 a survey of PEI, showed that approximately 75% of all platelets were transfused in hemato-oncological departments including paediatric divisions (Bundesgesundheitsblatt-Gesundheitsforschung-Gesundheitsschutz, 2015).

It is very difficult and challenging to predict precise need of blood products in swiftly changing clinical situations. If clinicians are able to monitor optimal oxygen supply and coagulation status, blood product transfusion can easily be optimized. As a result, these methods can aid and guide clinicians in making the decision for transfusion therapy (Meybohm et al., 2017). It is expected that these transfusion thresholds are developed from quality evidence and are based on rigorous clinical trials & studies that demonstrate improvement in patient outcome (Shander, Gross, Hill, Javidroozi, & Sledge, 2013).

In a Cochrane review (Paul A. Carless et al., 2010), transfusion strategies were discussed and the conclusion was that, restrictive transfusion strategies are associated with reduced infection and transfusion rates & volumes with keeping in check about worsening the outcome of the patient that includes mortality, cardiac events, stroke, pneumonia and thromboembolism (Paul A. Carless et al., 2010). However, Nichol et al. criticised this point that it might be too early to lower the thresholds to 7 g/dL and supported the restriction of transfusion strategy by saying that physicians should ideally weigh the risk-benefit profile for each individual patient for each unit of blood administered (Nichol, 2008).

Blood and its component safety in highly developed countries has always an important question for a long time. The blood safety and supply in these countries are threatened by some factors such as the aging of the population, globalisation, increased international travel and the proposed establishment of a blood market (Seifried & Mueller, 2011). On the contrary, the safety of allogeneic blood transfusion in European countries has risen significantly over the past fifteen years. All this has proven to be a success primarily due to improvements in the quality of blood donors, screening procedures, and the steps taken to control strict quality measures (Klein 2007).

According to quality assurance standards of European blood donations in clinical haemotherapy, testing the blood components and its adequate use currently requires greater attention because of escalated cost pressures in clinical care (Seifried & Mueller, 2011).

1.2. Quality management for blood establishments

The Directive 2005/62/EC of the European Commission denotes a standardisation and specifications for blood products use and their quality systems. The main motive of the commission is to securely supply blood products to the population therefore enhancing the production of self-catering blood and plasma products on a voluntary donation basis (EDQM, 2017).

The German Transfusion Act (Transfusionsgesetz-TFG) determines the quality and safety of the entire transfusion process. As per TFG guidelines, the blood bank centres and hospitals are obliged to follow basic standard requirements and procedures for collection processes. The requirements start with section § 4 "requirement of donation unit" to section § 23 "reporting" and simultaneously it is mandatory for them to follow the quality standard of the European Union ('Transfusionsgesetz - TFG', 2016).

According to the Council of Europe, quality and safety standards for collection, testing, processing, storage and distribution of blood and its products must abide by the given procedures in the table 1.2, which directly influence the cost of blood units and helps to understand the real cost estimation of blood transfusion processes (EDQM, 2015).

Table 1.2: Quality system standards and specifications (EDQM, 2015)

General Principles	Quality system: • Should have systematic approach toward quality • Quality management, quality assurance, continuous quality improvement should be at place • Quality should ensure that critical processes are specified in appropriate instructions
	Quality assurance: • Establishments and hospital blood banks should be supported by a quality assurance function • Should be validated prior to introduction and be re-validated at regular intervals

Personnel and Organisation	• Should be available in sufficient numbers • Should have up to date job descriptions • Should receive initial and continued training • Should be periodically assessed and evaluated • Should have safety and hygiene instructions in place
Premises	• General: mobile sites should be adapted and maintained to suit the activities • Blood donor area should be an area for confidential personal interviews • Blood collection should be carried out in an area intended for the safe withdrawal of blood from donor • Blood testing and processing areas should be a dedicated laboratory area for testing that is separate • Storage areas should provide for properly secure and segregated storage of different categories and equipment • Waste disposal area should be designated for the safe disposal of waste and disposable items
Equipment and materials	• Should be validated, calibrated and maintained • Should be selected to minimise any hazard • Reagents and materials should only from approved suppliers • Inventory records should be retained • Computerised systems should be protected
Documentation	• Should be in place and kept up to date • All significant changes should be reviewed, dated and signed
Blood collection, testing and processing	Donor eligibility: • Safe donor identification, suitability interview and eligibility assessment should be implemented and maintained • Donor interview should be conducted • Donor suitability records and final assessment should be signed by a qualified health professional
	Collection of blood and blood components: • Collection procedure should be of the identified donor • Processing should be CE-marked or comply with equivalent standards • Should minimise the risk of microbial contamination • Samples should be taken at the time of donation • Labelling of records should be designed to avoid any risk of identification
	Laboratory testing: • Testing procedures should be validated • Should be clearly defined procedures to resolve discrepant results • Data should confirm the suitability of any laboratory reagents • Laboratory testing should be regularly assessed
	Processing and validation: • Equipment and technical devices should be used in accordance with validated procedures. • Processing should be carried out using appropriate and validated procedures

	Labelling: • Should be labelled with relevant information • Should comply with the requirements of Annex III to Directive 2002/98/EC.
	Release of blood and blood components: • Should be a safe and secure system (authorised person) • Administrative records should be kept
Storage and distribution	• Should comply with Directive 2003/94/EC. • Should ensure quality during the entire storage period • Should have appropriate records of inventory and distribution • Packaging should maintain the integrity and storage temperature • Should ensure return product integrity is fulfilled
Non-Conformance	Recall: • Should assess product recall and initiate actions • Effective recall procedure should be in place • Actions should be taken within pre-defined periods of time
	Corrective and Preventive Action (CAPA): • A system to ensure CAPA should be in place • Data should be routinely analysed to identify the quality • All errors and accidents should be documented and investigated
Self-Inspection	• Self-inspection or audit systems should be in place for all parts of the operations • All results should be documented and appropriate CAPA

In Germany, other specific measures have been taken to improve the safety standard of blood transfusion processes in the last five years. For example, the introduction of HIV-1-NAT test systems with two target regions in 2012, and on update in opinions with "look-back procedures with regard to hepatitis-B infections" (2012/13), testing for antibodies against hepatitis-B core antigen (Anti-HBc) in the blood donation system (2014), and conditions for a donor deferral after travelling to endemic areas for West Nile Virus (WNV) in the year 2014 (PEI, 2017).

1.3. Guidelines and recommendations

It is important for International organisations to continuously improve blood management systems by constant quality assurance check and raising the pre-defined standards by making strong suggestions that ensure the health and safety of patients and providers.

1.3.1. World Health Organization (WHO)

The WHOs´ Blood Transfusion Safety (BTS) committee released guidelines on the appropriate use of blood and its products. The released guidelines assisted WHO Member states to develop and implement them in national policies by ensuring active collaboration between the blood transfusion services and clinicians in the management of patients who requires transfusions ('World Health Organisation', 2016). Clinical need should be the only basis for transfusion therapy and, patients should be informed of the known risks & benefits of blood transfusion and/or alternative therapies and furthermore, patients have the right to accept or refuse the procedure ('World Health Organisation', 2016).

Table 1.3: WHO key points for the appropriate use of blood and blood products (WHO, 2002)

Key points
1. Conditions leading to significant morbidity or mortality that cannot be prevented or managed effectively by other means, transfusion of safe blood products and its appropriate use is the only way for treating these complications. 2. Transfusion carries the risk of adverse reactions and infections associated with transfusion. Plasma can transmit many infections present in whole blood and there are very minimal indications for its transfusion. 3. Blood donated by family/replacement donors carries a higher risk of transfusion-transmissible infections than blood donated by voluntary non-remunerated donors. Paid blood donors generally have the highest incidence and prevalence of transfusion-transmissible infections. 4. Blood should not be transfused unless it has been obtained from appropriately selected donors, has been screened for transfusion transmissible infections and tested for compatibility between the donor's red cells and the antibodies in the patient's plasma, in accordance with national requirements. 5. The need for transfusion can often be avoided by: - The prevention or early diagnosis and treatment of anaemia and conditions that cause anaemia - The correction of anaemia and the replacement of depleted iron stores before planned surgery - The use of simple alternatives to transfusion, such as intravenous replacement fluids - Good anaesthetic and surgical management.

1.3.2. Council of Europe

The Council of Europe focuses on studying the ethical, legal and organisational aspects of blood transfusion with a view to ensuring quality, increasing availability, avoiding wastage, ensuring optimal use of blood supplies and analysing the possible ethical and organisational impact of new scientific developments (EDQM, 2017). The European Blood Transfusion Committee built the blood transfusion programme around three major principles: the non-commercialisation of substances given on the basis of a voluntary and non-remunerated donation; mutual assistance; and protection for both the donors and the recipients. The Council of Europe has emphasized on the exquisite nature of donated blood by pursuing the blood management agenda with regard to the implementation of blood management programs (EDQM, 2015). Thus, the Council of Europe has made the following blood management recommendations:

a. Development of preventive strategies to reduce blood loss;
b. Advocate on the use of alternatives to allogeneic blood transfusion;
c. Encourage measures to be taken to minimize blood loss and blood products due to technical reasons (CoE, 2002)(EDQM, 2015).

2. Objectives

The aim of this study is to gather information and to describe the situation of health care that is scrutinized under the misperception that blood transfusions are relatively inexpensive.

i. To determine the total cost of allogeneic blood transfusion in Germany.

The first objective focuses on the total allogeneic blood transfusion cost. Therefore, decision making and resource allocation in health care systems would be better informed if the actual cost of blood transfusion, as well as, all transfusion-related activities are known.

ii. To investigate to what extent transfusion of allogeneic blood products is a wise use of collective resources.

Blood supply and other essential services are sometimes overlooked which can affect the quality of care. This objective elaborates how the present resources are potentially implemented in the practical context of the blood transfusion services. The qualitative expert interviews raise the question for people or health care professionals that: "Is blood transfusion worth every cent we have spent?"

3. Methods

The study analysis consists of three consecutive methodological steps. First, is a prerequisite in preparation of the second and third step respectively. Each step is in close contact with the other in the blood transfusion process cost and management. Meanwhile, all methods give us an insight into the costs and resources used in allogeneic blood transfusions past, present and future in Germany.

The first step, described in the following section 3.1 “Literature search” aims to understand the current cost of allogeneic blood transfusion in Germany. This method serves the purpose of introducing the theoretical background while ensuring an adequate degree of practical application. The introduction of the method via literature search stays within the scope of the master thesis although a comprehensive analysis would be ideal.

The second step, in section 3.2 “Secondary data source information” is a comprehensive practical analysis, which helps to understand the current supply of blood products to complement the theoretical knowledge. This method shines a light on past and present resource consumption which enables us to understand the loops in the systems of how it must be filled, and in what way we must allocate the use of resources in the future to maximise its effect in scarcity.

The semi-structured expert interview is the third step (see section 3.3) which seeks to collect the information needed to answer the second research question. An expert’s information constitutes the central data source of the thesis. It strives to integrate the expertise in the current practice of blood transfusion management and their resources used on the ground level with possible solutions for the future.

Overall, all the methods described in this study focus to do justice with the research aim and its objectives.

3.1. Literature Search

In this review, the studies have aimed to estimate the cost associated with allogeneic blood transfusions in Germany. MEDLINE-PubMed and Advancing transfusion and cellular therapies worldwide databases (Cochrane database, Blood journal) were being searched to identify studies that reported the cost associated with allogeneic blood transfusion. The search strategy consisted of MeSH terms such as “blood transfusion,” “allogeneic blood transfusion,” “direct and indirect cost” and “hospital cost” with a time frame between January 2002 and January 2017, because of the new Directive by the Council of Europe in 2002. Limitations in terms language occurred, as studies included research papers predominantly in English along with two German studies. The Complete search strategy is provided in Table 3.1. Titles and abstracts of the identified articles were examined by the independent reviewers based on the eligibility criteria. Furthermore, the study shows the bibliographies and citation sections (i.e., snowballing technique) of the included articles for additional studies. The literature search below has several inclusion and exclusion criteria.

3.1.1. Inclusion criteria

Studies were included based on the following criteria:

- Studies on reported cost of allogeneic blood transfusion;
- Studies that reported direct costs and indirect cost. Cost-effectiveness, cost-benefit or cost-minimisation analytical studies in comparison to allogeneic blood transfusion;
- Any study that compared cost of blood transfusion in Germany with other European countries.

3.1.2. Exclusion criteria

Studies were excluded on the following criteria:

- Studies in which cost of autologous blood transfusion was determined;
- Studies conducted outside of Europe;
- Studies that did not have a clear methodological point of view.

3.1.3. Data collection

Study details were extracted by independent reviewers in a pre-specified data extraction grid. For the included studies, the following data was extracted: authors, country, year of data, cost elements and cost for single and double units of blood transfusions. In case of single unit, cost has been converted to double unit cost, to match with the criteria of the studies. Quality assessment of included studies was not performed.

Direct costs associated with allogeneic blood transfusion include the costs of: blood donation, pre-transfusion processes, issuing and delivery, transfusion processes, direct overhead and post transfusion costs. Each of these elements are divided into sub sections such as donor admission, screening, discharge, laboratory reagent, patient admission, pathologist, doctor, nursing staff, personal care cost and blood wastage cost. Personal cost is calculated based on current German wage statistics. Direct cost related to non-health care includes materials and administration. In case data available, pertinent information to complications associated during and after blood transfusion were not extracted.

Indirect costs include blood transfusion attributable costs such as premature morbidity (e.g., wages loss due to donation, healthcare and personal care takers). Time is assumed from the literature, and costs are calculated based on current German wage statistic systems (donors´ transportation costs to the blood bank). In this way, we can have a precise idea of German cost estimations. Opportunity costs are calculated based on leisure, and blood donation time.

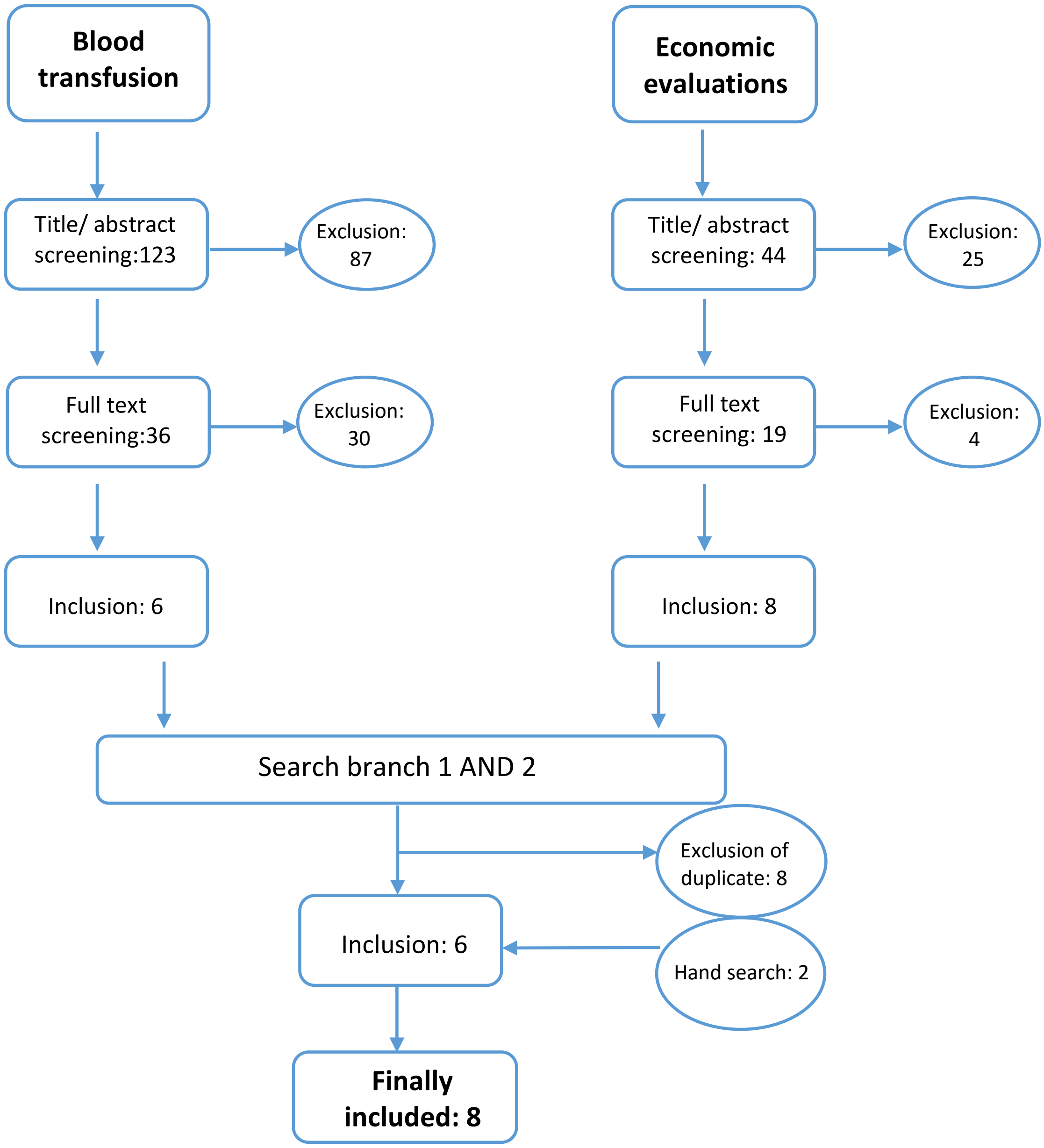
In cases where the costs were presented in currencies other than Euros (EUR, €), they were converted into Euros using the yearly mean exchange rate of local currencies. A cost analysis model was developed using Microsoft Excel 2016 (Microsoft Corporation, Impressa Systems, Santa Rosa, CA, USA). The converted costs were adjusted with the Consumer Price Index (CPI) as reported for each country and each year from the study time period to yield an inflation-adjusted costs in 2016. For this study purpose, CPI was an appropriate method to use because it measures the price changes of goods and services over time within a country. All these reported costs are estimated in mean figures.

Cost finding studies in Germany are also compared with other European countries like "Costs per 1-unit of transfused blood in Germany" with "Costs per 1-unit of transfused blood in all over Western European countries." In this light, some input parameters in the present model are based on simplified assumptions in accordance with the latest literature.

Table 3.1: Systematic literature research

Topics	Blood transfusion	Economic evaluations
Search term (In title OR abstract)	Allogeneic blood transfusion OR RBC transfusion OR Plasma transfusion OR Platelets transfusion OR Therapeutic single plasma	Direct cost OR Indirect cost OR Material cost OR Hospital cost OR Administration cost OR Transfusion complication cost OR Acquiring cost OR Delivering cost OR Administering cost OR Monitoring cost OR Labour cost OR Capital cost OR Benefit cost OR Cost saving OR Opportunity cost OR Economic OR Pharmacoeconomics OR Budget impact OR Efficiency OR Efficient OR Monetary OR Financial

Figure 3.1: Organogram of the methodology about the different search steps.



3.2. Cost and consumption estimation based on secondary data source

3.2.1. Model

A model is designed to identify the parameters which influence the future costs of the transfusion of RBCs, plasma and platelet supplies. Germany´s supply of blood components and RBCs´ production, loss & expiration amount is extrapolated from the data.

Model calculations from the societal perspective were conducted based on secondary data and literature researches. An exemplary 5-year period was selected. Included data has looked forward to the next four years to see future costs and demand of blood components. A cost analysis model is developed using Microsoft Excel 2016 (Microsoft Corporation, Impressa Systems, Santa Rosa, CA, USA).

3.2.2. Model Input

The Paul-Ehrlich Institute, Robert Koch Institute and the Council of Europe websites were searched to collect secondary data. The collection of data was based on German blood transfusion systems. Different data files and reports includes search terms such as "Blood supply in Germany", "Heamovigilance report", "Infektionsdaten" and "blood and blood component in Europe."

The downloaded secondary data was carefully analysed and extracted, based on the requirements of the research question. It has been interpreted for better understanding of blood & its individual product consumption.

3.2.3. Assumptions

The following assumptions were made:

a) There is no difference between the cost of blood units by type and RBC units.
b) Every patient received one unit of RBCs at minimum.
c) Whole blood donations were used for the collection of RBCs. In Germany, the yield of annual RBCs from the annual WBDs was 94.4% in 2013 (PEI, 2017). Estimated losses in WBDs are converted to estimated final losses of RBCs.

3.2.4. Base case

The model calculations for the base case describes the situation of RBCs, platelets, plasma consumption and their loss in the year 2011 in Germany, which was assumed as a starting point to calculate relative consumption and loss in the following year (PEI, 2017).

3.2.5. Model output

Model output is expressed as a total societal cost of blood transfusions and per capita cost. Yearly costs of blood transfusions in the future has been assumed based on regression analysis. The estimated number of the corresponding RBC's lost annually and consumption decay of RBCs, platelets and plasma has been calculated as a percentage. The expected impact of changes in the proportion of blood products in a decade is addressed on the basis of regression analysis (R-squared).

3.3. Expert interview method

Expert interviews was chosen as a semi-structured and responsive method that generates the required information quickly (Berg 2009: p.107-119, 128-149; Rubin 2012: p.95-101). The question of resource use and current practical application can only be resolved with contextual and practical knowledge. An interview with an expert creates an open opportunity to do justice in an explorative manner (Lichtman, 2013). A qualitative interview was conducted to elicit answers of an explanatory nature and to get general a perceptiveness of the research. It provides a more emic, contextualized and inductive approach with a personal involvement (Creswell, 2012: p. 35-41).

Random sampling of all interviewees was done purposely in order to identify enriched informative cases. The expert searches were based on literature findings of particular authors and subsequently a random email was sent to an expert, who has either published a research paper on blood transfusion cost or has a background in the German Red Cross. Thus, he/she had the knowledge regarding the structural procedures and decision making process at higher levels. The interview focused on the wise use of collective resources in the blood transfusion process. Therefore, this specific reasoning is used to refer to the precise contextual knowledge of blood transfusion challenges and highlights the room for improvement in general as a system (Lichtman, 2013: p. 241-246).

3.3.1. Structure of interview

Three stages were followed in the structure of the interview. It was conducted in such a way that each stage consisted of main questions that provided a structure to the interview. Follow-up questions were also often asked to elicit detailed and descriptive answers that led to the research questions (Rubin 2012: p.116-121). To manage the conversation some probe questions were also asked in the interview (keeping interview on target, clarifications, etc.) but have not been deliberately included as a part of the questionnaire (Rubin & Rubin, 2012: p. 117-118).

The three stages are:

- Challenges in current blood transfusion practices
- Shortcomings of whole process of allogeneic blood and/or cost systems
- Possible improvement in current process

The time frame for conducting interviews was approximately two months.

3.3.2. Interview analysis

The purpose of the interview was to analyse the view beyond a single aspect and towards a more general understanding in various aspects. For the summarisation and integration, SWOT analysis was done, which helped to establish an overall logic and integration in respect to the research question. For specific topic suggestions, TOWS matrix was performed to summarise the illustrated derived information.

4. Allogeneic blood transfusion

4.1. Theory and practice of costing allogeneic blood transfusion

In the presence of scarce resources, allocating a budget for transfusion services is a complicated process. The costs of blood transfusions are not easily identified & quantified and are sometimes under-estimated. This can be attributed to the complex nature of the processes and activities that exists throughout the entire blood transfusion chain (Matowa & Ndwabe, 2016).

To estimate the cost of blood transfusions several economic analyses have been conducted worldwide using different analytical aims, perspectives, and methods (Varney & Guest, 2003). Main methodological concerns in all the analyses are useful involving the fact that the transfusion-related costs captured with varying degrees of rigor and the determination of blood donation events, are costly contributors to health care expenditures (Shander, Hofmann, Gombotz, Theusinger, & Spahn, 2007). Several economic models have been updated, modified and developed to devise a comprehensive and standardized method which will improve the existing cost estimations (Fragoulakis et al., 2014).

The Activity Based Cost (ABC) model sums up all the cost of acquiring, delivering, administering and monitoring blood transfusions from the perspective of hospitals & blood banks (Shander et al., 2010). From a societal perspective, cost elements and interdependencies are associated with productivity loss to the donors & patients as well as personal care cost.
According to performed activities, all transfusion operations are combined and summed up in macro-activities. Thus, the model computes an individual process cost and total cost per unit transfused. These macro activities identification includes 4 episodes:

1. Donation (donor admission, donor interview, blood value assessment, blood donation, donor discharge, contribution to donor association)
2. Pre-transfusion process (Administration cost of Centre, Laboratory reagent for processing blood)

3. Transfusion process (Transport cost of blood bank, Patient admission, Compatibility testing, Preparing for transfusion, Transfusion cost)
4. Post transfusion (Post transfusion logistic, Waste management, Transfusion ADR and Complications, Follow up personal cost)

Each macro-activity is divided into different micro-activities that are deemed relevant for a detailed description of each stage of the transfusion process. Micro-activities are identified by the professionals who perform different tasks. All activities are eventually checked, selected and combined whenever necessary or, ruled out from the activity, if it is irrelevant in giving a reliable economic view of the blood transfusion process.

In the first stage of the ABC approach, direct and indirect costs are collected in cost pools and an activity map is presented that is narrowed down to blood units and transfusions. The second stage of the ABC approach is aimed at defining activity cost drivers for the mapped activities. Activity cost drivers is defined as the quantity of activities needed for producing blood transfusions (V. Santini, F. Truschi, A. Bertelli, & C. Lazzaro, 2013). Thus, the activity cost driver rate is determined by dividing the overall cost driven down to each activity by the related cost driver. For health care procedures, cost are traced from the activities by adding the activity cost rate to the quantity of each activity cost that is used for producing blood units and blood transfusions (V. Santini et al., 2013).

The process flow model given below (Table 4.1), captures both direct and indirect cost elements. The left side of the column reflects the direct cost elements of blood collection facilities associated with hospital cost and the societal costs are described in the right panel.

Table 4.1: Activity based traditional cost calculations of blood transfusion process

Direct cost	Blood transfusion process	Indirect cost
• Donor recruitment • Donor interview • Donor screening • Blood donation • Donor discharge	Donation	• Loss of wages due to donations (Visit cost) • Productivity loss of donors • Personal care of donors
• Administration cost of Centres • Laboratory reagent for processing blood	Blood processing	• Quality assessment • Training team cost • Capital cost (Equipment cost, Vehicle, Storage cost, Building cost) • Expired blood destruction cost
• Transport cost of blood bank • Patient admission • Compatibility testing • Preparing for transfusion • Transfusion cost (Medic and para medic cost)	Transfusion	• Personal care worker • Patient productivity loss • Potential Productivity loss of family members
• Post transfusion logistic • Waste management • Transfusion related adverse events • Follow up personal cost	Post Transfusion	• Expired blood destruction • Potential Productivity loss of family members

4.1.1. Direct costs

Direct material cost is the cost of the purchased products which are directly involved in the phase of the donation process (e.g., Donor recruitment, donor Interview, donor screening, blood donation, donor discharge and materials used in administering of blood bank).

For numerous hospital resources, a much larger cost is estimated for product acquisition cost which is necessary to run a transfusion medicine department. It includes the following procedures; to phlebotomise, schedule, concerning reagent, test and prepare patients that are eligible for transfusions, administer blood components to the recipient, monitor the entire transfusion event, treat reactions, document and file all mandatory information.

Some other costs like clerical routines and paperwork, cold-chain logistics, information technology (IT) support, human resource management, accounting, purchasing, risk management, cleaning, waste management, maintenance, training and education, quality management and general administration are also necessary to enable hospital transfusion services (Hofmann, Ozawa, Farrugia, Farmer, & Shander, 2013).

Measures carried out by medical and nursing staff that correlate with time is referred to as personal cost. It is determined by each work step taken at the time. Average personnel costs per minute for doctors and nurses considering the collective agreement for the respective year.

4.1.2. Indirect costs

Indirect cost is known as the loss of earnings associated with blood donations, that is premature mortality and morbidity (e.g., early retirement, work days lost, friction cost) associated with the cost of blood transfusion. By donating blood, absenteeism of the donors took place from their place of work which resulted in loss of productivity and as a consequence their earnings was reduced. The time spent in donating blood during working hours (where no loss of earnings was incurred) represented lost productivity to society. In the UK, it was estimated that blood donors spent 370,417 hours (318 734 - 422 099) off work (Varney & Guest, 2003). From this study sample the mean time was derived to estimate the individual costs of productivity and transport loss.

4.1.3. Other variable costs

Overhead cost: All other costs, including property, equipment, utilities, and personnel from other departments (e.g., hospital administrators, receptionists, and janitors).

Direct overhead costs: Cost that are estimated or added directly from the hospitals finance departments (e.g., pathologist; blood bank, laboratory, nursing staff training & education and license fees for software).

Indirect overhead cost: Administrative and general expenditures (administration and general expenditures included financial administration, telecommunications, information technology, executive offices, purchasing, human resources development), depreciation on buildings & fixed assets, employee benefits, operations of plant, laundry, housekeeping, nursing administration, central services/ supplies, and others were added as a percentage of the process cost.

Opportunity cost: The time spent by the donors and their relatives for donating blood during working hours, days off from work and other relevant expenses.

Intangible cost: Some non-financial losses due to blood transfusion such as inconvenience, discomfort, leisure time.

4.1.4. Adverse reactions and complications costs

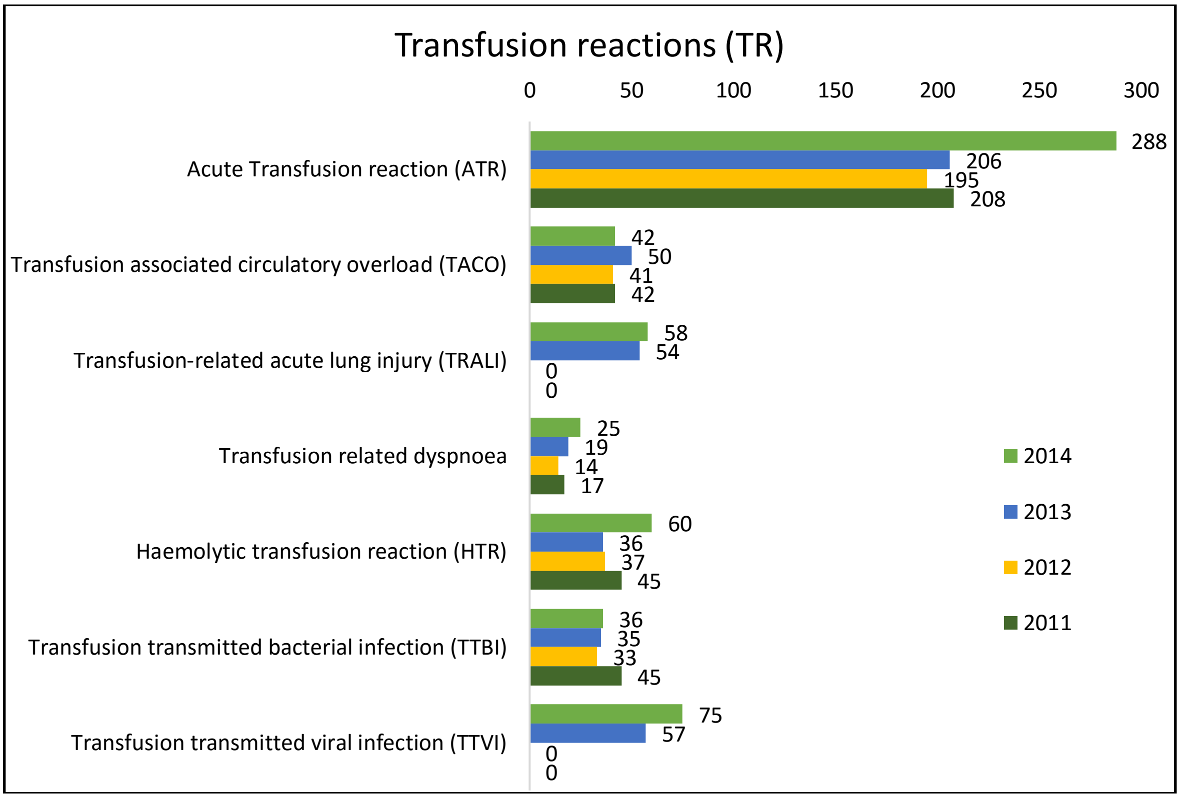
Transfusion related adverse events are costly components. Generally it is regarded as uncontrollable and the costliest contributor to the healthcare expenditures (Blumberg, 1997). Adverse event costs that are associated with the long-term consequences are among the hardest to quantify (Goodnough *et al.*, 1999).

Referring to the period from 2013 to 2014, the most frequently suspected diagnosis was (Figure 4.1) ATR>TACO>HTR>Abo incompatibility>TRALI> TTBI> TTVI and the most common transfusion related death was: ATR=TACO>HTR=AB0 Incompatibility>TRALI=TTBI=TTVI (PEI, 2014).

Table 4.2: List of adverse reactions associated with blood transfusions (CDC, 2017) (European committee on blood transfusion, 2016)

Allergic transfusion reaction (ATR)	Transfusion-associated circulatory overload (TACO)
Acute haemolytic transfusion reaction (AHTR)	Transfusion-related acute lung injury (TRALI)
Delayed haemolytic transfusion reaction (DHTR)	Transfusion-associated dyspnoea (TAD)
Delayed serologic transfusion reaction (DSTR)	Transfusion-associated graft vs. host disease (TAGVHD)
Febrile non-haemolytic transfusion reaction (FNHTR)	Transfusion-transmitted infection (TTI)
Hypotensive transfusion reaction	Post-transfusion purpura (PTP)
Transfusion – HBV	Transfusion – HCV
Transfusion – Bacterial	Transfusion – HIV
Transfusion – Malaria	Transfusion – Other viral
Transfusion Parasitic	Transfusion Other serious

Figure 4.1: Transfusion reactions in Germany – 2011 to 2014 (PEI, 2014)



4.1.5. Latest blood cost development

Collecting and maintaining a blood supply free from potentially infectious viruses and bacteria is enormously costly from a societal and payer perspective (Van Hulst, De Wolf, Staginnus, Ruitenberg, & Postma, 2002). Extensive processing and testing is required for the donated blood to be transfused. Advancement in the protective technologies against existing & emerging blood safety risks, increased donor recruitment & retention costs has contributed in rising of the expenditure for managing a safe and adequate blood supply. Other costs involved include the rising costs of labour, stringent regulatory demands, and the need for compliance with voluntary industry standards (Matowa & Ndwabe, 2016). Shrinkage in blood donor pools due to aging in population, restrictions on blood donor eligibility and operative procedures increasing the demand, recruitment effort needs to be reinforced to replace deferred donors, resulting in increasing incremental cost for each additional unit donated (Jackson, Busch, Stramer, & AuBuchon, 2003)(Vamvakas, 1996).

Germany is covering 100% of infectious agent testing against HIV 1+2, HBsAg, HBc, HCV, Syphilis and NAT testing for HIV and HCV (L.R. van Hoeven, M.P. Janssen, & G. Rautmann, 2013)**.** Therefore, health care providers or government institutions, have to pay the price for allogeneic blood components (Agrawal et al., 2006).

Independent associations between blood transfusions and increased admissions to intensive care units, hospital stays and other adverse events is being shown by the recent systematic review and meta-analysis of randomized controlled trials. All these events increase the hospital costs and we can clearly see from adjusted DRG that there is a high adjusted incremental cost in transfused patients compared to non-transfused patients (Trentino et al., 2015).

Understanding the costs associated with blood products requires comprehensive knowledge about blood transfusions and along with administrative health care sectors worldwide.

4.2. Supply of blood and its products

In spite of recent improvements in blood safety, a finite risk of transfusion-transmitted infections remains, along with risks from new pathogens arising that could infect the blood supply (Ludlam et al., 2006). The production and consumption of red blood cells (RBC), platelets, plasma & its derivatives and other blood components (e.g. hematopoietic stem cells, lymphocyte and blood coagulation factors) are interlinked and sensitive to unidimensional decisions. Changes in the production of one blood component may have consequences for the availability and quality of other components (Berger et al., 2016).

Available data for Germany indicates that total blood donations as well as apheresis blood donations are needed to meet the requirements of a flexible and sufficient supply for all kinds of patients (PEI, 2017). The German Society for Transfusion Medicine and Immune Haematology recommended the provision of both types of platelets to avoid the hazards of critical shortage in the platelet supply, as early as 2011 (dgti, 2011). In this context, extensive elaborations have been published on different aspects of the product supply in Germany, e.g., on the quality of APCs compared to PPCs, on reimbursement, on the advantages of decentralized small apheresis donation units close to the hospital (dgti, 2011).

The revised, restrictive reimbursement practices of the health insurance companies jeopardize the successful use and application of both platelet concentrates in Germany for many years to the detriment of the patients. The German Society for Transfusion Medicine and Immunohematology recommends that both platelet preparations continue to be available (dgti, 2011). A restriction to treatment with only one of the two possible preparations would lead to a critical supply situation. Still the question on the optimal proportion of blood and its products´ production has not been answered in Germany.

5. Results

5.1. Allogeneic blood transfusion costs

The given study identifies a wide range of estimated cost for blood transfusion in Germany. The present analysis done, captures direct, indirect and opportunistic cost of a single unit of blood transfused in Germany and cost of single & double units of blood transfused in Europe. Finally, the total cost of the whole blood transfusion process in terms of government perspectives have also been found.

From the provider's perspective, the mean direct allogeneic blood unit cost (Table 5.1), includes collection, production, and distribution is estimated approximately €272.71. This mean cost does not include indirect and opportunity costs. The mean indirect cost and opportunity cost per unit of blood transfusion (Table 5.2) is estimated at €33.20 and €62.00 respectively. In the hospital transfusion service the mean cost of blood acquisition and processing cost of allogeneic blood unit (direct donors cost, laboratory reagents, patient testing & admission and transportation) is €113.54 and €99,70. The mean non-healthcare cost of a unit of allogeneic blood (material and administration) is almost €22.00.

In 2016, the mean cost per 2-unit of transfused blood in Europe is €888.56 and the societal unit costs of blood transfusion in Europe has risen from €770,49 to €888.56. This indicates that around 16 % of the total cost has been escalated. Hence, it shows transfusion costs in this period have substantially increased all over the western European countries.

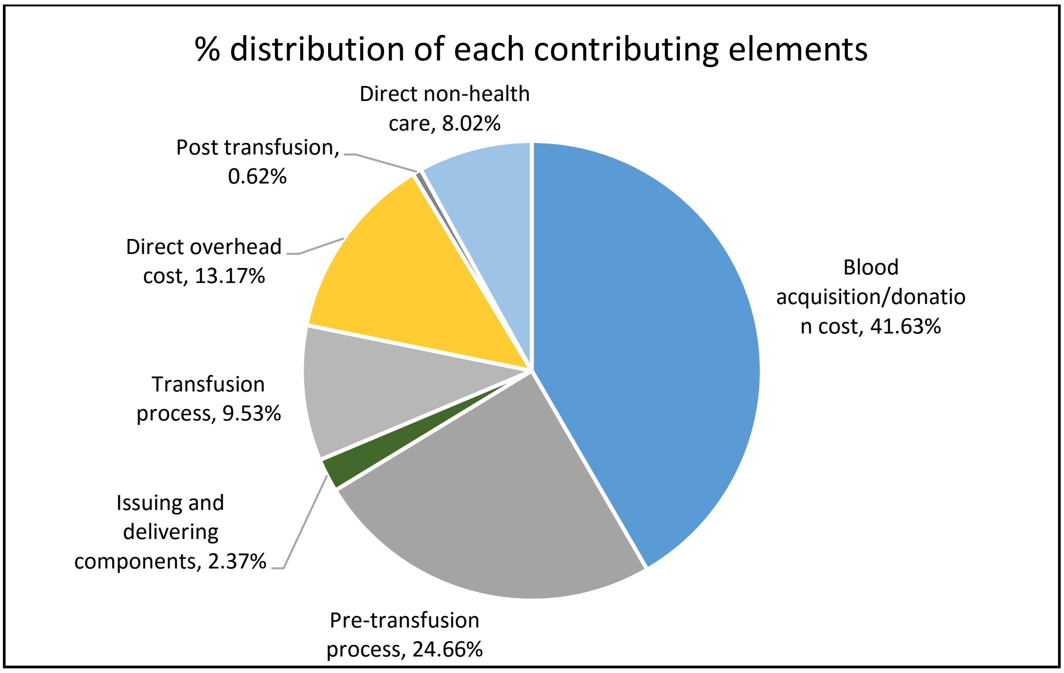
According to total cost perspective, if we assume RBC transfusion as blood transfusion, then total blood transfusion cost (Figure 5.2) was €1.18 billion in 2011, but it decreased to €0.98 billion in 2015. If we analyse the regression analysis of this data, then we can interpret that this is going to be €0.80 billion by 2019. So, this blood transfusion cost per capita represents €13.30 of total direct burden on Germany's economy.

Table 5.1: Direct cost of single allogeneic blood transfusion in Germany

Main activity in ABT	Sub activities	Authors	Country	Year of data	Cost/time provided by the study	Converted EUR*	2016 EUR†	Average cost
Direct Cost								
Direct health Care								
Blood acquisition/donation cost	Blood acquisition cost	Hönemann et al. (2013)	Germany	2011	€97.00	€97.00	€102.00	€113.54
	Donation cost	V.Santini et al. (2014)	Italy	2008	€113.60	€113.60	€125.08	
Pre-transfusion process	Laboratory reagent	Hönemann et al. (2013)	Germany	2011	€7.88	€7.88	€8.29	€6.21
		Shander et al. (2010)	Austria	2007	$7.89	€5.76	€6.66	
		Shander et al. (2010)	Switzerland	2007	$4.96	€3.62	€3.69	
	Patient blood testing process	Shander et al. (2010)	Austria	2007	$10.54	€7.70	€8.90	€35.49
		Shander et al. (2010)	Switzerland	2007	$13.37	€9.77	€9.95	
		V.Santini et al. (2014)	Italy	2008	€88.10	€88.10	€97.00	
		Kleinerüschkamp et al.(2016)	Germany	2013	€25.65	€25.65	€26.09	
	Patient admission	V.Santini et al. (2014)	Italy	2008	€7.70	€7.70	€8.48	€8.48
	Preparing for transfusion	V.Santini et al. (2014)	Italy	2008	€15.50	€15.50	€17.07	€17.07
Issuing and delivering component	Transport cost of blood bank	Hönemann et al. (2013)	Germany	2011	€5.38	€5.38	€5.66	€6.46
		Shander et al. (2010)	Austria	2007	$12.42	€9.09	€10.49	
		Shander et al. (2010)	Switzerland	2007	$4.33	€3.16	€3.22	
Transfusion process	Transfusion process cost	V.Santini et al. (2014)	Italy	2008	€23.60	€23.60	€25.99	€25.99
Direct overhead cost	Laboratory assistance	Hönemann et al. (2013)	Germany	2011	€33.03	€33.03	€36.37	€35.91
	Doctor	Hönemann et al. (2013)	Germany	2011	€28.82	€28.82	€31.08	
	Nurses §	Shander et al. (2010)	AT/CH	2016	116.72 min	€41.86	€41.86	
	Personal cost	Kleinerüschkamp et al.(2016)	Germany	2013	€30.42	€30.42	€30.94	
		V.Fragoulakis et al. (2014)	Greece	2012	€38.84	€38.84	€39.32	
Post transfusion	Post transfusion logistic	Shander et al. (2010)	Austria	2007	$2.82	€2.06	€2.38	€1.69
		Shander et al. (2010)	Switzerland	2007	$2.22	€1.62	€1.65	
	Waste management	Kleinerüschkamp et al.(2016)	Germany	2013	$2.35	€2.35	€2.39	
		V. Santini, 2014	Italy	2008	€0.30	€0.30	€0.33	
							Total Direct healthcare cost:	**€250.84**
Direct non-health Care								
Direct non-health Care	Material of blood bank	Hönemann et al. (2013)	Germany	2011	€4.45	€4.45	€4.90	€4.90
	Administering of transfusions	Shander et al. (2010)	Austria	2007	$33.86	€24.74	€28.61	€16.98
		Shander et al. (2010)	Switzerland	2007	$12.42	€9.08	€9.24	
	Administering & Material	V.Fragoulakis et al. (2014)	Greece	2012	€12.92	€12.92	€13.08	
							Total Direct non-healthcare cost:	**€21.88**
							Total direct cost (Direct health care cost+Direct non-health care cost):	**€272.71**

* Exchange rates source: http://www.oanda.com/currency/historical-rates/. † Consumer price index source: http://www.global-rates.com.
* Cost has calculated based on average income and worked hours (OECD 2016 data): https://data.oecd.org/germany.htm
§ Nurses wages sources: http://www.steuerklassen.com/gehalt/krankenschwester/

Figure 5.1: % cost distribution of each contributing elements



As per this study, the mean blood donation cost is around 42.00% of the total direct cost which is the highest in contributing elements. This includes blood donor´s recruitment, interview, screening, blood donation and discharge. The second leading element is the pre-transfusion process, which expresses 25.00% of the total cost. Direct non-healthcare cost accounts 8.00% in total. Direct overhead cost, transfusion process, transport and post transfusion cost are 13.17%, 9.53%, 2.37% and 0.62% respectively.

Figure 5.2: Total blood transfusion costs in Germany

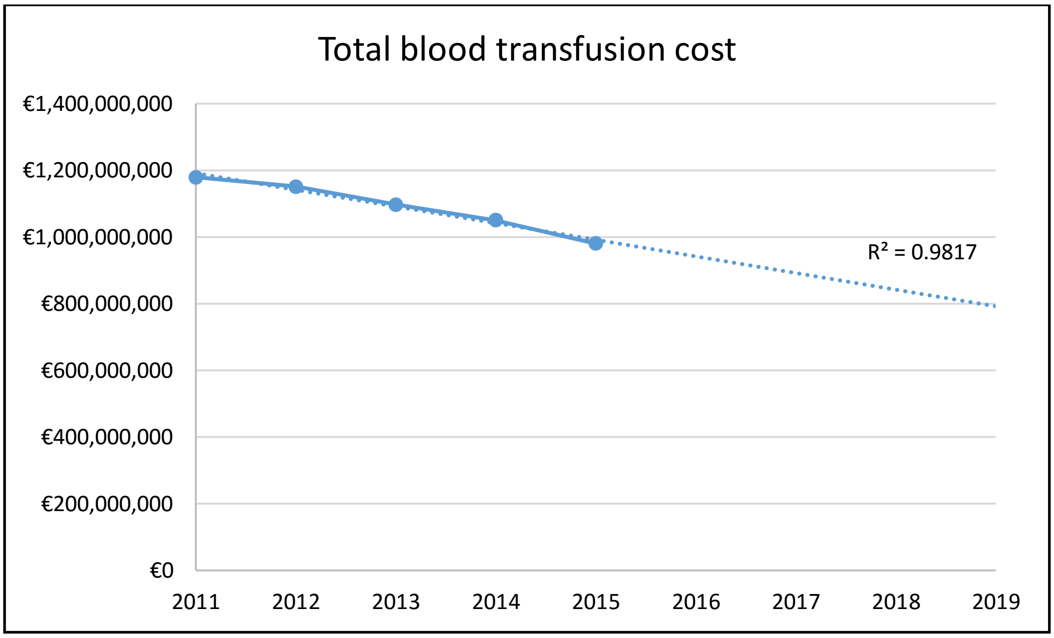


Table 5.2: Indirect and opportunity cost based on current German wage statistics

Activity	Assumption and sources	Country	Year of data	Cost/time provided by the study	Converted EUR*	2016 EUR†	Average cost
Indirect cost							
Loss wages due to donation (only 14% donor´s wages loss)°	Loss on wages and time due to donation assumed from Varney & Guest (2003). Wages are calculated based on OECD average German income and working hours.	UK	2001	7.73 min	€3.81	€3.81	€6.67
	V.Fragoulakis et al. (2014)	Greece	2012	€9.27	€9.27	€9.52	
Personal care taker (family) & Productivity loss of relatives ^	Care taker time assumed from Shander et al. (2010). Care taker costs are calculated based on average German Pflegepersonal.	AT/CH	2007	20.75 min	€4.67	€4.67	€3.53
	V.Fragoulakis et al. (2014)	Greece	2012	€2.33	€2.33	€2.39	
Donors´ transportation cost to blood bank	V.Fragoulakis et al. (2014)	Greece	2012	€2.15	€2.15	€2.21	€2.21
Day off with compensation	V.Fragoulakis et al. (2014)	Greece	2012	€20.26	€20.26	€20.80	€20.80
						Total indirect cost:	**€33.21**
Opportunity cost							
Used leisure time°	Leisure time loss due to donation assumed from Varney & Guest (2003). Wages costs are calculated based on OECD average German income and working hours.	UK	2001	75.6 min	€37.23	€37.23	€37.23
Blood donation time°	Blood donation time assumed from Varney & Guest (2003). Wages are calculated based on OECD average German income and working hours.	UK	2001	50.3 min	€24.77	€24.77	€24.77
						Total opportunity cost:	**€62.00**

* Exchange rates source: http://www.oanda.com/currency/historical-rates/. † Consumer price index source: http://www.global-rates.com.
^ Personal care worker: https://www.gehalt.de/beruf/allgemeines-pflegepersonal. ° Cost has calculated based on average income and worked hours (OECD 2016 data): https://data.oecd.org/germany.htm

Table 5.3: Costs per two and one unit of transfused blood in Europe according to the studies

Authors	Country	Year of data	Cost provided by the study	Converted EUR*	2016 EUR†	Population in 2016‡	Coefficient	Weighted Cost
Costs per 2- blood unit In Europe according to the studies								
Glenngard et al (2005)	Sweden	2003	€702.00	€702.00	€805.61	9,851,017	0.031	€24.97
Shander et al (2010)	Switzerland	2007	$1,222.88	€893.68	€909.89	7,866,500	0.025	€22.52
Shander et al (2010)	Austria	2007	$1,044.90	€763.61	€882.77	8,700,471	0.027	€24.17
Bellinghen et al (2003)	France	2002	€792.00	€792.00	€955.48	66,661,621	0.210	€200.40
Bellinghen et al (2003)	Austria	2002	€722.00	€722.00	€938.87	8,700,471	0.027	€25.70
Agrawal et al (2006)	UK	2004	£546.12	€804.86	€1,059.33	62,435,709	0.196	€208.10
V. Santini et al. (2008)	Italy	2008	€964.20	€964.20	€1,061.65	60,665,551	0.191	€202.64
V.Fragoulakis et al. (2014)	Greece	2012	€699.06	€699.06	€707.74	10,783,748	0.034	€24.01
Jörg et al. (2013)	Germany	2011	€593.00	€593.00	€603.62	82,162,000	0.259	€156.04
Total						**317,827,088**	**1.000**	**€888.56**
Costs per 1- blood unit In Europe according to the studies								
Shander et al. (2010)	Switzerland	2007	$193.70	€141.56	€144.12	7,866,500	0.031	€4.49
Shander et al. (2010)	Austria	2007	$153.72	€112.34	€129.87	8,700,471	0.034	€4.48
V. Santini et al. (2014)	Italy	2008	€346.90	€346.90	€381.96	60,665,551	0.240	€91.83
V.Fragoulakis et al. (2014)	Greece	2012	€165.49	€165.49	€167.54	10,783,748	0.043	€7.16
Hönemann et al. (2013)	Germany	2011	€176.00	€176.00	€185.07	82,162,000	0.326	€60.26
Jörg et al. (2013)	Germany	2013	€320.00	€320.00	€325.73	82,162,000	0.326	€106.06
Total						**252,340,270**	**1.000**	**€274.27**

* Exchange rates source: http://www.oanda.com/currency/historical-rates/ , † CPI source: http://www.global-rates.com/
‡ Population source: http://epp.eurostat.ec.europa.eu/tgm/table.do?tab=table&language=en&pcode=tps00001&tableSelection=1&footnotes=yes&labeling=labels&plugin=1

5.2. Insights into the management of ABT

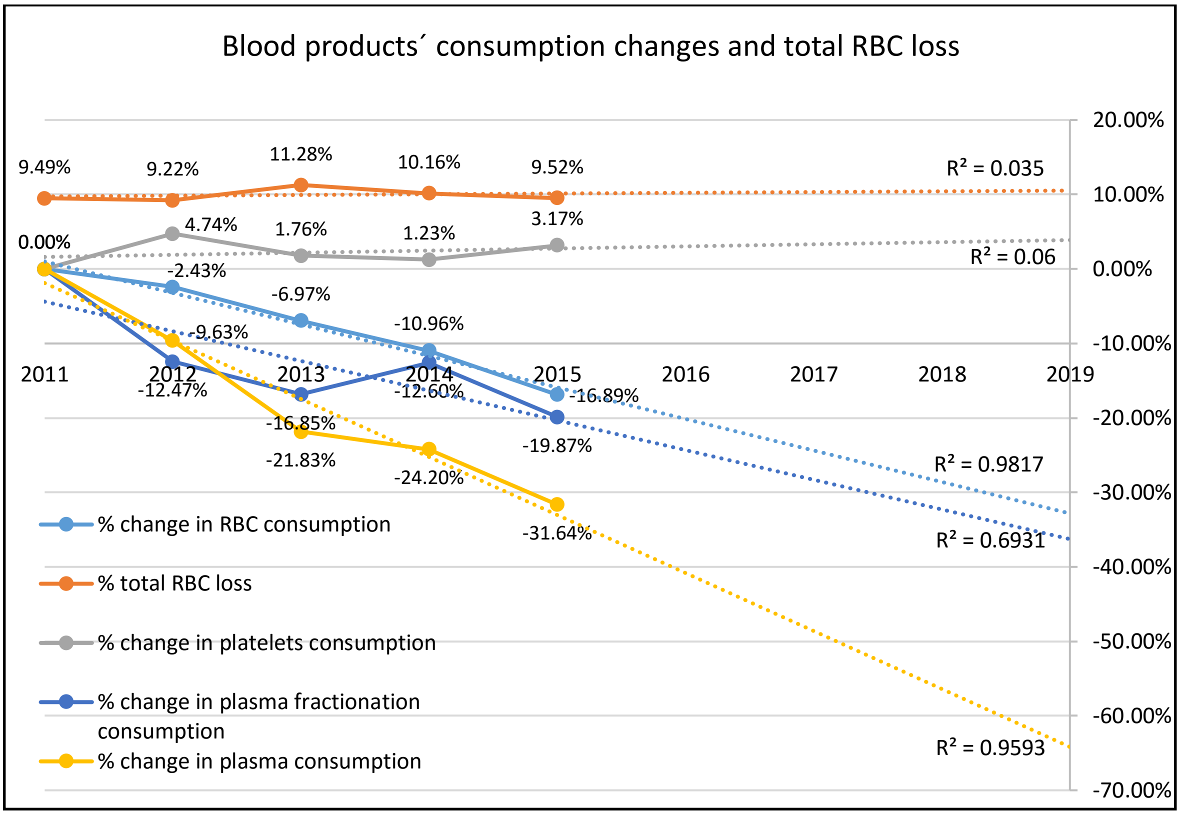
Blood management has been defined as the appropriate use of blood and blood components with a goal of minimising their use. In Germany, WBDs decreased by 6.0% from 2011 to 2013 and by 9.9% from 2013 to 2015. Simultaneously, the number of WBDs per 1,000 inhabitants has decreased from 61 to 50 from 2011 to 2015, whereas the number of apheresis donations per 1,000 inhabitants has increased from 33 to 34 from 2011 to 2015.

A concomitant reduction in the consumption of RBCs was seen (Figure 5.3) in recent years that is 2.43% from 2011 to 2012, 4.54% from 2012 to 2013 and 5.93% from 2014 to 2015, apparently due to the more restrictive use of blood products and the introduction of the patient blood management concept. Thus, it shows that it can gradually decrease up to 35% until 2019. Total RBC loss is still constant from 2011 to 2015, which is around 10.00%

In plasma consumption, we can see a sharp regression (Figure 5.3). It shows approximately 32.00% plasma and a 20.00% plasma fractionation plunge, from 2011. It can further fall by up to 65% to 70% by 2019.

Platelet consumption expresses constant use in current medical practice. The need for platelet use is closely associated with the treatment of haematological disorders of which its utilisation increases with increasing age, that is around 3.0% to 4.0%. In view of the demographic development, additional platelet concentrates will be required in the near future.

Figure 5.3: Blood product consumption changes and total RBC loss



5.2.1. SWOT Analysis of Expert Interview

As per previous sections, it has been shown that Germany´s blood transfusion cost and services is endowed with growth opportunities and at the same time also beset with some strong challenges. The country excels in technological innovations and is Europe´s largest market in the blood services sector and one of a leading consumer of blood and its products.

Germany´s transfusion services have many advantages compared to other countries such as free blood donations, patient blood management, a strong hospital network and qualified expert in the field. This can help in many ways to overcome the difficulties in current blood transfusion procedures.

Blood transfusion processes are associated with various threats in current practices, which begin with unintentional transfusion to ended up on worst outcomes. These are because of lack of proper regulations, education & knowledge transferred in medical routine, blood demand of donors & hospitals and price pressure on blood supplier.

This is an indicator for the need of implementing frugal innovations that can provide an affordable excellence and provide blood and its products that fit this criterion. An opportunity lies in meeting the challenge of catering to new trends with affordable prices. Those opportunities include political interventions, improvement in the quality of transfusion process and shift towards a blood transfusion alternatives.

The proper handling of blood transfusion processes and implementation of guidelines can convey quality treatment in patients, reduction in cost of treatment and decrease in mortality and morbidity. The following TOWS Matrix (Table 5.4) shows thematically structured interview results.

Table 5.4: TOWS Matrix of experts´ Interview better

	WEAKNESSES 1. To convince people for blood transfusion 2. Lack of education and knowledge transfer in medical routine 3. Lack of proper regulations (e.g. transfusion in anaemic patients) 4. To meet the specific blood demand of donors and hospitals for supplier 5. Pressure on blood supplier to reduce price on blood unit which affects the quality	**STRENGTHS** 1. A very strong hospital network 2. Voluntary/Free blood donations all over the country 3. Qualified expert in the field 4. Patient blood management has started and expanding rapidly
OPPORTUNITIES 1. Political interventions 2. Boost the alternative treatment of transfusion 3. Ground level process improvement (e.g. on supply, primary treatment) 4. Improve blood product quality by new methods and technology	Weakness - Opportunities strategy • New/Change amendment or law for better handling (W3, O1) • Quality treatment for patient (W2, W4, W5, O2, O4) • Reduction in blood transfusion cost (W2, W3, O3, O4)	Strength - Opportunities strategy • Better treatment for patients (S3, O2) • Ultimate decrease in cost of treatment (S2, O2, O3)
THREATS 1. Blood transfusion´s adverse reactions and complications 2. Worst outcome of treatment 3. Unintentional transfusion in patients	Weakness - Threats strategy • Avoid surgical transfusion (W2, W3, T3)	Strength - Threats strategy • Decrease in morbidity and mortality (S1, S4, T1, T2) • Improved use of resource (S3, S4, T3)

6. Discussion

In various European countries, differences in utilisation rates for blood components are not correlated, but substantial differences are commonly seen in either clinical care or mortality rates. Higher usage of blood components in Europe does not necessarily interpret higher quality supportive care compared to other developed countries. That is why the system is changing and many experts are shifting themselves from conventional transfusion to bloodless medicine (Seifried & Mueller, 2011).

For different diseases blood is a determined source which competes with everything that comes in its way. Blood transfusion activity based cost model is robust which provides the most appropriate estimates of the cost for developing a comprehensive model to determine the current economic realities. It facilitates the research in enhancing the blood usage and controls expenditures so that resources may be channelled towards other diagnostic, therapeutic and technological initiatives. The model can also be adapted by the institutions to increase institutional efficiency and to reduce costs with quality care at each point.

The study results provide important insights into the actual costs of transfusion. The results of activity based single unit cost (€272.71) is somewhat the same with literature study finding (€274.27). Product acquisition costs contribute around 42% transfusion related expenditure. Whereas, blood acquisition costs in Shander et al. study were 21% to 32% (Shander et al., 2010). Thus, the cost of blood transfusion should be considered according to specific countries and regions.

The findings of this study represent an update of previous estimates, as well as an improvement in methods used for the determination of the cost of blood transfusion in Germany. Activity based cost analysis have shown that allogeneic blood transfusions are costlier than previously estimated. It will facilitate decision making about the cost-effectiveness of interventions to replace blood usage by providing an appropriate benchmark for comparing cost relation to clinical benefits. When analysing cost-effectiveness of therapies like ESAs, lenalidomide, hypomethylating agents and diseases such as MDS, chronic transfusion dependence etc. this study proves to be helpful for the specific evaluation of diseases and therapies in health economics (V. Santini et al., 2013).

It can provide an estimate of program costs and its benefits before its implementation. Cost analysis can improve understanding of program operations and explains which levels of intervention are most cost-effective. Other benefits include unexpected cost analysis, fiscal accountability in programs, helps to set priorities when resources are limited.

Qualitative studies show that the present resource allocation is diversified, which has more potential to improve in a reasonable fashion. From qualitative studies, it can be signified that the comprehensive resource in practical analysis shall be achieved. It will provide a better overall understanding of the system, challenges, coordination and increased reflection on specific uses of the resources and its applicability in future strategic development.

For transplantation of blood, allogeneic blood transfusion holds great importance, but at the same time it can have a negative impact. It can be harmful for the recipients because of the infusion of foreign antigens in greater quantities in their blood circulation, resulting in multiple inflammatory and immunological reactions (Flohé, Kobbe, & Nast-Kolb, 2007). The treatment for these events is assumed to be a costly factor, for example, its impact on in-patient length of stay or extra nursing time. A precise estimation in these events is very demanding because of regional variations and differences in transfusion sites depending on medical speciality (Rottenkolber et al., 2012).

6.1. Alternatives for blood transfusion

Novel pathogen reduction methods and algorithms need to be evaluated, validated and implemented in daily routines for blood donor screening. Specific cellular products, gene therapy and immunotherapy are innovative aspects, which will help in bringing regenerative medicine and cellular therapy to blossom. Stem cell therapies in acute myocardial infarction and chronic heart failure are just two examples of the extraordinary developments and is currently underway in this field (Assmus et al., 2006) (Schächinger et al., 2006). Thromboelastometry-based restrictive transfusion management helped in avoiding unnecessary plasma and platelet transfusion. It facilitated the reduction in the incidence of transfusion-related adverse events and transfusion-associated hospital costs (Görlinger & Saner, 2015).

There are other numerous therapeutic alternatives to allogeneic blood transfusion that have proven to be effective in the circumstances like treating anaemia and thrombocytopenia for example, suspending anticoagulants & antiplatelet agents, reducing routine phlebotomies, utilizing less traumatic surgical techniques, use of topical and systemic haemostatic agents, acute normovolemic hemodilution, anaemia tolerance (supplemental oxygen and normothermia), operative blood recovery (dos Santos et al., 2014).

With evidence of elevation in the erythrocyte´s mass & coagulation status, reducing blood loss and improving anaemia tolerance, there are multiple clinical and surgical strategies to cope with these conditions.

There are three different types of blood transfusion alternatives in surgery, that includes the pre-operative, intra-operative and post-operative period. In the preoperative period, erythropoietin and autologous blood donation is done from haematopoietic stem cells. Intraoperatively, acute normovolemic hemodilution, cell salvage and re-transfusion, pharmacologic haemorrhage reduction with antifibrinolytics, surgical technique, acceptance of minimal haemoglobin concentrations, future use of artificial oxygen carriers. Postoperatively, cell salvage and re-transfusion, acceptance of minimal haemoglobin concentrations, pharmacological haemorrhage reduction with antifibrinolytics (Madjdpour, Heindl, & Spahn, 2006). Transfusion alternatives should be incorporated into medical practice to reduce hospital cost, decrease the consumption of blood components, and diminish morbidity and mortality.

6.2. Future challenges in blood transfusion process

Policies supporting restrictive use of allogeneic blood transfusion led to less advertising and mobilising of healthy volunteer blood donors. This resulted in a dramatic drop in blood donations and gradual decrease in the production of blood products which jeopardizes the blood supply of a country.

Expected demographic changes by an aging population will potentially decrease the number of donors. With the rise of cancer cases, demand for blood products, especially platelets consumption will be increased. The shrinking process in the donor population has been accelerated, in particular since 2015 (Ehling & Pötzsch, 2010)(PEI, 2017). This process should be encouraged in a comprehensive way that adequate use of scarce cellular blood components is made to elude current shortages of blood donations. Donor motivation and its development will be essential in the upcoming years.

In Germany, blood components are considered as a pharmaceutical drug, so it is not easy to find evidence based recommendations regarding transfusion triggers or adequate support strategies for blood components in chronically transfused patients (Seifried & Mueller, 2011).

New blood substitutes as well as growth factors such as erythropoietin, thrombopoietin or granulocyte colony-stimulating factor provide some examples of more problematic situations. Additionally, harvesting and storing of haematopoietic stem cells and other alternatives is expensive and their clinical application is not common in Germany. 'Zero risk' in cellular, gene and haemotherapy is not possible, however, society should strive for it and this must be funded for further development in the future.

6.3. Limitations

6.3.1. Limitations of literature review method

As per literature findings in allogeneic blood transfusion, several cost components were estimated with an acceptable level of accuracy, but quality assessment has not been conducted.

It must also be noted that the cost of a blood transfusion unit estimated from other countries might be irrelevant to Germany, because of the relative prices, and the perception of analysis differs between countries and their economic models.

Not all types of costs were taken into consideration connected with transfusion services (I.C.U., hospital stay, complications in transfusion) because of their inaccuracy. Thus, the final cost might be significantly higher compared to the present estimated cost.

Average procurement prices for blood transfusion is highly variable between hospitals, which represent the second highest percent (25%) of cost in our findings.

For pre-transfusion activities and transfusion administration, additional laboratory and material expenses may differ from the findings, which can be 3–5 times higher than the present cost (Rottenkolber et al., 2012). For example, storage, blood typing, antibody screening test, cross-matching, transfusion reactions, follow-up tracking, blood count and coagulation profile (Cantor, Hudson, Lichtiger, & Rubenstein, 1998).

The amount of time spent by the donors donating blood has been assumed in monetary terms as general. Productivity losses have been calculated in a way consistent with other economic studies. It can also be discussed that donor might not suffer lost productivity and leisure time in donating blood because absenteeism from their work would be compensated by the other individuals present at the work, simultaneously performing both the task of themselves as well as of the donor.

Generally, all wages were evaluated by desktop research and may differ from current prices because of market fluctuations.

6.3.2. Limitations of the model

An economic analysis is, by necessity, a simplification, which tries to emulate the process from a technical point of view. It is necessary to make assumptions when constructing the study or model. This model´s assumptions are based on the scarce published data due to the lack of comprehensive evidence. Consequently, the following limitations arise which should be taken into consideration when interpreting the presented results:

In similar method studies, a common concern is that the estimation of blood cost is based only on red blood cells consumption, without taking into consideration other blood products (e.g. fresh frozen plasma, platelets). So, a comprehensive model should also include data on platelets, plasma & its derivatives, hematopoietic stem cells as well as lymphocytes as these plays a vital role in allogeneic transfusion processes.

Reasons for discontinued donations as well as loss of whole blood are unknown but still we consider it as a total loss in RBCs´ production.

6.3.3. Limitations of the Interview method

More rich, vivid and extensive information could be generated by the involvement of more participants for the expert interviews, who cover diverse backgrounds from different perspectives like authors of other published studies from Germany & Europe as well as experts in practice fields (haematologist, private physicians).

The study covers only telephonic interview, resulting in a reduction of social cues. For this telephonic conversation, only limited questions have been designed and asked within a given time period, which may deny or misunderstand the factual information.

7. Conclusion and Outlook

In Germany and across Europe, the safety and quality of blood and its products supply, as per the devised guidelines is very good and is getting even better than in earlier years. Despite elaborate processes in advanced technology and its practical applicability, scientific assistance is still required.

In health care, reliance on blood transfusion causes a remarkable economic burden on patients, society and health systems. In every setting, economic and resource analysis have the potential to be supportive tool for blood management. Thus, to investigate, it is of interest how to facilitate the successful transfer of the tools from a scientific sphere to a common analysis in blood management, which may help to change the economic perception of blood transfusions.

The outcome of the study can help in better understanding of resources used which might inform us in various aspects. A proper and planned blood transfusion management can bring an ample amount of economic benefits to payers and hospitals who must be aware of their expenses to the health care system. For payers, it could help in various aspects like lowering cost through less administration of allogeneic blood products, accurate diagnosis & treatment, increased efficiency through optimized care, reduced hospital visits or length of stay and lesser re-treatments through blood management. Noticeably, none of the costs are more valuable than the patient. They are embedded in an organized treatment process, which saves them from the trouble of looking for the appropriate specialist themselves, costly double & multiple examinations as well as unnecessary stress for the patients is avoided and sick time in hospitals is reduced.

Successful blood management results in lower probability of allogeneic blood transfusion. Consequently, lower cost is associated with the treatment of transfusion related to adverse events and infections, potential cost-savings for hospitals and the healthcare system compared to standard treatment practices (decrease or reduction in morbidity, hospital stay, ICU stay, operating room stay, ventilation, complication rates, multi-organ failure and the corresponding resource consumption).

It must be stressed that the cost of producing a unit of blood is not insignificant. Cost of transfusion needs to be complemented with the figures to have a complete picture of producing and using one and two unit of blood locally. Research on blood services like other health system services needs to take initiative to improve the effectiveness of their operations and to contribute evidence for refining their policies nationally and internationally. Scientific evidence about blood services needs to be developed and the research capacity should be generated that will aptly inform indigenous policies and practices in transfusion medicine. This cannot be achieved unless there is a broad framework available for German blood services.

In their blood services, further elevation of research capacity would allow extensive work in various research prioritized areas that can be accurately pursued. Activity based costing studies for other allogeneic blood components should be conducted such as costing of the short, mid and long term adverse outcomes of transfusion and meaningful secondary end points for such cost-effectiveness studies. The frugal and cost effective solutions are also needed on the side of blood supply. Eventually, the chosen research design and methods can be drawn-out further to improve the results with more detailed analysis.

At the end, attaining the euro figures for per-unit cost of blood was a lengthy and complex task and the financial implications of this study are still considerable. To improve patient outcomes with the imperative of working within tight financial parameters, hospital executives must engage clinicians to be responsible for both clinical and financial outcomes. Findings of this study demonstrates best practice of allogeneic blood management that appears strongly aligned to cost savings and quality treatment, which may further assist the decision makers like legislators, policy makers, and other healthcare professionals.

Recommendations for blood transfusion

To overcome the transfusion associated multiple disadvantages (limited availability, high cost, multiple side effects), transfusion guidelines and alternatives should be available. It is recommended that hospitals should make an effort to build up their own transfusion committees. Hence, the first step should be the baseline evaluation of current blood use, patient outcomes as well as the costs by transfusion committee. Afterwards, hospitals should compare their data against external benchmarks to determine their performance level. The same committee should consist of multidisciplinary medical staff to develop guidelines for transfusions and ensure that they are followed. Secondly, this transfusion committee should develop working groups in specialties where maximum blood is consumed such as cardiac surgery, orthopaedic surgery, critical care, trauma, gynaecology and oncology. So, by following these steps, the transfusions in the hospitals will be under control and patients and hospitals will get more benefits than before.

Interview by the experts emphasized upon the multiple therapeutic options to reduce the number of transfused patients and to manage accurately the amount of blood and its components administered to each patient. If needed then it should be fundamental to change the transfusional attitude, especially in relation to anaemia tolerance or tranexamic acid to adults and children undergoing surgery, intra-operative cell salvage with tranexamic acid. Some of the methods are simple & safe and can easily be implemented. Iron supplement in anaemia and electronically identifying patients to improve the safety and efficiency of the blood transfusion process and should be carefully orchestrated.

Patient blood management (PBM) with reduced cost should be achieved leading to better outcomes. The concept of patient blood management with its three pillars (optimise patients cell, minimise blood loss, harness & optimise physiological tolerance) has been adopted by the World Health Assembly's 63rd session (WHA) and public authorities are urged to support the establishing of PBM as a new standard of care ('World Health Organisation', 2016). At the end, activity based costing studies for single PBM modalities should be conducted and cost-effectiveness studies looking at QALY gained or DALY averted through single PBM modalities should be designed and conducted. Clinicians, hospital administrators and authorities can significantly benefit from PBM and need to be informed accordingly.

Training courses for nurses, technicians and physicians should be conducted to upgrade skills concerning transfusion indications, transfusion triggers, handling of blood components, liberal and restrictive transfusion regimes, storage and transportation.

There must be a strategic plan to overcome the difficulties caused by limited resources, which should be based on the efficient provision of a safe and sustainable supply of blood & its components and these services that should meet all safety, quality, and compliance standards. The primary focus should be to modernise each stage of the blood supply chain from the collection of blood to the processing and testing of it in a centralized environment and its issue and delivery to hospitals. Both internal and external audits, should be done to ensure adherence to standard operating procedures and haemotherapy guidelines.

Development and production of novel cellular therapeutics are promising and challenging tasks for modern transfusion medicine. Therefore, governments should be willing to fund and support attempts to achieve it.

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Glossary

- **Allogeneic donation:** Blood and blood components collected from an individual and intended for transfusion to another individual, for use in medical devices or as starting material/raw material for manufacturing into medicinal products.
- **Annual cost:** The cost of an intervention, calculated on a yearly basis, including all the annually payable capital costs as well as the yearly recurrent costs.
- **Annualized costs:** The annual share of the initial cost of capital equipment or investments, spread over the life of the project usually modified to take account of depreciation.
- **Apheresis:** A method of obtaining one or more blood components by machine processing of whole blood in which the residual components of the blood are returned to the donor during or at the end of the process.
- **Autologous donation:** Blood and blood components collected from an individual and intended solely for subsequent autologous transfusion or other human application to that same individual.
- **Cost benefit analysis:** an economic evaluation technique in which outcomes are expressed in monetary terms.
- **Cost utility analysis:** Economic evaluations where the outcomes are measured in health units which capture not just the quantitative but also the qualitative aspects of the outcome, such as quality of life.
- **Cost-effectiveness analysis:** Economic evaluation with outcomes measured in health units.
- **Cost:** The value of resources usually expressed in monetary terms.
- **Direct cost:** Resources used in the design, implementation, receipt and continuation of a healthcare intervention.
- **Economic evaluation:** The systematic assessment and interpretation of the value of a healthcare intervention. It is done by systematically examining the relationship between their costs and outcomes.
- **Financial (budgetary) cost:** The accounting cost of a good or service usually representing the original (historical) amount paid distinct from the opportunity cost.

- **Indirect cost:** The value of resources expended by patients and their carers to enable individuals to receive an intervention.
- **Intangible cost:** The costs of discomfort, pain, anxiety or inconvenience.
- **Outcomes:** Change in status as a result of the system processes (in the health services context, the change in health status as a result of care).
- **Overhead cost:** Costs that are not incurred directly from providing patient care but are necessary to support the organization overall (e.g. personnel functions).
- **Plasma, fresh-frozen:** The supernatant plasma separated from a whole blood donation or plasma collected by apheresis, frozen and stored.
- **Plasma:** The liquid portion of the blood in which the cells are suspended. Plasma may be separated from the cellular portion of a whole blood collection for therapeutic use as fresh-frozen plasma or further processed to cryo- precipitate and cryoprecipitate-depleted plasma for transfusion. It may be used for the manufacture of medicinal products derived from human blood and human plasma or used in the preparation of pooled platelets, or pooled, leucocyte-depleted platelets. It may also be used for re-suspension of red cell preparations for exchange transfusion or perinatal transfusion.
- **Platelets, apheresis:** A concentrated suspension of blood platelets obtained by apheresis.
- **Recurrent cost:** The value of recurrent resources with useful lives of less than one year that have to be purchased at least once a year.
- **Total (economic) cost:** The sum of all the costs of an intervention or health problem.
- **Whole blood:** A single blood donation.