

**Methods for assessing the costs of
transfusion management strategies in
cardiac surgery**

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Publications and presentations related to this thesis

Publications

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Presentations

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Abstract

Methods for assessing the costs of transfusion management strategies in cardiac surgery

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A blood transfusion is one of the most common hospital procedures, yet there is a lack of reliable information on the costs of administering blood. This thesis aims to fill this information gap, and considers the impact on total costs of alternative transfusion management strategies in the National Health Service (NHS) in the United Kingdom. A high user of blood transfusion, cardiac surgery, acts as a clinical exemplar.

Comprehensive estimates of the costs of administering blood are first produced. The costs of administering blood add substantially to the costs of the blood products themselves, costs for red blood cells are 40% higher when the costs of administration are added to red blood cell costs.

These cost estimates were used to more accurately cost blood products transfused (compared to the costs of blood products only) in two economic evaluations assessing firstly, the cost-effectiveness of a restrictive versus a liberal red blood cell transfusion threshold after cardiac surgery, and secondly, the cost-effectiveness of introducing bedside tests of haemostatic function in cardiac surgery. Both economic evaluations showed little difference in costs or outcomes between the groups and uncertainty around the cost-effectiveness results. While a restrictive threshold reduces costs associated with transfusion compared to a liberal threshold, there is no evidence based on detailed and comprehensive costings, to suggest that a restrictive threshold saves the NHS money overall.

Reliable resource use data are vital for economic evaluations, and a subgroup of patients in both economic evaluations enabled resource use data collected from alternative sources to be compared. There was strong agreement between primary (clinical trial) data and routine datasets for data available from both sources, however, primary data captured post-operative complications more comprehensively than routine datasets.

This thesis provides hospital managers and health economists with accurate information on the costs of administering blood for budget impact assessments and economic evaluations.

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List of abbreviations

A&E	Accident and emergency
AKI	Acute kidney injury
ARDS	Acute respiratory distress syndrome
BHI	Bristol Heart Institute
BMS	Biomedical scientist
BNF	British National Formulary
CABG	Coronary artery bypass grafting
CADTH	Canadian Agency for Drugs and Technologies in Health
CBA	Cost-benefit analysis
CCB	Clinical concern about bleeding
CCC	Concordance correlation coefficient
CEA	Cost-effectiveness analysis
CEAC(s)	Cost-effectiveness acceptability curve(s)
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CICU	Cardiac intensive care unit
CPB	Cardiopulmonary bypass
CMA	Cost-minimisation analysis
CRFs	Case report forms
CT	Computerised tomography
CUA	Cost-utility analysis
DCE	Discrete choice experiment
ED	Emergency department
eMIT	Electronic marketing information tool
EQ-5D	EuroQoL five dimensions questionnaire
FFP	Fresh frozen plasma
GLM	Generalised linear model
GP	General Practitioner
Hb	Haemoglobin
HCHS	Hospital and community health services (inflation index)
HDU	High dependency unit
HES	Hospital Episode Statistics
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Information technology
IV	Intravenous
LOS	Length of stay
LY(s)	Life-year(s)
MAE	Mean absolute error
MeSH	Medical Subject Headings

MI	Myocardial infarction
MRI	Magnetic resonance imaging
MSE	Mean squared error
NACSA	National Adult Cardiac Surgery Audit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NHS	National Health Service
NHSBT	NHS Blood and Transplant
NSTS	NHS Strategic Tracing Service
OLS	Ordinary least squares
OUH	Oxford University Hospitals
PATS	Patient analysis and tracking system
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Patient blood management
POC	Point-of-care
PSA	Probabilistic sensitivity analysis
QALY(s)	Quality-adjusted life-year(s)
rFVIIa	Recombinant activated factor VII
RBC	Red blood cell
RCT	Randomised controlled trial
ROC	Receiver operating characteristic
SATO	Senior Assistant Technical Officer
SD	Standard deviation
SE	Standard error
SHOT	Serious hazards of transfusion haemovigilance scheme
TOPPS	'Trial of prophylactic versus no prophylactic platelet transfusions'
UK	United Kingdom
US	United States (of America)
WHO	World Health Organization
WTE	Whole-time equivalent

Chapter 1: Introduction

The overall aim of this thesis is to provide reliable and comprehensive estimates of the costs to the National Health Service (NHS) of administering blood in the United Kingdom (UK). Then, to illustrate the usefulness of these estimates in applied economic evaluations involving transfusion, the cost-effectiveness of two transfusion management strategies in cardiac surgery is assessed. Before giving specific details of the thesis aims, objectives and structure, I provide a short introduction to the history and current practice of blood transfusion.

1.1 Blood transfusion

“The history of blood transfusion is marked by numerous bright pages but also some dark moments,” Douglas Starr (1998).[1]

Blood transfusion is the intravenous administration of blood into a patient's circulation and is perhaps one of the greatest achievements of modern medicine. Every year millions of lives around the world are saved by the transfusion of safe blood and blood components.[2] Transfusions are given to prevent or treat a clinical problem caused by a deficiency in the blood, either as a result of blood loss or the lack of a particular blood component. Transfusions are commonly given to increase oxygen supply, as well as to maintain fluid levels and replace clotting factors. Whole blood is rarely transfused today; instead donated blood is separated into its constituent parts, and patients are given components such as red blood cells (RBCs), platelets and plasma. The early success of blood transfusions led to their widespread and sometimes inappropriate use in much the same way as antibiotics are used today. However, donor blood is a scarce and costly resource and transfusions are not without risk; infections may be transmitted by transfusion, and reactions may occur between the donor and recipient's blood. Furthermore, there is now a recognition that

transfusions have been overused, and that giving more blood may not be beneficial and may even cause harm.[3-5] The challenge for modern medicine is to use alternatives to transfusion where they exist, and to give transfusions only when the benefits are thought to outweigh the risks.[6]

1.2 History of blood transfusions

To understand the current issues and debates concerning blood transfusion, it is important to start with an appreciation of the history of transfusion. After many disastrous attempts at transfusing blood centuries ago, the first successful transfusion of human blood was achieved by a British obstetrician James Blundell in 1818. In the early part of the 20th century transfusions were cumbersome, accomplished by suturing the blood vessels of the donor and recipient together, and resulted in severe haemolytic reactions (the destruction of RBCs due to incompatible blood types) in more than 30% of cases.[7] Fortunately, significant advances were coming: following the discovery of the ABO blood groups, Reuben Ottenberg (an American surgeon) became the first to identify the blood types of donors and patients. He avoided mixing incompatible ABO blood groups, thus reducing the number of severe reactions. The multiple-syringe technique introduced by Edward Lindeman in 1913 avoided the need for suturing blood vessels; he inserted needles into the donor and the recipient, and used a syringe to withdraw and reinject blood.

While the procedure had improved significantly by the 1920s, blood could not yet be stored for any length of time, so the donor and patient needed to be in close proximity. Storing of blood was pioneered in Russia by Sergei Yudin, and by the mid-1930s Russia had at least 60 large blood storage facilities and more than 500 subsidiaries, making blood available to all parts of the country. America and Europe followed their example, and it was the American, Bernard Fantus, who established a facility in Chicago in 1937, and called it a 'blood bank'. Blood banks were timely, as the need for blood grew enormously during World

War II. Further advances in transfusion practice were made during this time: it became possible to separate plasma from blood and produce freeze-dried plasma, and to separate albumin (a protein) from plasma. These products were used extensively by the American military as volume expanders; indeed by the end of 1943, they are reported to have received two and a half million packages of dried plasma and 125,000 ampoules of albumin.[1]

After the war, it became more difficult to find volunteers willing to donate blood; England and France continued with voluntary non-remunerated donors, but many countries paid donors for blood in the 1950s and 60s. However, it became apparent that deaths from transfusion due to transmitted infection were higher in paid donor blood than unpaid donor blood. While unpaid donors are motivated by a desire to help others rather than financial gain, and have no reason to withhold information which may make them unsuitable to donate, the same may not be true for paid donors, hence the pressure to eliminate payment. The pressure to recruit sufficient willing altruistic donors to maintain supply remains an issue today.[8, 9]

The ability to fractionate blood (separate it into its constituent parts) enabled specific components to be used for different purposes. For example, it led to effective treatment becoming available for people with haemophilia (who have clotting factor deficiencies), firstly in the form of cryoprecipitate, a concentrated form of coagulation proteins, and subsequently in the development of a concentrated form of Factor VIII, the specific clotting factor that haemophiliacs often lack. These treatments dramatically improved the life expectancy and quality of life of patients with haemophilia. However, to produce Factor VIII, the raw plasma from thousands of donors was pooled which greatly increased the risk of viral contaminations, since one infected donor would contaminate the entire pool. In what Lord Robert Winston has described as “*the worst treatment disaster in the history of the National Health Service*”, 4,800 patients with haemophilia in the UK were infected with hepatitis C from infected blood products in the late 1970s and early 1980s, 1,200 of whom

also contracted human immunodeficiency virus (HIV).[10] Such events have created substantial concern about the safety of blood transfusion. As a result, blood is now extensively tested for infections such as HIV with the aim of maximising safety, and while some of these tests are cost-saving, others are very expensive for the small additional benefit they contribute (and in other areas of clinical practice would not be considered cost-effective).[11, 12]

1.3 Benefits and risks of blood transfusion

While the transfusion of safe blood components is a life-saving treatment for patients across many clinical specialties if used appropriately,[5] the benefits of transfusion are not easily quantifiable.[13] Indeed this hypothesis has never actually been proven in a prospective randomised controlled trial.[3] In developing countries, blood is needed for the treatment of severe haemorrhage, anaemia and complications of pregnancy and childbirth. In sub-Saharan Africa where the risk of maternal death is one in 16, obstetric haemorrhage is responsible for up to 50% of these deaths. Malaria is a major contributing factor to life-threatening anaemia in countries where it is endemic. In developed countries, blood is used primarily for advanced medical and surgical procedures, chemotherapy, trauma and the treatment of haematological disorders.[2] Major advances in surgery, where the risk of bleeding may be substantial, have been possible due to transfusions.

Despite such benefits of transfusion, transfusion is not risk-free. While the possibility of transfusion-transmitted infections such as HIV and hepatitis are the more well-known risks of transfusion, these events are now very rare in developed countries with a relatively safe supply of donor blood; indeed in the UK there were no cases of HIV or hepatitis C being transmitted via transfusion between 2004 and 2014, and just four cases of hepatitis B.[14] Transfusion-associated reactions including reactions due to incorrect blood components being given, are more common but still rare; in 2014 there were 14 incidents per 10,000

components reported to the UK Serious Hazards of Transfusion (SHOT) haemovigilance scheme (this also includes transfusion-transmitted infections).[14] However, the less well-known risks of immunosuppression (a reduction in the immune response, increasing the incidence of infection in transfused patients) or organ dysfunction are much more common and can potentially affect any patient given a transfusion.[15, 16] Given such risks, transfusions should only be given when necessary and appropriate.

1.4 Transfusion in practice in the UK

NHS Blood and Transplant (the blood service for England and North Wales) supplies more products each year than any other NHS organisation; in 2014 it issued hospitals with approximately 1.7 million units of RBCs, 275,000 units of platelets and 334,000 units of frozen components, mainly fresh frozen plasma (FFP).[14] Patients who are transfused RBCs during a hospital admission receive on average 4.0 units, those who receive platelets or FFP receive on average 3.2 and 6.0 units respectively.[17] In a recent survey of RBC use, 67% of RBC units were given to medical patients, 27% to surgical patients and 6% to obstetrics and gynaecology patients.[18] The median age of recipients was 69 years (interquartile range 51-80 years) and 52% of units were given to males. The highest number of RBC units transfused for a medical indication were for anaemia, with similar numbers for non-haematological anaemia and haematological disease, each 27% of all units. Cardiac surgery had the highest surgical usage at 6% of all RBCs.[18] Platelets are most commonly used for haematological indications (27%), cardiac procedures (17%), and paediatrics (13%), while FFP is most frequently used for digestive indications (21%) (largely gastrointestinal bleeding and colorectal surgery), with 15% used for hepatobiliary conditions (affecting the liver and bile ducts) and 12% used for cardiac indications.[17]

Donor blood is considered as a scarce resource. Only 4% of the eligible population give blood,[19] and the number of blood donors fell by 20% between 2000-2005, largely due to

the introduction of more stringent donor selection criteria to reduce the risk of transmission of variant Creutzfeldt-Jakob disease, putting enormous pressure on the supply of donor blood.[20] Donor blood is also considered as an expensive resource: while blood is given freely by altruistic donors, the steps involved in collecting blood donations, processing them into components and performing an increasing number of safety tests consumes substantial resources.

Between 1998 and 2012 the '*Better Blood Transfusion*' initiative driven by the UK's Chief Medical Officers provided a focus for improving the safe and appropriate use of blood with the publication of recommendations to improve transfusion practice in a series of Health Service Circulars.[21-23] This initiative has been superseded by '*Patient Blood Management*', an international initiative to optimise care for patients at risk of transfusion.[19] Significant progress has been made; blood use fell by 17% between 2001 and 2007,[9] which was attributable to a reduction in demand for surgical indications, largely through the acceptance of lower transfusion thresholds in elective surgery, but also as a result of better blood management in terms of improved surgical and anaesthetic technique, identification and treatment of pre-operative anaemia and use of transfusion alternatives.[6] However, demand for blood is expected to rise in the next five to ten years,[9] transfusion rates are much higher in older people so an increasingly ageing population will increase demand.[24] While blood use has fallen in surgical procedures such as primary joint replacement and coronary-artery bypass grafting, an ageing population will require more complex surgery such as recurrent joint replacement and combined coronary-artery bypass grafting with valve surgery, procedures for which transfusions are still frequently required.[9]

The early success of transfusions led to their widespread application. However, there is now an evolving evidence base which challenges some previously accepted indications for transfusion, and errs towards using less blood. A recent systematic review of randomised controlled trials (RCTs) of restrictive (lower) RBC transfusion thresholds versus more liberal

thresholds found that restrictive transfusion was safe in most clinical settings (with the possible exception of patients with coronary artery disease or traumatic brain injury), and that liberal transfusion did not convey any benefit to patients.[4] Similarly no evidence was found of any benefits of a higher platelet transfusion threshold compared to the standard transfusion threshold.[25] A systematic review of 80 trials of FFP found little evidence of any consistent benefit from using FFP prophylactically or therapeutically.[26] To ensure effective practice, this evidence needs to be recognised by doctors and clinical practice altered accordingly. Over-transfusion is a problem for two reasons, firstly patients are being unnecessarily exposed to the risks associated with transfusion, and secondly blood is a scarce resource.

1.5 Costs

The costs of transfusion are believed to be substantial, but accurate estimates of total transfusion costs in the UK are not available. The costs of the blood products themselves are known: in 2014/15 hospitals in England and North Wales paid NHS Blood and Transplant approximately £289 million for blood products.[27] However, much less is known about the total costs of transfusion, which it is estimated could be 3.2 to 4.8 times higher than the acquisition costs.[28] In addition to the blood products, the costs of transfusion include the costs of safely selecting blood products for a patient and administering and monitoring the transfusion, and the costs associated with related morbidity.

Since little is known about the full economic costs of blood transfusion in the UK, we do not know whether scarce resources (such as blood products and staff time) are being used efficiently. We need to understand where blood really is needed and identify situations where blood may not be needed. It is important to produce comprehensive and reliable estimates of the resources and costs required for blood transfusion for two reasons. Firstly,

a greater transparency and understanding of the costs associated with transfusion could assist the '*Patient Blood Management*' initiative to promote more appropriate use of this increasingly scarce resource. Secondly, estimating the true cost of blood transfusion has the potential to lead to better informed resource allocation decisions in transfusion. Once more reliable estimates of the costs of transfusion are available, the potential exists for more accurate estimates of the cost-effectiveness of new policies or interventions aimed at reducing the use of blood to be made. At present the cost savings likely to be realised by reducing blood transfusions will be significantly underestimated if only the costs of the blood products are taken in to account, and as a consequence, the results of cost-effectiveness studies may be biased in favour of the status quo and ultimately lead to erroneous policy decisions. As well as the costs of transfusion, such evaluations also require detailed resource use data; primary data could be collected specifically for the study or existing data sources could be used. In many clinical areas such as cardiac surgery, where there is uncertainty around optimal transfusion practice, it is likely that efficiency could be improved.

1.6 Thesis aims and objectives

The overall aim of this thesis is to provide reliable and comprehensive estimates of the costs of administering blood in the UK NHS, and to illustrate the usefulness of these estimates in applied economic evaluations involving transfusion, by assessing the cost-effectiveness of two transfusion management strategies in cardiac surgery.

The objectives of this thesis are:

- 1) to estimate the costs to the NHS of administering transfusions of RBCs, platelets and FFP;
- 2) to assess the cost-effectiveness of a restrictive versus a liberal RBC transfusion threshold after cardiac surgery;

- 3) to assess the cost-effectiveness of introducing bedside testing devices of haemostatic function in cardiac surgery;
- 4) to compare resource use data collected from primary data collection and routine datasets.

1.7 Structure of the thesis

A brief description of the seven further chapters of this thesis is now provided.

Chapter 2 introduces economic evaluation and its use in healthcare decision-making. Different types of economic evaluation are described as well as two complementary frameworks for their conduct, which will be used in later chapters. The second half of the chapter focuses on the cost component of an economic evaluation, the steps required to perform a costing study and alternative approaches to costing are described.

Chapter 3 provides the clinical background for this thesis. The chapter begins with an introduction to blood, different types of transfusion and adverse transfusion reactions, before transfusion practice in cardiac surgery is outlined. The costs associated with transfusion are also described, and the chapter concludes with a literature review of the costs of administering blood.

Chapter 4 describes two detailed micro-costing studies which have been undertaken to estimate the cost of two aspects of administering blood. The first study estimates the costs of transfusion laboratory inputs to identify a patient's blood group, and safely issue blood products. The second study estimates the costs of nursing inputs needed to order and administer blood on a haematology day unit. The final element of this chapter explores the generalisability of the costs of administering blood on a day unit with two further settings

(theatre and the emergency department) through four semi-structured interviews with nurses.

Chapter 5 begins by summarising what is known about the benefits and risks of alternative transfusion strategies after cardiac surgery, and in particular the cost-effectiveness of alternative transfusion thresholds. The chapter then reports the first of two applied economic evaluations conducted for the thesis, assessing the cost-effectiveness of a restrictive versus a liberal RBC transfusion threshold after cardiac surgery as part of an RCT. In order to estimate costs, very detailed resource use data were collected on bespoke case report forms during the hospital stay and after discharge to three months post-operatively. The results obtained using costs estimated in Chapter 4 are compared to results using existing prices to establish whether cost-effectiveness decisions are altered by improvements in estimates of the cost of administering blood.

Chapter 6 describes the processes involved in developing a decision model to assess the cost-effectiveness of introducing bedside tests to identify clotting abnormalities and guide treatment in cardiac surgery, and presents the cost-effectiveness results. The chapter describes the structure of the model, and how parameters are estimated, many from an observational study. Cost-effectiveness results are presented together with a range of sensitivity analyses assessing the impact on results of variation in key uncertainties in the model including the cost of administering blood.

Drawing on the previous two chapters, Chapter 7 compares resource use data collected from primary data collection (Chapter 5) and routine sources (Chapter 6) for a subgroup of patients who were in both the trial and the observational study. The level of agreement between sources for resource use items and the magnitude of differences are assessed, and the effect of this on the costs of resource use is presented. Findings are also used to quantify the under-reporting of complication costs in the observational study, which in turn

is used to inform an additional sensitivity analysis around the health economic model presented in Chapter 6.

Finally, Chapter 8 summarises the findings of the thesis, and discusses their generalisability and the policy implications as well as the challenges that arose during the conduct of the work. Areas for further research are also identified.

1.8 Contribution to the literature

This thesis will contribute to the literature in three ways, firstly by generating unit costs of administering transfusions for use in economic evaluations and to assist hospital managers and policy-makers, secondly by providing health economic evidence around alternative transfusion strategies in cardiac surgery, and thirdly by adding to literature on whether resource use data can reliably be obtained from routine datasets for the purposes of economic evaluation.

Blood transfusions are not limited to one particular specialty and may be given to patients of all ages for a wide range of conditions, and as such are one of the most common procedures in hospital. Health economists conducting economic evaluations involving critically ill patients in intensive care, and clinical areas as diverse as orthopaedics and cancer, are likely to need unit costs of transfusion for use in their studies. Accurate estimates are not currently available, and this thesis will contribute significantly to this literature (Chapter 4).

The health economic evidence base around transfusion management strategies in cardiac surgery is currently very limited. This thesis will contribute evidence around two such strategies, alternative transfusion thresholds after surgery and the use of rapid bedside tests after surgery to guide treatment (Chapters 5 and 6).

There are moves to make greater use of routine datasets within healthcare for research, and specifically for economic evaluation, but there is a lack of evidence on whether these can reliably provide the information required. The comparisons made in Chapter 7 between resource use data collected for the same patients from case report forms and routine datasets will contribute to this literature and can be used to inform future studies.

1.9 Conclusion

This chapter has provided an introduction to the thesis, described its aims and an outline of the chapters that follow, and described its contribution to the literature. The next chapter introduces economic evaluation, which is integral to each of the subsequent chapters.

Chapter 2: Economic evaluation and costing approaches

2.1 Introduction

This chapter begins by introducing economic evaluation and the rationale for its use, and summarises the different types of economic evaluation. Two frameworks for conducting economic evaluations are described: approaches based on patient-level studies (clinical trials and observational studies) and decision-analytical modelling. The chapter then focuses on the cost component of an economic evaluation, and the steps required to perform a costing study. Alternative approaches to valuing resources such as top-down and micro-costing are considered. Finally, common adjustments to cost data such as discounting are described, and issues for consideration when analysing cost data such as missing data are summarised.

2.2 Rationale for economic evaluation

A starting point for the rationale for economic evaluation, is the discipline of economics itself. Economics is the study of how individuals and societies choose to allocate scarce resources among competing alternative uses (for example the production of different goods and services). Health economics is the particular application of economics to health, and to how resources are allocated to alternative interventions to improve or maintain health or to prevent disease. Resources such as land, labour and capital are scarce, and therefore it is necessary to make choices about how they are used. Deciding to allocate resources for one particular use implies that they cannot be used for an alternative purpose. There is an opportunity cost associated with allocating resources to one particular activity, which is the benefits forgone from not undertaking the next best activity. Resources should be used as efficiently as possible, to generate the maximum benefit to society.

Standard economic theory suggests that efficiency could be achieved in the context of a free market (an unregulated market without government intervention). For commodities with many consumers and producers, for which consumers have perfect information, and for which there are no externalities (spillover effects of other people's production or consumption on the wider society), the free market is a very efficient resource allocation mechanism. The price of the good or service will naturally settle at the point where the quantity demanded by consumers equals the quantity produced by suppliers, an equilibrium. For commodities such as televisions for example, transactions take place between consumers and suppliers in a largely unregulated market.

Whilst there are many examples of markets where little or no government intervention is required and where consumers and producers are able to operate efficiently, there are several markets which are often considered to fail and are prone to significant government intervention, such as education, defence and healthcare. With healthcare, consumers tend not to know when they are going to be ill and need healthcare, and in a free market, this uncertainty leads to voluntary insurance markets.[29] Private insurance systems in turn have two particular problems: moral hazard (those with insurance may alter their behaviour and take more risks due to being insured) and adverse selection (buyers of insurance are more informed about their risks of disease than insurance sellers).[30, 31] Moral hazard may create excess demand for medical care, and the market may not reach equilibrium. Adverse selection can result in under-insurance of low risk people, since insurance companies cannot identify them and offer them a low enough premium to attract their business. There are other ways in which the market may fail for healthcare, for example externalities are not taken into account in a free market. These can be positive (vaccinations benefit the community as a whole, as well as the individual) or negative (spread of antibiotic resistance as a result of inappropriate use of antibiotics).[32] A further failure of the market can arise due to the asymmetry of information between providers and consumers. Doctors (providers) act on the patients' (consumers') behalf to both demand

and supply healthcare, since patients generally do not have sufficient medical knowledge to make informed choices about healthcare independently. Patients do not therefore have perfect information, one of the requirements for a free market to achieve optimal outcomes.[33] Finally, given the asymmetries of information between providers and consumers of healthcare and the potentially serious consequences of mistreatment, there is a need for professional licensure in healthcare,[33] which gives some degree of market power to those holding a licence and in the extreme this could limit supply or push up prices and the market would not reach equilibrium.

Given all these different ways in which the market can fail in healthcare,[34] it is generally agreed that extensive government intervention is likely to provide greater benefit to society, than no (or minimal) intervention.[33] Indeed, internationally many governments intervene at some level in the financing and provision of healthcare. In the UK, there was a free market in healthcare in the early part of the 20th century, but growing concerns about inequity led to the introduction of the NHS in 1948, with the aim of making comprehensive healthcare available to all, regardless of their ability to pay.[35] The NHS is financed largely by a budget allocated via general taxation. Even though the aim is to provide healthcare for all, it still needs to be rationed in some way. There are many subjective ways which could be used to determine who gets care and who does not, but ideally a more objective measure would be used. Care could be rationed by choosing only the lowest cost treatments, or only the most effective treatments. However the former ignores efficacy and is likely to reduce the quality of care provided, and the latter ignores costs, and therefore these are likely to escalate. Alternatively costs and effects could be considered together, and economic evaluation used to identify the most cost-effective treatments which would maximise health gains from the budget available.

Economic evaluation is an explicit decision tool for making choices. It is often defined as *“the comparative analysis of alternative courses of action in terms of both their costs and*

consequences".[36] In economic evaluation, the costs and outcomes of different interventions are explicitly computed and compared, to identify interventions which represent best value for money. Economic evaluations are always comparative, one intervention is compared to another (or to several others); the appropriate comparator for a new intervention is the current standard treatment(s) (or no treatment, if there is currently nothing available).

2.3 Types of economic evaluation

There are different types of economic evaluation. The costing part of evaluations is usually similar with resource use valued in monetary terms, it is the way in which outcomes are measured that varies and determines the type of study, as described next.

2.3.1 Cost-minimisation analysis

In the early health economics literature, when two alternatives were compared and found to achieve a given outcome to broadly the same extent, the least costly option was preferred.[36] This is known as a cost-minimisation analysis (CMA). In a seminal paper by Briggs and O'Brien (in 2001),[37] it was argued that the remit for CMA should be much narrower and that it is only appropriate when equivalence of outcomes has been demonstrated, not in situations when no difference is found, since studies may be underpowered to detect differences. It has since been argued that even this definition is too broad, and CMA is only appropriate where the difference in costs is so large, that no plausible difference in outcome could change the conclusions.[38] CMA is no longer considered as a form of a full economic evaluation,[36] but is still used by some researchers.

2.3.2 Cost-consequences analysis

A cost-consequences analysis is considered to be a full form of economic evaluation since both costs and outcomes of alternatives are compared. Results are presented in a disaggregated format however; costs and outcomes are not combined in anyway. This does allow information on a range of different outcomes to be included, which may be helpful to decision-makers who can select the outcomes that are relevant to their setting.

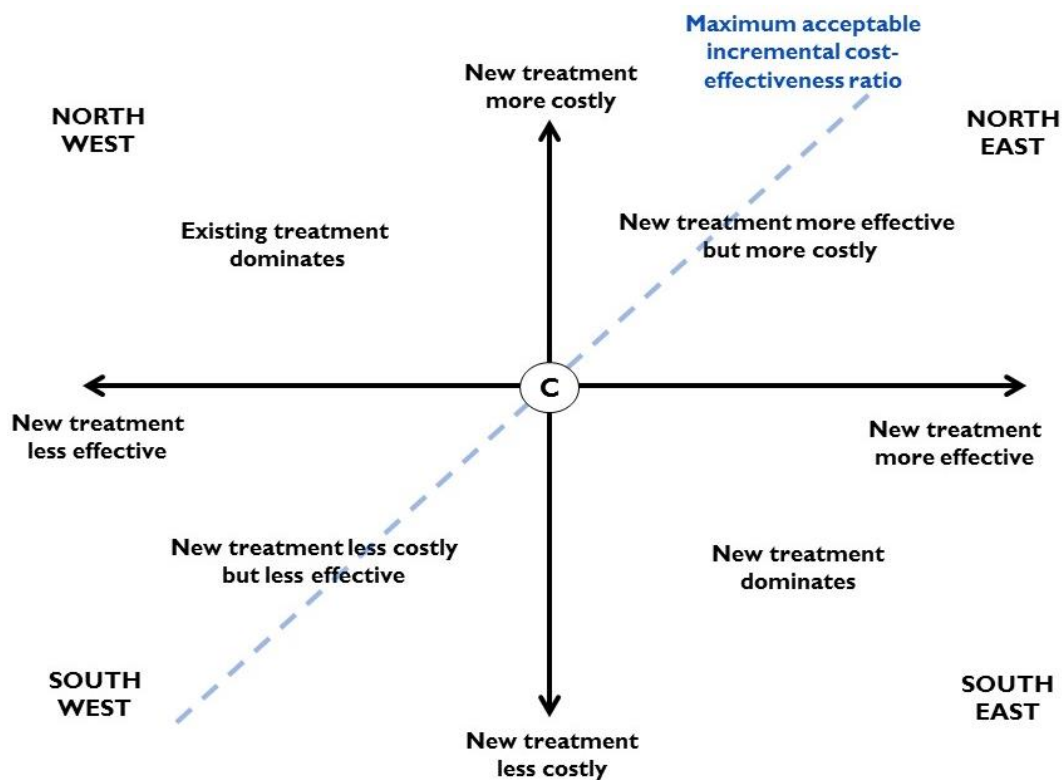
2.3.3 Cost-effectiveness analysis

In a cost-effectiveness analysis (CEA), two (or more) alternatives are compared using costs, and a single outcome measure expressed in natural health-related units,[36] such as life-years gained, the number of cases detected (when comparing for example alternative cancer screening options), or symptom-free days (when comparing alternative asthma treatments). In a CEA, the difference in costs between the alternatives (the incremental cost) is compared to the difference in effects (the incremental effectiveness). The decision rule for determining which intervention to adopt is straightforward when an intervention is both less costly and more effective than a comparator (the intervention is cost-effective and 'dominates' the comparator), or when an intervention is both more costly and less effective than a comparator (the intervention is not cost-effective and is 'dominated' by the comparator). Most frequently an intervention is more costly and more effective than a comparator; there is a trade-off between the additional costs and effects, and an intervention is considered cost-effective if the additional benefits are thought to be worth the additional cost. In this situation the incremental cost-effectiveness ratio (ICER) is calculated; the incremental costs are divided by the incremental effects, producing an incremental cost per unit of outcome, for example an incremental cost per life-year gained.[36] (They could equivalently be expressed as an incremental effect per unit of cost, so life-years gained per pound spent). This ICER is then compared to the maximum acceptable ICER (or ceiling ratio), which is the maximum amount society is willing to pay

for a one unit increase in health outcome. If the ICER falls below this ceiling ratio, the intervention is considered cost-effective. Occasionally an intervention is less costly and less effective than a comparator, and a judgement needs to be made about the size of the cost savings relative to the benefits forgone. The ICER is also used in this situation, and compared to the ceiling ratio.

The decision problem can be presented visually on the cost-effectiveness plane (**Figure 2.1**). Relative to the comparator (the 'C' in the middle of the diagram at the origin), the incremental costs and effects of the intervention are plotted, and the resulting point sits in one of the four quadrants of the cost-effectiveness plane. If the point corresponding to the incremental costs and effects of the intervention is to the right or below the maximum acceptable ICER, then the intervention is considered cost-effective.

Figure 2.1: The cost-effectiveness plane



CEA can be used to compare different interventions, as long as outcomes are expressed in the same natural units. It can therefore be used to compare the number of cases detected across many different screening programmes, even across different diseases, but it cannot be used to compare the number of cases detected with the number of symptom-free days for asthma interventions or life-years gained from heart transplantation. This is a limitation of CEA: to maximise the health benefit from a finite healthcare budget, comparisons need to be made across a broad range of healthcare interventions for different diseases and different aspects of health being addressed, and for the full spectrum of interventions from screening programmes and prevention strategies, to alternative treatment options and palliative care.

2.3.4 Cost-utility analysis

Cost-utility analysis (CUA) is a particular form of CEA, where two (or more) alternatives are again compared using costs, and a single outcome measure. This time the outcome is a composite measure of quality and quantity of life, known as a utility measure, most commonly quality-adjusted life-years (QALYs).[39] The concept of the QALY was developed to take account of the fact that while some interventions save lives, the quality of life during the additional length of life could be reduced.[40] The number of QALYs gained by an intervention is calculated by multiplying the length of life gained by the intervention by the value of the quality of life experienced over that time. Health-related quality of life is measured on a scale from zero to one, where zero represents death and one represents perfect health. Alternatives to the QALY are available, for example, disability-adjusted life-years are a composite measure of mortality and disability, and are often used to assess the cost-effectiveness of interventions in developing countries, but are rarely used in medical decision-making in the UK.[41]

The rules for determining which intervention to adopt are the same as those described above for CEA. The advantage of CUA over CEA is that because the QALY is a generic outcome measure that can be used across virtually all interventions, it allows comparisons to be made across a broad range of healthcare interventions. CUA can therefore be used not only to compare between screening programmes for example, but also to compare the relative cost-effectiveness of asthma treatment with cancer screening programmes and heart surgery.

In England and Wales, the National Institute for Health and Care Excellence (NICE) makes judgements about what represents good value for money within the NHS. There is no explicit threshold, since this would imply that efficiency is the dominant criteria over all considerations (such as the availability of alternative treatment options, or whether the treatment is for a rare disease). However, interventions are generally considered as cost-effective if the ICER falls below £20,000 per QALY gained.[42] Other Health Technology Assessment agencies such as the Canadian Agency for Drugs and Technologies in Health (CADTH), and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia also have implicit cost per QALY thresholds: CAN\$50,000 for CADTH and AUS\$42,000 for PBAC.[43]

2.3.5 Cost-benefit analysis

In a cost-benefit analysis (CBA), costs and outcomes are again compared, but in this case outcomes as well as costs are expressed in monetary units. This requires health outcomes, such as a symptom-free day to be valued in monetary terms. In the UK, with a very limited market for healthcare, market prices cannot be used to place monetary values on health outcomes: there is no opportunity to infer a value on a healthcare good as few individuals directly purchase healthcare.[36] Instead, techniques such as asking individuals to estimate their willingness-to-pay for different health outcomes,[44] or discrete choice

experiments (DCEs),[45] can be used to value health outcomes in monetary terms. In a DCE individuals are asked to repeatedly choose between alternative scenarios describing different levels of a set of attributes, in this case including a cost attribute.

The results of CBAs are presented either as a simple sum representing the net benefits (benefits minus costs) of an intervention, or as a ratio of benefits to costs. The decision rule for determining whether to adopt an intervention is straightforward; if the net benefits are positive, or the ratio of benefits to costs is greater than one, then the new intervention is adopted. As outcomes are measured in common monetary units, CBA can be used to compare a broad range of health interventions.

In practice, relatively few CBAs are conducted, and while the majority of studies are CEAs, the proportion of CUAs is growing over time, (from 11% in 1999 to 30% in 2009).[38]

2.4 Issues for consideration when undertaking an economic evaluation

Perspective

An important consideration in an economic evaluation is the perspective (viewpoint) of the analysis which determines which relevant costs and outcomes should be measured. In applied work, the perspective is frequently that of the payer, but could also be the individual, government or an aggregation of all costs and outcomes regardless of who bears them, known as the societal perspective. This incorporates productivity losses by individuals who have time off work. In the UK, guidelines produced by NICE recommend that an NHS and personal social services perspective be adopted.[46]

Time horizon

The time horizon of an economic evaluation (the time period over which costs and outcomes are compared) should extend far enough into the future to capture all the costs and outcomes which might be expected to differ as a result of an intervention. If reduced mortality is an expected outcome then a lifetime time horizon is recommended.[46] Bias will be introduced if some costs or outcomes attributable to an intervention are not captured.

For health economists in the UK, the NICE publication “Guide to the methods of technology appraisal 2013” is a key source of guidance on conducting economic evaluations.[46] Other useful sources are the Drummond checklist for critically appraising evaluations,[47] and for the reporting of evaluations, the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[48]

2.5 Frameworks for conducting economic evaluation

When planning an economic evaluation, as well as determining the appropriate type of study for a given decision problem and considering the perspective and the time horizon, it is also necessary to decide how the study will be conducted. While there are a number of frameworks or approaches for conducting studies, they can be divided into two broad categories: patient-level studies and decision-analytic modelling studies. Both frameworks will be used in later chapters. It is sometimes appropriate to combine these approaches within the same study.

2.5.1 Patient-level studies

Patient-level studies, as the name suggests, use data on individual patients from clinical studies as a vehicle for undertaking an economic evaluation.[36] The evaluation uses only data collected in the study, data on resource use and outcomes are collected for study

participants and used to directly compare the costs and effects of different interventions. The clinical study is likely to be either an RCT or an observational study.

RCTs are frequently the study design of choice for measuring the effectiveness of healthcare interventions. Patients are randomly allocated to one of the interventions under evaluation, and where possible, clinicians, patients and analysts are blinded to each patient's allocation. These features are designed to provide internal validity, allowing us to conclude that any benefits are due to the intervention itself, and not to other factors (confounding).[36] As the use of RCTs has grown over the last 30 years, so has the use of RCTs as the vehicle for economic evaluation. An RCT can be conducted to assess the efficacy of an intervention, that is to understand whether an intervention can work (sometimes known as an explanatory approach), or to assess the effectiveness of an intervention, to determine whether an intervention would work in practice if it was implemented (sometimes known as the pragmatic approach).[49] It is more appropriate to conduct an economic evaluation alongside the latter, and to evaluate the cost-effectiveness of an intervention as closely to 'real-world' conditions as possible. Pragmatic RCTs (such as the REFLUX trial),[50] aim to balance the goals of minimising bias whilst maintaining generalisability. From the economist's perspective, conducting an economic evaluation alongside an RCT is attractive: data can be collected prospectively and rigorously, and efficiently, since some of the economic data required will already be being collected as part of the clinical evaluation.

While well-executed RCTs are considered by many to provide the most reliable scientific evidence, and rank above observational studies in the hierarchy of evidence,[51] not all questions can be addressed by an RCT. It may be impractical or unethical to conduct an RCT, for example for a rare disease where it would only be possible to recruit a very small number of patients. Furthermore, if there are strict inclusion criteria for a trial, the results may not be generalisable to the population of interest. By contrast observational studies,

where patients receive treatment under usual care, often include a broader range of patients. These are highly pragmatic studies since they are based on routine practice. They are a particularly valuable vehicle for evaluation in situations where a trial would be impractical, for example to evaluate the introduction of policy initiatives. Observational studies can be conducted prospectively or retrospectively. Retrospective studies tend to rely on existing administrative datasets, and while this is often a low-cost source of data, important information may be unavailable. If observational studies are conducted prospectively, there is greater opportunity to collect information on patient characteristics which can be used to adjust for the imbalance between groups due to the lack of randomisation, and address the issue of confounding. The debate on whether treatment effects estimated from observational studies are consistent with those estimated from RCTs has been ongoing for many years.[52-55]

It is worthwhile to mention an additional source of data: in recent years, there have been moves towards making greater use of large and complex datasets, so called 'Big Data'. [56] According to the UK Government, which has made a significant commitment to Big Data, identifying it as one of the 'Eight Great Technologies' which it hopes will promote economic growth: *"Big Data refers to both large volumes of data with high level of complexity and the analytical methods applied to them which require more advanced techniques and technologies in order to derive meaningful information and insights in real time"*. [57] There has been considerable investment in Big Data in healthcare, for example in the UK Biobank, which recruited 500,000 people aged 40-69 years between 2006 and 2010, and captured detailed information about their health (including blood, saliva, and urine samples), and is following them up over time. Resources such as this can be used to support research that was simply not possible before. With vast datasets it is possible to identify rare side-effects more quickly for example, however, health economists may need to develop new methods and new skills for working with such data.[58] There is strong interest in this area and the developments required; Big Data has been the topic of plenary sessions at both the 2014

and 2015 International Society for Pharmacoeconomics and Outcomes Research (ISPOR) international meetings.

2.5.2 Decision-analytic modelling studies

While there are advantages of patient-level studies, there are also concerns that relying on a single study has limitations,[59] and that to inform decision-making about efficient allocation of healthcare resources, economic evaluation needs to draw on evidence from a range of sources. Decision-makers need information on all relevant comparators, but a single study may not compare all the relevant alternatives. Decision-analytic modelling defines a set of mathematical relationships between the consequences of alternative treatment options being evaluated, and each consequence has a cost and outcome. [36, 60] Consequences are often in the form of health states in Markov models, and pathways in decision trees. Decision-analytic modelling allows evidence from a number of sources to be synthesised and used in decision-making. Patient-level studies may not have a sufficiently long time horizon to capture all the costs and effects associated with an intervention, a decision model can be used to extrapolate costs and effects to a longer time horizon.

Decision-analytic modelling provides a systematic approach to decision-making;[60] for each alternative intervention being compared, an explicit set of consequences are defined. The likelihood of each consequence is defined by its probability, and each consequence has an associated cost and outcome attached. For each intervention, the expected costs are calculated by summing the cost of each possible consequence of that intervention multiplied by the probability of the consequence. Expected outcomes are similarly calculated, and then expected costs and outcomes between alternative interventions can be compared. A key feature of decision modelling is to allow for uncertainty which will exist around most of the model parameters (probabilities, costs and outcomes); uncertainty in

inputs can be propagated in sensitivity analyses to assess its impact on the outcome of interest.

Once the decision problem has been specified, the recipient population defined and the specific options to be assessed determined, the decision model needs to be conceptualised and structured.[61] The most frequently used techniques for implementing a model are decision trees and Markov models. A decision tree provides a visual representation of the decision problem. For each option being evaluated, all possible outcomes and events that might occur are mapped out in a series of mutually exclusive branches and pathways.[60] Probabilities for each outcome or event are assigned to each branch in the pathways. Decision trees are suited to modelling short term processes, but can get very complex and very 'bushy', if used to assess long term prognoses, which would require more and more branches to be added to capture subsequent events.[36] Time is not explicitly defined in a decision tree, so time dependency is also difficult to implement. If these limitations are an issue, a Markov model may be more appropriate. Markov models are based on a series of mutually exclusive health states, which reflect important stages of a condition or disease.[60] The probability that a patient is in a given state is assessed over a number of discrete time periods or cycles. At the end of each cycle patients can move between health states, based on pre-defined transition probabilities. Each health state is associated with a cost and an outcome, and by running the model for a number of cycles, estimates of the total costs and outcomes for the pre-specified time horizon can be generated. It is possible to combine approaches, for example to assess the short term impact of an intervention using a decision tree, and then extend this using a Markov model to assess long term consequences on an annual basis.[36] This will be demonstrated in the model presented in Chapter 6.

2.6 Costing within economic evaluation

The remainder of this chapter focuses on the costing side of an economic evaluation, since a substantial part of the empirical work presented in later chapters of this thesis attempts to address the evidence gap in the area of costing of blood transfusion. While this part of an evaluation is usually fairly standard in the sense that resource use is valued in monetary terms, there are several approaches that can be used for costing, which measure resource use and costs to different levels of detail. Historically methodological developments in economic evaluation have focused on the benefit rather than the costing component of evaluations. As the use of evidence from economic evaluations has been increasingly used by bodies such as NICE to inform decision making, there has been a growing recognition that costing methods need to be consistent and transparent, and costing methods are a key part of the NICE guidance on technology appraisals.[46]

Costs are calculated by quantifying elements of resource use (cost generating events, such as a day in hospital), multiplying each of these by their respective unit costs, and summing together. There are three stages in performing a cost analysis, firstly the identification of relevant resources, the measurement or quantification of resources and finally their valuation.

2.6.1 Identifying costs

Costs associated with healthcare interventions fall into four broad categories: costs arising from resources used in the health sector, in other sectors, by the patient or their family, and productivity losses (or gains).[36] The range of costs that should be included within a study will depend on the perspective adopted: if an NHS and personal social services perspective is adopted, then only costs incurred within these areas should be included. NHS resources might include hospital stays, outpatient appointments and/or general practitioner (GP) visits, while personal social services covers residential care, day care, support for those

with learning difficulties or disabilities, and domiciliary care. If a societal perspective is adopted then all costs regardless of who bears them should be captured, including productivity losses.

2.6.2 Measuring and valuing costs

Once relevant costs have been identified, individual items then need to be measured and valued. If a hospital stay needs to be costed for example, the number of days in hospital could be measured, and valued using a cost per bed day. While the measurement of quantities of resources and then the valuation of resources in unit costs or prices are two distinct tasks, it is helpful to consider them simultaneously. Generally there is little benefit in measuring resources to a great level of detail, if it is then not possible to obtain unit costs to value the resource use in such great detail; the reverse is also true.

When measuring and valuing resource use, consideration should be given to the different types and nature of costs that might be incurred. Some costs are fixed over at least the short term, and vary with time rather than quantity, and will be incurred even if unused. The costs of leased equipment where purchasers are tied in for a period of time, rent and some salary costs are examples of fixed costs. Variable costs directly relate to the level of output, the more that is produced the higher the costs; the costs associated with consumables are usually variable costs. Average costs per output can be calculated as the total costs (fixed and variable) divided by the volume of output. If a service is already up and running, marginal costs may be of greater interest, that is, the additional cost of producing one extra unit of output; if fixed costs have been incurred this is likely to be less than the average cost per unit of output.

There are a number of ways in which resource use information can be obtained. Economic evaluations conducted alongside RCTs may capture resource use data prospectively on

bespoke case report forms (CRFs). Alternatively individual patient data might be obtained from administrative databases, or directly from patients' case notes. Some information, such as information on primary care visits or out-of-pocket expenditure, may only be available by asking patients: postal or telephone follow up questionnaires can be used to capture such information, or patients can be asked to keep a diary of such events or expenditure during the course of a study. Some economic evaluations are conducted without the use of individual patient data, using summary data from the literature or other published sources.

Careful consideration needs to be given to the way in which resource use information is collected. While the use of existing (often administrative) datasets may be a reliable source, and avoids the duplication of effort, this data may not be collected with the same rigour as data on CRFs within a trial setting for example, and may not be subject to the same checks. The level of detail required for a study simply may not exist within existing datasets. It may also be time consuming to identify individual study patients in existing datasets, and link them together. Collecting data on CRFs generates more work for research staff, but allows the health economist to have more control over exactly which data are collected (within reason!). There is often a balance to strike between the detail on resources that economists would like to capture in order to accurately cost resource use, and the desire by other researchers to keep CRFs as short as possible, to reduce the burden on research staff and patients, and encourage a high completion or response rate. Costing using alternative sources of patient-level resource use information will be considered further in Chapter 7.

For valuing resource use, many economic evaluations make use of readily available costs. NHS Reference Costs published annually by the Department of Health provide national average unit costs for NHS hospital care and community-based services in England and Wales.[62] Unit costs for elective and non-elective inpatient care, day cases, outpatients, emergency medicine and a range of other services are provided by Healthcare Resource

Group (HRG) codes, (which group patient care into activity thought to have similar levels of resource use) or split by speciality codes. These national costs are averages across a number of hospitals and may be considered transferable across different hospitals and therefore appropriate for a multi-centre study, but less applicable to a single centre study. However, they may simply not have the level of detail required – for example if two surgical techniques being compared share the same HRG code, NHS Reference Costs would not differentiate between them. Another source of readily available costs is the annual report, Unit Costs of Health and Social Care produced by the Personal Social Services Research Unit at the University of Kent.[63] This covers both hospital and community-based healthcare staff such as primary healthcare staff, as well as services for specific patient groups and aids and adaptation for the home. Both these sources will be used in later chapters of this thesis.

The way in which costs are measured and valued will in part be determined by the general approach to costing that is adopted, and alternative approaches are described next.

2.6.3 Top-down versus bottom-up costing

The actual collection of cost data can be undertaken to different levels of precision, the two ends of the spectrum are top-down costing and bottom-up costing.[36, 64] Top-down costing identifies the total cost of delivering a service, and divides this by the total number of recipients. It uses relatively large units of measurement, such as the average cost across all patients for a day in hospital. Alternatively, bottom-up costing or micro-costing requires the measurement of all individual components of resource use (or at least much smaller components of resource use), such as staff time, consumables, laboratory tests and drugs.

Although top-down costing is acknowledged to generate less accurate costs than bottom-up costing,[65, 66] it is often used to value resource use, since it has fewer data

requirements, and can make use of national sources of unit costs such as NHS Reference Costs (described above). It is labour intensive to use a bottom-up approach, and even within very detailed studies, it is unlikely that this approach would be deemed necessary for all resource use. It is important to consider the relative magnitude of each cost category.[36] If a particular cost category is well known to have little bearing on the overall costs, for example for patients having cardiac surgery, the relative cost of fluids is very small, then it is not worthwhile investing considerable effort in recording the type and quantity of fluid given to each patient, when a common fluid type and quantity could be assumed and valued.

Due to the large units of measurement, top-down costing may not reveal the relative contribution to costs of individual activities, limiting transparency.[66] If an intervention is expected to impact on the frequency of complications for example, then a top-down approach to costing complications may be sufficient. If an intervention is expected to impact on the severity of complications, then a more detailed, bottom-up approach to costing may be required to reflect the differences between the groups.[36] The impact of the intervention on resource use needs to be carefully considered.

In practice, different cost items are likely to be measured to different levels of precision within the same study. Greatest effort should be focused on the likely key drivers of costs, and also on the elements likely to differ between the interventions being compared.[67]

2.6.4 Adjustments to cost data

Once resource quantities and unit cost data have been collected, there are several adjustments that may need to be made prior to analysis. Care needs to be taken to avoid double counting of costs, and adjustments may need to be made to account for differential

timing of costs, both in terms of when they are incurred and ensuring that costs are presented in a common base year.

Double counting

When costing an intervention, it is important to consider what is included in each element of cost, to ensure that parts are not counted (and costed) twice. When costing cardiac surgery for example, resource use information might be collected on the type of surgery and length of stay in hospital for each patient. If NHS Reference Costs are used to cost the surgery,[62] then costs associated with the average length of stay will need to be stripped out, since these costs are already included within NHS Reference Costs. Length of stay can then be costed more accurately on an individual patient basis.

Inflation

Some interventions can be given, and hence their costs incurred, over several years; equally trials may take place over a number of years and costs may be collected at different time points in the trial. Costs should be presented in a common base year and adjusted to eliminate the effects of inflation.[67] The Hospital and Community Health Services (HCHS) inflation index can be used to inflate older costs to the base year.[63]

Discounting

Discounting is used to adjust for any differential timing of costs incurred and benefits gained. Individuals generally prefer to receive benefits earlier and incur costs later. Differential weightings should therefore be given to costs and benefits occurring at different times to account for this 'time preference'. A cost of £100 in the future should be given less weight than a cost of £100 incurred now, through discounting.[67] Costs, effects and cost-effectiveness should be presented in present values. Guidelines recommend the same annual discount rate be used for costs and effects,[46] and the UK Treasury currently advocates a discount rate of 3.5%.[68]

Capital costs are likely to differ from year to year; often they will be incurred at the start of a programme only, but the equipment will be used over a number of years. In order to apportion capital costs appropriately, it is helpful to annuitise the costs of the equipment and calculate an equivalent annual cost, which can then be apportioned across the number of uses per year. An equivalent annual cost can be calculated based on the purchase price, the lifespan of the equipment and the interest rate (for details of the calculation method, see Drummond *et al.* (2015)).[36] Maintenance costs can also be added to the equivalent annual cost and apportioned across the number of uses per year.

2.6.5 Analysing cost data

Once resource use has been quantified and valued, and any necessary adjustments to the cost data made, total costs can be calculated, in preparation for analysis. The nature of cost data can present particular issues for its analysis. Cost data are typically positively skewed, as costs are non-negative and some patients (with complications or requiring hospitalisation for example) incur very high costs. There may also be a few extreme outliers. However, the arithmetic mean cost is always the statistic of interest in economic evaluations, even if the data are not normally distributed.[69] Policy makers are concerned with the total cost of an intervention, and the impact on their budgets. It is the mean cost, combined with the total number of patients, which estimates the total cost. Analyses need to focus on mean costs but also take account of the distribution, as described next.

The costs of two interventions can be compared using hypothesis testing, (comparing the null hypothesis that there is no difference in costs between the groups, with an alternative hypothesis that there is a difference) or estimation, (estimating the mean cost difference between the groups and the associated confidence interval). Estimation is more useful since it provides information about the size of the effect and its uncertainty, as well as its

statistical significance.[36, 70] Many methods have been proposed for comparing the difference between two groups, Mihaylova *et al.* (2011) provides a comprehensive review of these methods.[71] Methods assuming that the data are normally distributed, such as ordinary least squares regression, have been shown to be robust to some skewness in the data and may well suffice, although extreme outliers may cause problems.[72] A log transformation may well reduce the skewness in the data, but log estimates are not of interest *per se*, and while estimates can be back transformed to the original scale, this is non-trivial.[73] While generalised linear models are a more complex approach, they focus on mean costs and are flexible.[74] Non-parametric bootstrapping is a popular method and can handle skewed data appropriately. Bootstrapping is a resampling procedure: the observed data are used as an empirical estimate of the unknown population, and are repeatedly sampled with replacement as though sampling from the population.[75] Parametric methods allow predictions to be made from the assumed model, which is not possible with non-parametric methods. To inform the choice of analysis method, it is vital that the data are carefully examined – in terms of their distribution and shape, and outliers – to determine what assumptions about the distribution can reasonably be made. Simple methods are preferred, applying the Central Limit Theorem is increasingly considered appropriate and sample means are assumed to follow a Normal distribution.

Missing cost data

Missing cost data are a common problem in economic evaluations using patient-level data, primarily because of the large number of variables being collected.[67] Data may be missing because patients were lost to follow up, or did not fully complete a questionnaire, or items on a CRF may not have been fully completed. A simple method of handling missing data is to only include patients with no missing data, known as complete case analysis. In a detailed study, there could easily be 100 variables included in the costing; even if only 1% of the data are missing, there might only be 50% of patients included in a complete case analysis. A lot of information would have been discarded, and mean costs would be

estimated with less precision than if this information had been used. Furthermore this would generate biased estimates of mean costs, if the likelihood of missing data depends on some of the covariates, for example if missing data are due to patients dropping out of a study and this appears to relate to a treatment group, perhaps due to unpleasant side-effects or lack of benefit from the treatment.

A more appropriate method for handling missing data is to use multiple imputation.[76] Multiple imputation uses regression to predict a number m of values for each missing data cell, and enables all variables used in the economic evaluation and demographic data (both complete and incomplete) to be used to predict the values of missing data cells. Recent guidelines recommend multiple imputation using a series of chained regression equations.[77] Rubin's Rule can then be used to summarise data across the m datasets.[78] This approach accounts for the variability both within and between imputed datasets and takes uncertainty in the estimated mean into account.

Published studies have tended to poorly report the level of missing data and methods used to handle it, and complete case analysis is still widely used.[79] Greater consideration of this issue in both the conduct and the reporting of economic evaluations would enable the risk of bias to be assessed.

2.7 Discussion and conclusion

This chapter has introduced economic evaluation and its use in healthcare decision-making. Cost-effectiveness and cost-utility analyses are the most common types of evaluation,[38] and cost-utility analyses will be seen in practice in Chapters 5 and 6. The empirical work in these chapters will use both frameworks described in this chapter. The CUA in Chapter 5 is conducted alongside an RCT, whereas the CUA in Chapter 6 uses decision-analytic modelling, combining a decision tree with a Markov model.

The second half of this chapter focussed on the cost component of an economic evaluation and the steps required to perform a costing study. As well as the costing components of the evaluations presented in Chapters 5 and 6, Chapters 4 and 7 are devoted to costing. Chapter 4 presents two micro-costing studies, which generate estimates of the costs of laboratory inputs into transfusion and the costs of administering transfusions. Chapter 7 compares alternative sources of resource use information on the same group of patients, and the effect this has on cost estimates.

The next chapter provides the clinical setting for the empirical research in later chapters, blood and transfusion in the context of cardiac surgery. The chapter also presents a literature review of the costs of blood transfusion to further place later empirical work into context.

Chapter 3: Transfusion practice and costs

3.1 Introduction

This chapter provides the clinical background for the thesis, and aims to describe blood transfusion and the importance of its costs. It begins with an introduction to blood, the supply of blood and the blood components that are used in transfusion. Cardiac surgery is then introduced, which is a high volume user of donor blood. There is evidence of wide variation in transfusion practice in cardiac surgery in the UK with many patients receiving inappropriate transfusions, in part due to a lack of evidence on the clinical and cost-effectiveness of alternative transfusion practices. To assess cost-effectiveness, information is required not only on the costs of blood components but also on the costs of giving blood safely to patients. This chapter therefore concludes by presenting a literature review of the costs of administering blood.

3.2 Blood and blood transfusions

As this thesis is largely about blood transfusion, blood is described in detail as it is key to interpreting the rest of the thesis.

3.2.1 Blood

Blood is made up of three main types of blood cells suspended in plasma: erythrocytes (RBCs), leukocytes (white blood cells), and thrombocytes (platelets). Plasma is mostly water, but also contains proteins, immunoglobulins (antibodies) and blood clotting factors. By volume, plasma makes up about 54% of whole blood, RBCs constitute about 45% and white cells (and platelets) about 0.7%. An average adult has approximately five litres of blood.

The primary function of RBCs is to transport oxygen around the body via a binding process between oxygen and a protein called haemoglobin. If patients lack RBCs or haemoglobin this can cause anaemia. In mild cases, this leads to feelings of tiredness and weakness, while in more severe cases this can lead to confusion and loss of consciousness, as well as adverse outcomes for surgical patients, for example the need for respiratory support.[80] RBCs are produced in the bone marrow in a process called erythropoiesis, and have a lifespan of 110-120 days.[6] The hormone erythropoietin stimulates the production of RBCs. This is produced by the kidney, hence renal failure can also contribute to anaemia.

White blood cells are part of the immune system and defend the body against bacterial or fungal infections. Their lifespan can range from a few days to a year. Patients with neutropenia (abnormally low levels of the most common type of white blood cells) are at risk of bacterial infection, and without the ability to fight the infection, can become seriously ill if not treated quickly.

Platelets have a critical role in stopping bleeding (alongside proteins and other clotting factors) through the formation of blood clots. If there are too few platelets in the blood, this can impair haemostasis and excessive bleeding may occur. If there are too many platelets, blood clots (thrombosis) can occur when there is no bleeding, causing blockages in blood vessels and in some cases causing a stroke, myocardial infarction or pulmonary embolism. Platelets have a lifespan of between four and nine days and low platelet counts can arise due to either overconsumption or underproduction. For example, if there is a significant decrease in platelet production in the bone marrow, patients will quickly become deficient in platelets, a condition known as thrombocytopenia. The short lifespan of platelets presents a constant challenge to transfusion services, since donated platelets have an equally short shelf life.

3.2.2 Blood groups

Identifying a patient's blood group is a key factor in safe transfusion practice. Blood groups (or types) are defined by the presence or absence of different proteins (antigens) on the surface of RBCs. Various systems of classification exist, but the most important are considered to be the ABO and Rhesus blood group systems. In the ABO system, there are four blood groups (A, B, AB, and O) defined by the presence or absence of two antigens, A and B. People in group A have the A antigen, those in group B have the B antigen, those in group AB have both antigens, and those in group O have neither antigen. Antibodies are produced by the immune system to recognise and attack 'foreign' antigens. People in group A have the A antigen, but consider the B antigen as foreign and may produce anti-B antibodies. Similarly those in group B may produce anti-A antibodies. People in group AB have both antigens and therefore make neither antibody, while those in group O have neither antigen so may produce both antibodies. Antibodies anti-A and anti-B are found in plasma and may respond to antigens A and B respectively; if blood from an incompatible group is transfused to a patient, RBCs will stick together in clumps and then haemolyse (rupture) resulting in an acute haemolytic transfusion reaction, which can be fatal if severe.[81]

In the Rhesus (Rh) group system, one antigen of interest is RhD: patients whose RBCs have this antigen are known as Rh positive and those without it are known as Rh negative. The anti-D antibody is not usually found in the plasma of a Rh negative person, unless they have been exposed to Rh positive blood, either by transfusion or in childbirth (if a Rh negative mother has a Rh positive child).

If a patient requires blood, it is important to ensure that they do not have antibodies in their plasma which will recognise antigens in the donor blood and cause a serious reaction. In the early experiments with transfusion in the 20th century, it was the transfusion of

incompatible blood which frequently resulted in post-transfusion reactions and death. Transfusion reactions are discussed in more detail later in this chapter.

3.2.3 Supply of blood

As described in Chapter 1, blood transfusions can be life-saving, are an effective treatment for anaemia and for complications of pregnancy and childbirth (particularly in developing countries), and have supported major advances in surgery where the risk of bleeding is substantial.[2] In order to meet the needs of patients requiring transfusion, a safe and sufficient supply of blood from donors is required. Globally, it is estimated that 103 million blood donations are collected annually.[82] In the UK, United States (US) and most developed countries, blood is donated by altruistic donors on a voluntary and unpaid basis. In developing countries, family/replacement donors are common: either family members donate specifically for their relative, or a family member or friend of the recipient donates blood to 'replace' what has been used. Alternatively donors may be paid. Given the consistently higher prevalence of transfusion-transmitted infections in blood from family/replacement and paid donors, the World Health Organization (WHO) has set a goal that all countries should obtain all their blood supplies from voluntary unpaid donors by 2020.[82] To minimise the risk of transmitting infections between donors and potential recipients, WHO also recommends that only volunteers who have a low risk of blood-borne infections should be allowed to donate, and all donations should routinely be screened for infections such as HIV, hepatitis B and C and syphilis.[82] Blood donations are screened for microbiological markers of infection (commonly antibody screening tests), and any that screen positive are discarded. It is a challenge to recruit and retain enough safe donors in the UK, as elsewhere in the world.

All blood donations are serologically tested to identify the important blood groups including ABO and Rh blood groups and are screened for significant RBC antibodies. Blood is then

processed into different components: RBCs, platelets, FFP and cryoprecipitate (derived from plasma), thus a single donation may be used to treat several different patients. An alternative to whole blood donation is to collect a specific blood component by a process called apheresis, in which blood from a donor is passed through a machine which collects one component and returns the rest of the blood to the donor. This allows more than one unit of a blood component to be collected from a donor, thus reducing the exposure of patients to multiple donors. Platelets are commonly collected this way in the UK.

3.2.4 Types of blood transfusion

Transfusions are given to correct a deficiency in the blood, either due to blood loss or the lack of a particular component. Transfusions of RBCs, platelets, FFP and cryoprecipitate are given for different purposes.

RBC transfusions are given to increase the supply of oxygen around the body in order to treat anaemia and heavy blood loss. For stable adults in hospital, a transfusion trigger of a haemoglobin (Hb) level of 7-8g/dl is considered acceptable and safe,[83] but is not the only important factor; consideration should also be given to whether the patient is symptomatic, has co-morbidities such as coronary disease,[84] whether the anaemia is chronic or acute, and whether there are alternatives to transfusion.[6]

Platelet transfusions are given to aid clotting, and to prevent or treat bleeding in patients with thrombocytopenia or leukaemia. If patients are bleeding heavily and lose a lot of blood, they may get dilutional thrombocytopenia, and require platelets. FFP is also given to aid clotting, generally for patients with severe blood loss from surgery, trauma or childbirth. Cryoprecipitate has fewer indications for treatment but is recommended when fibrinogen levels are critically low.[83] Coagulation factors (derived from plasma) are generally indicated for congenital deficiencies.

Blood for transfusion obtained from donors is known as allogeneic blood. Some patients undergoing elective treatment can receive autologous blood (their own blood back), by salvaging and recycling it during or after an operation (intra- or post-operative cell salvage). The risks of transfusion reactions (described next) are lower with autologous blood compared to allogeneic blood transfusion.

3.2.5 Adverse reactions related to transfusion

Blood transfusion is a common procedure, and while the risk of serious side-effects is low, it is not risk-free. Adverse reactions to transfusion can be divided into several classes: transfusion-transmitted infections, immunological complications of blood transfusion, and errors in the processing and safe administration of blood (for example incorrect patient identification, which can then lead to events such as haemolysis). While there is greater public awareness of the risk of viral or bacterial transfusion-transmitted infections, such as contracting HIV or hepatitis C, these are extremely rare events in developed countries. Perversely, immunological complications represent the vast majority of transfusion reactions reported to the UK Serious Hazards of Transfusion (SHOT) haemovigilance scheme. Acute immunological complications occur within 24 hours of transfusion, while delayed transfusion reactions occur 5-10 days after transfusion. Non-haemolytic febrile reactions, which cause a fever, are the most common (but not serious) complication.[6] The most frequent serious complications are acute allergic or febrile transfusion reactions and acute haemolytic reactions (often as a consequence of the immune system destroying transfused RBCs due to an ABO incompatible transfusion).[14] These complications may result in major morbidity (and potentially death) and may lead to intensive care admission, ventilation, acute renal failure or major haemorrhage due to transfusion-related coagulopathy;[6] these complications could therefore result in significant healthcare resource use.

Having introduced blood and blood transfusion, their use in a specific clinical area is considered.

3.3 Blood transfusion in cardiac surgery

This thesis focuses on blood use in cardiac surgery. Patients undergoing cardiac surgery are a vulnerable group with respect to transfusion, and may require RBCs, platelets or FFP. This section begins by introducing cardiac surgery, before describing the reasons for transfusion and current transfusion practice in this area.

3.3.1 Cardiac surgery

Over 36,000 cardiac surgical procedures were carried out in the UK in 2013/14.[85] Given the rising levels of obesity in the developed world, and the associated increased risk of coronary heart disease, the need for cardiac surgery may well increase in the future. Traditionally and still most frequently, cardiac surgery is performed by cutting open the chest and dividing the breast bone, a procedure known as open heart surgery. However, the two most common types of cardiac surgery – coronary artery bypass grafting (CABG) and valve repair or replacement surgery – can be performed as minimally invasive surgery through a small incision between the ribs. This greatly reduces surgical trauma and allows patients to recover more quickly.[86]

Cardiac surgery is often performed with the heart stopped using a heart-lung machine and cardiopulmonary bypass (CPB). CPB is used to divert deoxygenated blood returning to the heart to a pump oxygenator, which returns oxygenated blood directly to the aorta and pumps it round the body, thus bypassing the heart and lungs. The use of CPB allows surgeons to operate on a still and bloodless heart. However, CPB is associated with impaired haemostasis, due to changes in platelet function and coagulation, increasing the

risk of bleeding. Since CPB is not risk-free, some cardiac surgery is performed 'off-pump', although this is more technically demanding as the heart is still beating and moving.

There are different types of cardiac surgery, but the vast majority of procedures performed are CABG surgery or surgery on the heart valves. Over recent years (2004-2013) the proportion of all cardiac surgery involving valve repair or replacement has increased, with a corresponding fall in the proportion due to isolated CABG.[85] In 2013/14, isolated CABG comprised 49% of all cardiac surgery, while the proportion due to valve surgery (with or without CABG or other procedures) was 40%.[85]

CABG surgery is the most common surgical treatment for coronary heart disease, and is needed when one or more coronary arteries become narrow or blocked. CABG improves the blood supply to the cardiac muscle and relieves angina pain. It is usually performed as an open heart procedure in which a section of blood vessel is grafted between the aorta and the affected coronary artery beyond the obstruction in the artery, thus bypassing it and improving the blood supply to the heart. Where several blockages are present, double or triple grafts are performed, hence the terms double or triple heart bypass.

Valve surgery involves the repair or replacement of any of the four heart valves. Valves can become narrowed (stenosis) or leaky, which allows blood to flow backwards (regurgitation). Valves in the left side of the heart most frequently become defective, since the left side pumps blood all around the body and experiences greater pressure.

Data on every patient in the UK who undergoes heart surgery is collected as part of the National Adult Cardiac Surgery Audit (NACSA) and information from this audit is published in the Blue Book online (<http://bluebook.scts.org>).[85] In 2013/14, the average age of patients undergoing cardiac surgery was 67 years, and the majority of patients were male (72%). The overall in-hospital mortality rate for cardiac surgery was 2.7% but this varied

by procedure: the mortality rate for isolated CABG was 1.5%, whereas the mortality rate for combined mitral valve replacement and CABG was 10.3%.

This thesis focuses on costs, but outcomes are equally important, and work is underway to develop a core outcome set in cardiac surgery.[87, 88] The results of clinical trials and other research studies can be compared more easily, and potentially combined, if a common set of outcomes have been collected.

Cardiac surgery has always been a significant consumer of blood products.[86] Major advances in many surgical fields have been made possible due to transfusion, and this is particularly true of cardiac surgery, where developments have been highly dependent on transfusion.[86] The reasons for this are described next.

3.3.2 Transfusion practice in cardiac surgery

Post-operative haemorrhage is a common complication of heart surgery due to the surgical techniques used. Open heart surgery frequently involves a large chest incision, which contributes to bleeding and surgical trauma, and CPB is known to cause derangements in platelet function and coagulation causing haemostatic defects. Furthermore, patients may be on medication for heart disease (anti-platelet drugs) which contribute to abnormal blood clotting. A defect in the blood's ability to clot results in coagulopathy, and excessive bleeding may occur. Anaemia is also common after cardiac surgery. For these reasons, patients undergoing cardiac surgery are at risk of needing RBCs, platelets or FFP.

Cardiac surgery is a high volume user of donor blood, and is reported to use 6% of all RBCs, 12% of FFP and 17% of platelets in England and North Wales.[17, 18] Of all the surgical specialities, cardiac surgery uses the greatest number of RBCs.[18] While half of patients do not require a blood transfusion, a minority of patients (15-20%) consume more

than 80% of blood products transfused peri-operatively.[89] However, there is huge variation in practice internationally,[90, 91] and in the UK: Stover *et al.* (1998) reported that the percentage of CABG patients transfused ranged from 20-95% in UK cardiac surgery units.[92] This variation may have reduced over time but still remains high: a 2011 UK survey reported that 22-67% of CABG patients across different centres were transfused.[93] While RBC transfusion is vital for patients with life-threatening bleeding, many decisions to transfuse are based on a haemoglobin concentrate falling below a level which concerns a clinician.[94] This level varies between clinicians and across hospitals, contributing to the variation in RBC transfusion rates. Platelet and plasma transfusion rates also vary, ranging between 5-45% for CABG patients in the UK,[93] and varying even more widely in the US.[90] These variations cannot be explained by pre-operative patient characteristics or surgical factors such as length of time on CPB, and may instead be related to systematic differences in transfusion practice. For example, Stover *et al.* (1998) demonstrated that institution was a significant independent predictor of RBC transfusion risk in cardiac surgery,[92] while UK national and regional audits of transfusion practice against guidelines have consistently found evidence that 10-25% of blood products are transfused inappropriately.[5, 95, 96] Much of the variation is due to transfusions which are avoidable, but occur because there is a lack of high quality evidence on which to base transfusion decisions.[90] As well as a need for evidence on the clinical effectiveness of alternative transfusion practices, it is vital that the cost-effectiveness of alternative transfusion practices is assessed to ensure that best use is being made of NHS resources, including donor blood. To do this, information is needed on the costs associated with transfusion.

3.4 Costs associated with transfusion

Reliable estimates of the costs of transfusion are required to assess the costs and cost-effectiveness of alternative transfusion practices. Information is needed on the costs of

giving blood safely to patients, as well as the costs of the blood components, since blood administration involves a number of steps and resources. First, a blood sample needs to be taken and sent to the transfusion laboratory. Then the patient's blood group must be identified, and appropriate blood products matched for the patient and issued. These blood products then need to be transported to the patient and administered safely, and the patient must be monitored for any adverse events or transfusion reactions. To be able to issue products for patients in a timely manner, transfusion laboratories need to maintain a sufficient supply of blood products whilst minimising wastage. In England and North Wales, NHS Blood and Transplant (NHSBT) uses a detailed activity-based costing approach to determine the price of blood components (personal communication with Mick Burton, Divisional Finance Director, NHSBT, 25/09/2012). The National Commissioning Group for Blood formally reviews and agrees these prices each year. The prices set by NHSBT can be considered as reliable estimates of the costs of blood products since they are based on detailed data collection, however, there are no reliable regional or national estimates of the costs of giving blood safely to patients. This chapter therefore concludes with a literature review of the costs of administering blood.

3.4.1 Literature review of the costs of administering blood

A literature review was undertaken to identify references which report the costs of administering blood to establish what is known in this field, and to identify costs which can act as comparators to the micro-costing work presented in the next chapter. Papers were sought which used primary or secondary data to estimate the costs of administering blood in a developed country. Electronic search strategies were developed for two databases (Medline and Embase), combining terms for blood transfusion and cost, to search for potential studies which used primary or secondary data to estimate the costs of administering blood in a developed country. Searches were limited to references published from 2003 onwards to ensure results were relevant to current practice. A quality

assessment of included studies was conducted. Full details of the methods and results of the literature review are provided in **Appendices 1-5**. This section provides a short summary of the findings, and describes the studies most relevant to a UK setting.

The literature review identified 10 studies which estimated the costs associated with transfusion beyond the costs of the blood products themselves. Cost estimates were typically based on multi-centre prospective studies conducted from a healthcare perspective using a bottom-up costing approach, and captured transfusion laboratory inputs, blood administration at the patient's bedside, transfusion reactions, and sometimes the costs of conveying blood around the hospital. Estimates of costs associated with transfusion ranged from £48 to £482 per unit of RBCs transfused.

Three of the studies were conducted in the UK and each was of above-average quality (compared to all 10 included studies). These are therefore the most relevant studies from a UK perspective. Although only studies in developed countries were sought, given the number of steps involved in the transfusion process, there are likely to be differences in practice between countries. For example, the US has a formal consent procedure for blood transfusion which does not exist in the UK. There may also be differences in the type of staff responsible for different aspects of transfusion. Of the three UK studies, Varney and Guest took a top-down approach and therefore did not present disaggregated costs making it difficult to compare findings with current practice and other studies,[97] Agrawal *et al.* undertook primary data collection in the transfusion laboratory and on the ward to estimate the inputs associated with transfusion,[98] and the most recent study conducted as part of the NICE guidelines on blood transfusion updated the findings in Agrawal *et al.* using expert opinion and updated unit costs.[83] The evidence in the NICE guidelines on blood transfusion is therefore the most applicable to UK current practice. These guidelines report that the cost of RBC transfusion (excluding blood products) is £74 for the first unit and £48 for subsequent units (in 2015 prices). However, these estimates have a number of

limitations. First, although Agrawal *et al.* undertook data collection for each transfusion-related procedure in the transfusion laboratory and on the ward using a time-and-motion study, only five observations were recorded for each procedure. The variation between patients is unlikely to be captured in so few observations. Second, in the NICE guidelines, some of these time estimates were updated using expert opinion to reflect changes in practice in the last ten years. Ideally further primary data should be collected to more reliably estimate the time inputs to transfusion. Third, activities undertaken in the transfusion laboratory that do not result in transfusion were not considered, for example, blood products that are issued and returned unused to the laboratory. Fourth, the costs associated with blood bank machines and disposables were taken from Agrawal *et al.* for the NICE guidelines, but is it likely that these costs have changed significantly in the ten years since this study was conducted. Fifth, wastage figures were also based on Agrawal *et al.*, but more recent estimates of wastage are available.[99] Finally, although not necessarily a limitation, the cost estimates in the NICE guidelines do not allow for increased length of stay due to transfusion. This is difficult to estimate accurately (indeed appropriate transfusion may reduce length of stay); ideally length of stay (which is likely to be a key cost driver) would be collected on an individual patient basis within an economic evaluation and added separately to the costs of transfusion. In summary, although the cost estimates in the NICE guidelines are currently the most relevant estimates in a UK setting, there is significant scope to improve these estimates.

3.5 Conclusions

This chapter has provided the clinical background for the thesis – in terms of both blood transfusion and the use of blood in cardiac surgery – and highlighted the importance of estimating the costs associated with transfusion. Although a literature review found few estimates of the costs of administering blood, it is clear that these costs are considerable. Considering only the costs of blood components when costing transfusion would

significantly underestimate costs, and if these costs are then used in an economic evaluation this could bias the results in favour of the strategy with the greater blood use (by making that strategy appear less costly than it really is). In the extreme, this could result in misleading recommendations being made from cost-effectiveness studies. Given the uncertainty around the optimal use of blood (in many clinical specialties), and to ensure best use is made of this scarce resource, there is an urgent need for the cost-effectiveness as well as the clinical effectiveness of alternative transfusion practices to be assessed, which requires reliable estimates of the costs associated with transfusion. While the cost estimates generated in the NICE guidelines are the most relevant to current practice in the UK,[83] there is uncertainty surrounding some aspects of these estimates and their reliability could be greatly improved by some new primary data collection. The next chapter aims to produce reliable estimates of the costs of administering blood to patients, by undertaking two detailed costing studies of the transfusion laboratory inputs and nursing staff inputs into transfusion.

Chapter 4: The cost of administering blood

4.1 Introduction

As described in Chapter 3, the total costs of transfusion (administering blood) exceed the cost of the blood products themselves as purchased from a blood supplier, due to the hospital transfusion laboratory costs of storage and matching for patients, and for safe administration. However, accurate estimates of the costs of administering blood are not available. The best estimates from a UK perspective are based on just five observations at each of two hospitals (St Bartholomew's Hospital, London and Broomfield Hospital, Chelmsford) in 2004,[98] combined with expert opinion.[83] Clinical practice is likely to have evolved in the 12 years since the observations were collected. Furthermore, generating national cost estimates of administration on data from just two hospitals is not ideal. Recent detailed data on resource use associated with each aspect of administering blood have simply not been collected in the UK. It is not possible to determine whether best use is being made of blood components, a scarce resource derived from donations, if it is unclear how much transfusions actually cost.

More reliable estimates of the costs of transfusion would assist the clinical community in promoting more appropriate use of blood. One of the *Patient Blood Management* (PBM) recommendations in 2014 was that blood components should be transfused one unit at a time for patients who are not bleeding, and that patients should be reassessed to determine whether further transfusion was required.[100] Even though one of the aims of the PBM approach is to reduce healthcare costs, the financial consequences of recommendations such as the single unit transfusion policy can only be fully assessed if the total costs associated with transfusion are known.

Furthermore, to fully understand the financial impact of such transfusion policies, it is necessary to be able to separate out individual components of the costs of administering blood; it is possible that a transfusion policy might have different effects on different components of the costs. If the single unit transfusion policy is successful, then many patients will receive one rather than two units of blood, and the costs of all aspects of transfusion should decrease. If the policy is not successful, and frequently a second unit is still requested, this could actually increase the costs of transfusion. A second request for blood would need to be made by staff on the ward, and hospital transfusion laboratory staff would have to issue blood on two separate occasions (this is likely to be more time consuming than issuing two units at the same time). The (potentially different) impact of policy changes on the hospital transfusion laboratory and ward staff can only be assessed if detailed information is available on the components of the costs of transfusion.

More generally, more reliable estimates of the unit costs of transfusion would be useful inputs for many economic evaluations. Without reliable estimates of the costs of administering blood, it is likely that these costs will simply be excluded from economic evaluations of blood transfusion strategies or healthcare interventions where patients may be given blood. This is potentially problematic: if two or more interventions with different blood use are compared in an economic evaluation, a failure to fully account for the costs of transfusion would bias the cost results in favour of the intervention with the greater blood use (by making that strategy appear less costly than it really is), and might result in misleading recommendations on cost-effectiveness grounds being made. The aim of this chapter is to generate accurate estimates of the costs of administering transfusions, through detailed measurement and valuation of resource inputs. This chapter describes two detailed micro-costing studies (since this approach can generate more accurate costs in an economic evaluation context than a top-down approach),[65, 66] which estimate the costs of two inputs into transfusion: transfusion laboratory inputs and nursing staff inputs. The micro-costing study of laboratory inputs is described first.

4.2 Micro-costing study of laboratory inputs for grouping and issuing blood

4.2.1 Introduction

When transfusions are given, the blood of recipients and donors needs to be compatible to prevent serious and even fatal reactions. Hospital transfusion laboratories have four key functions:

- 1) To identify patients' blood group;
- 2) To identify and issue compatible blood products for patients;
- 3) To maintain and manage stocks of blood products to ensure they are available when required, including in emergencies;
- 4) To provide advice and support to clinical staff, particularly around appropriate ordering, adverse events and transfusion reactions.

For a patient who needs a transfusion, or might need a transfusion (for example a patient due to undergo surgery), a blood sample will be sent to the transfusion laboratory and analysed to identify the patient's blood group and whether they have any RBC antibodies. This process is termed a group and screen and is also done regularly by the transfusion laboratory for antenatal patients. If an antibody is detected in the screening process, its specificity needs to be determined to establish whether it is clinically significant, (this is done by testing a patient's plasma against an identification panel of reagent RBCs).

If a patient needs RBCs, then donor RBCs are selected for a patient based on their blood group and antibody status, and a compatibility test is performed to check that the donor's blood is compatible with that of the recipient, a process known as cross-matching. This can be done electronically if a patient has a negative antibody screen, otherwise a serological

cross-match is performed where drops of a patient's serum and donor RBCs are mixed together. Cross-matching is only required for RBCs, other blood products can be issued electronically, just based on a patient's blood group.

Transfusion laboratories need to balance maintaining a sufficient supply of blood products which might be required at some point, with minimising wastage of products (blood products have a limited shelf life). A large number of RBC units will be cross-matched and issued for patients about to undergo surgery but will not be required, approximately 50% of RBCs issued for patients are returned to the transfusion laboratory unused. This needs to be factored in to blood orders, and managing supply. Blood products also need to be stored appropriately; RBCs are kept in fridges at a constant temperature of 4°C, platelets are kept agitated in incubators at a constant temperature of 22°C, and FFP and cryoprecipitate are stored frozen, and require thawing before issue.

Clearly there are costs associated with group and screens, cross-matching and issuing, and storing and maintaining a sufficient supply of blood products. The costs of these activities are rarely identified or included within economic evaluations: perhaps because costs are thought to be small (even though they may be frequently incurred) and unit costs are not readily available. This micro-costing study aims to generate accurate estimates of the costs of transfusion laboratory inputs associated with administering transfusions of blood products.

4.2.2 Methods

The collection of cost data can be undertaken to different levels of precision, the most precise being micro-costing (or bottom-up costing), which requires the measurement of all individual components of resource use.[36] A micro-costing study was undertaken to estimate the laboratory inputs for grouping and issuing blood, in terms of the staff time,

consumables and equipment costs associated with these activities at two hospitals. Transfusion laboratories with managers and staff willing to take part were sought from the South Central region to enable regular site visits to take place more easily. The study was undertaken in the transfusion laboratories of one teaching hospital (the John Radcliffe Hospital, Oxford University Hospitals (OUH) NHS Foundation Trust, Oxford) and one district general hospital (Royal Berkshire Hospital, Royal Berkshire NHS Foundation Trust, Reading).

The transfusion laboratory at Oxford is staffed by one laboratory manager, 3.2 whole-time equivalent (WTE) senior biomedical scientists (BMS), four BMS and one Senior Assistant Technical Officer (SATO). There are less staff in the transfusion laboratory at Reading: one laboratory manager, two WTE senior BMS, two BMS and one SATO. The antibody screen in Oxford is undertaken by a solid phase screen (Immucor Capture R technology) and an immediate spin microplate technique is used for ABO grouping. Both antibody screens and ABO grouping are performed by column technology from BioRad (DiaMed) at Reading.

There were three elements to data collection: quantifying the direct inputs into transfusion related activities, quantifying the indirect staff time associated with transfusion related activities, and a questionnaire to capture the capital equipment used by the transfusion laboratory, and also the annual activity of the laboratory over which indirect staff time and capital equipment could be apportioned. All data collection forms were developed in close consultation with transfusion laboratory staff, and were piloted before introduction. Data collection forms were completed by transfusion laboratory staff. Data collection was undertaken between February and July 2013 at Oxford, and between May and December 2013 at Reading.

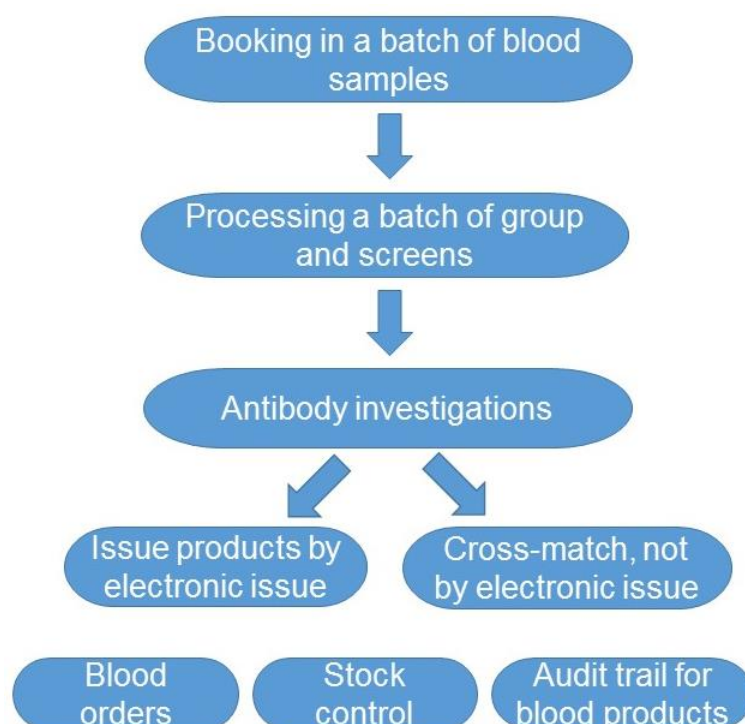
This study was reviewed and approved by the University of Oxford Central University Research Ethics Committee, and by OUH NHS Foundation Trust and Royal Berkshire NHS

Foundation Trust. All staff in each transfusion laboratory were sent a letter inviting them to take part in the study. The letter contained each member of staff's 'unique number'; they were asked to use this on data collection forms so that it was possible to determine that a number of different staff members had completed forms, without using names. Also enclosed was an information sheet, consent forms and copies of the data collection forms. Staff who were willing to take part were asked to sign the consent form, and place the form in the data collection box in the transfusion laboratory.

Direct inputs into transfusion related activities

Data collection forms were developed for each of the different laboratory inputs into transfusion shown in **Figure 4.1**. Data collection forms can be found in **Appendix 6**. There were small differences between the two sets of data collection forms to reflect the slightly different practices at each hospital. For Oxford, seven data collection forms were developed, which each covered a different step in the transfusion process. For Reading, eight data collection forms were developed from the forms designed for Oxford. There was no form associated with blood ordering at Oxford, because blood products were automatically replenished by NHSBT as part of a pilot project looking at stock management, so the laboratory does not spend time ordering or booking in arrivals. An audit was done by transfusion laboratory staff before this system was introduced; on average they spent six minutes three times a day ordering blood products, and 48 minutes per day receiving and booking in blood products. Since automatic replenishment was atypical for transfusion laboratories, these previous time estimates were used to incorporate the time associated with blood orders into the Oxford costs so that results reflect practice more generally, and for direct comparison with Reading.

Figure 4.1: Direct inputs into transfusion



The forms were designed to capture the staff time and, where necessary, the consumables associated with a step in the transfusion process. BMS and other staff who work in the transfusion laboratory (such as SATOs) were asked to complete a form each time they undertook the activities summarised in **Figure 4.1**. Some activities were captured for a group of patients if this is what happened in practice, for example a number of blood samples would be booked in together, and batches of group and screen tests would be done on the analyser at the same time; other activities tended to be recorded for one patient at a time, for example antibody investigations and issuing products. Each process was split into a series of individual tasks. Only staff time that was spent directly related to the process was captured, for example the time taken to set the analysers running was captured but not the time taken for them to run, since staff were undertaking other activities during this time. For processes where the consumables required were standard (based on information provided by the transfusion laboratory managers), this information was not collected on the form, but these items were costed.

Indirect staff time associated with transfusion related activities

While non-senior staff spend all their time on the activities summarised in **Figure 4.1**, senior BMS spend a significant amount of time on non-bench activities such as training, stock issues, supply and reagent issues and validation of new equipment. This is vital to the running of the transfusion laboratory, so this indirect time needs to be taken into account when costing laboratory inputs into transfusion. Senior BMS and the transfusion laboratory managers at each hospital were asked to complete an additional data collection form capturing time spent on bench and non-bench activities for a week (see **Appendix 7** for data collection forms).

Costing questionnaire

A questionnaire on the capital equipment and activity of the transfusion laboratory was also completed by each transfusion laboratory manager. For items of equipment which were owned, this captured the cost, year purchased and anticipated lifespan of the item, and any maintenance costs. For items that were leased, the annual lease and maintenance costs were captured. In terms of activity, the number of group and screens done for transfusion and antenatal purposes were recorded as well as the number of electronic and non-electronic cross-matches. In terms of the blood products themselves, the number of units of RBCs, platelets and frozen products (FFP and cryoprecipitate) received from the stock holding unit, issued, and transfused were recorded. This questionnaire can be found in **Appendix 8**.

Data analysis

The data collected on the direct inputs into transfusion (**Figure 4.1**) were entered into Microsoft Excel 2013.[101] Missing data on the forms were summarised and explored. Given the number of variables being collected, even small amounts of missing data would likely result in large amounts of information being discarded if a complete case analysis

was undertaken, which would be very inefficient. Imputation methods were therefore required to handle missing data and allow all available data to be used; mean imputation was used. It is recognised that mean imputation is not recommended for handling missing data in economic evaluations, multiple imputation methods are preferred.[76, 77, 102, 103] However, there were very few variables which could have been included in regression equations (staff identifier and other times) and these were not anticipated to be good predictors of the missing times, and therefore multiple imputation methods were not considered appropriate. Uncertainty around time estimates will have been underestimated with mean imputation, but since the aim is to estimate mean unit costs, this is less of an issue here than when presenting the results of an economic evaluation.

For each of the direct inputs into transfusion, the mean staff time associated with each process was calculated. Where times were recorded for more than one sample, the total time was divided by the number in the batch, to calculate the time per sample. This direct staff time was costed at a Band 6. Where applicable, consumables were costed and the mean cost of consumables for that form calculated. Data from the forms completed by the Senior BMS and the transfusion laboratory managers on indirect time were summarised into the total time per day spent on bench and non-bench activities, and the average percentage of time spent on non-bench activities calculated. Indirect time associated with Senior BMS and transfusion laboratory managers were costed at Bands 7 and 8a respectively. The cost of this time was then apportioned across the total activity of the transfusion laboratory (defined as the sum of the total number of groups and screens and units of blood issued). For each item of equipment reported on the capital questionnaire, the equivalent annual cost was calculated, based on the purchase price (inflated to current prices), the estimated lifespan of the equipment and a discount rate of 3.5%,[68] and maintenance costs if applicable. This cost was then apportioned over the total number of uses of the equipment per year. Information technology (IT) equipment was apportioned

across the total activity of the transfusion laboratory. Analysis of the data collected was conducted in Microsoft Excel 2013.

Unit costs were sought to value resource use. To cost staff time, mid-points of salary ranges for each Band were taken from Agenda for Change salary scales for England from April 2014.[104] In order to calculate an hourly rate, staff were assumed to work 42 weeks per year, and 37.5 hours per week (this incorporates annual leave, sickness and study days).[105] Staff salaries were inflated by 20% to incorporate National Insurance and Superannuation. Consumable costs and the costs of capital equipment were obtained from the transfusion laboratories, and where necessary were inflated to 2014/15 prices using the Hospital and Community Health Services (HCHS) inflation index.[105, 106] Value added tax at 20% was included in all cost estimates. Overheads were also included, calculated at 20% of the cost per activity. Costs are presented in 2014/15 prices.

The data collected were used to generate cost estimates of various activities of the transfusion laboratories. Some patients just require a group and screen, but never need blood. Others have a group and screen and blood issued; for some this is not required, but for others this is transfused. Costs associated with these three scenarios were generated: the cost per group and screen, the cost per unit issued and the cost per unit transfused. For the costs associated with issuing and transfusing blood, this was done separately for RBCs (which require cross-matching) and non-RBCs (platelets, FFP and cryoprecipitate, which do not require cross-matching). Unit cost estimates were generated separately for Oxford and Reading and then an average of the two costs calculated. This unweighted average cost does not therefore reflect the different levels of activity at each hospital, but with only two sites and two costs to weight, it is not clear that this would have produced costs that are more reflective of the national picture.

The cost per group and screen incorporated the costs of the direct inputs of staff time, consumables and equipment, the indirect inputs of senior staff time and IT equipment, and overheads. The costs per unit issued were calculated in the same way but included additional indirect costs. Blood products cannot be issued unless the transfusion laboratory maintains a supply of them. The indirect costs of ordering blood products, managing the stock and keeping track of blood products were therefore included in the cost per issue; these activities have been apportioned across all blood products issued. For the cost per RBC unit cross-match and issue, the capital costs associated with storing RBCs were included, apportioned across all RBCs issued. Similarly for the cost per non-RBC unit issued, the costs of storing these products were included.

The costs per unit transfused incorporate the costs of group and screens and issuing products. For every unit of blood transfused, on average more than one group and screen has been performed and more than one unit of blood has been issued, since for some patients a group and screen is performed but blood is never requested, and for others blood is requested but is returned unused to the transfusion laboratory. Clearly group and screens and issues that do not result in transfusion still incur costs to the transfusion laboratory. To ensure that all the costs of the transfusion laboratory were incorporated into the costs associated with transfusion the average number of group and screens and units issued per unit transfused were calculated for Oxford and Reading, and incorporated into the cost per unit transfused. This was done separately for RBCs and non-RBCs.

4.2.3 Results

A total of 148 data collection forms of direct inputs into transfusion practice were completed at Oxford, along with 11 forms capturing Senior BMS time on bench and non-bench related activity. At Reading, the corresponding numbers were 62 and 9 respectively. These 232 forms were completed by 28 staff members at Oxford and 16 staff members at Reading.

The capital questionnaire was completed at both hospitals by the transfusion laboratory managers; all information requested was provided with one exception for both hospitals, it was not possible to obtain estimates of the running costs and overheads for either transfusion laboratory.

Missing data on data collection forms were summarised. There were no missing times on the forms collecting information on the audit trail of blood products (Forms 7 and 8 at Oxford and Reading respectively), and no missing data on the forms capturing the Senior BMS time on bench and non-bench related activity. At Oxford, the staff time on four of the 143 Forms 1-6 on the direct inputs into transfusion were unusable (times not meaningfully completed), and 13% of the times on the remaining forms were missing and needed to be imputed. The largest amount of missing data was on Form 6 (41%), which captured the time to process and store returns of blood from three locations; staff completed this form when returns came from any location, but as they did not necessarily all come at the same time of day, times for other locations were frequently missing. At Reading, none of Forms 1-7 were completely unusable, and overall 18% of times were missing and needed to be imputed. The largest amounts of missing data were on Form 1 (24%) where times had started to be recorded on six forms but were not completed, and on Form 7 (42%), which captured the time associated with ordering blood products at several times in a day, and tended not to be completed for all the time points. In eyeballing the data, there was nothing to suggest that forms with missing data were very different to forms with complete data; staff may just have forgotten to complete forms, particularly after interruptions (commonplace in the laboratory) or when tasks are not done all in one go. Consumables were recorded on Form 3 only at Oxford, and this section was completed on 7/24 (29%) forms. Consumables were captured on Forms 2, 4 and 5 at Reading, and were recorded for 9/11 (82%), 1/2 (50%), and 1/1 (100%) forms respectively. Consumables left blank were assumed not to have been used, so no information on consumables was imputed.

Tables 4.1 and **4.2** summarise the findings from the data collection forms of direct inputs into transfusion practice. The average staff time associated with each direct input is presented along with the costs of the staff time and consumables. Results are broadly similar at the two transfusion laboratories. It takes just three to four minutes per sample to book in and process a group and screen, and three minutes to electronically issue a blood product. Serological cross-matching takes nine or ten minutes, and antibody investigations considerably longer, on average 32 minutes at Oxford and 19 minutes at Reading.

Figures 4.2 and **4.3** summarise the activities of the transfusion laboratories in terms of the number of group and screens performed, and the blood products that were managed, for the most recent year at the time of data collection (data captured on the costing questionnaire) and for 2014/15 (data subsequently provided by the transfusion laboratory managers). A greater proportion of group and screens are done for transfusion in Oxford compared to Reading. The number of group and screens performed for transfusion has increased a little since the time of data collection. **Figure 4.3** shows the number of units of blood products received from the stock holding unit, the number of units issued, and the number of units transfused; all of which have reduced since the time of data collection. The number of RBC units issued has fallen by more than 20% at each hospital. The analyses that follow are based on the activity data for 2014/15.

Table 4.1: Staff time and the costs of staff time and consumables associated with direct laboratory inputs into transfusion, Oxford

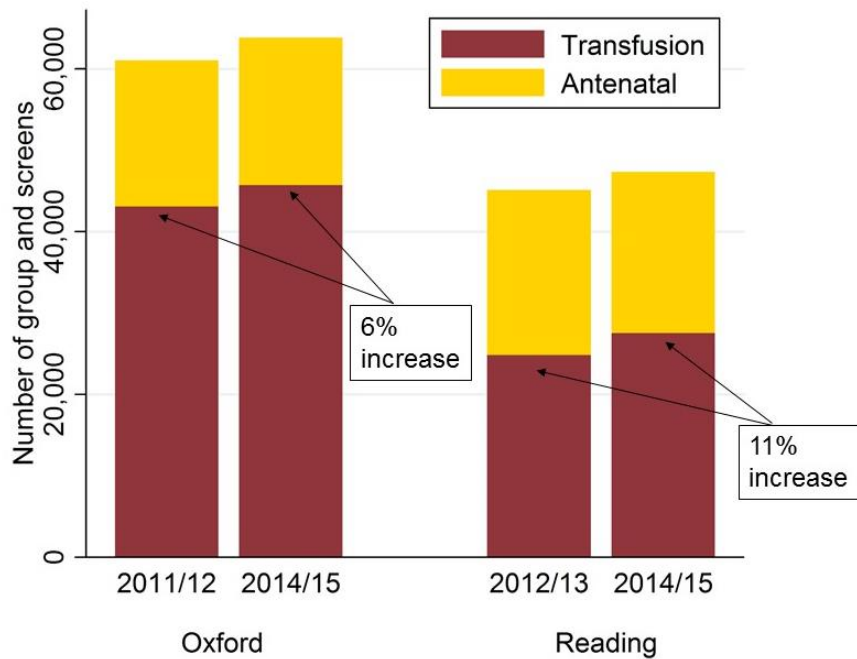
Form	Number of forms completed	Mean (standard deviation) staff time (minutes)	Cost of staff time (£)	Cost of consumables (£)
1 Booking in a batch of blood samples	20	Per sample 1.7 (0.5)	0.65	0
2 Processing a batch of group and screens	25	Per patient 1.9 (0.7)	0.73	2.35
3 Antibody investigations	24	Per patient 32.0 (18.3)	12.25	12.27
4 Issue products by electronic issue	25	Per product issued 3.2 (1.6)	1.23	0
5 Cross-match, not by electronic issue	26	Per product issued 9.6 (6.3)	3.68	0.47
6 Stock control	23	Per day 52 (19.4)	19.91	0
7 Audit trail for blood products	5	Per unit transfused 0.34 (0.18)	0.13	0

Table 4.2: Staff time and the costs of staff time and consumables associated with direct laboratory inputs into transfusion, Reading

Form	Number of forms completed	Mean (standard deviation) staff time (minutes)	Cost of staff time (£)	Cost of consumables (£)
1 Booking in a batch of blood samples and processing the group and screens	20	Per sample 2.6 (1.1)	1.00	2.24
2 Antibody investigations	11	Per patient 19.0 (12.9)	7.28	11.30
3 Issue products by electronic issue	18	Per product issued 2.8 (0.7)	1.07	0
4 Automated cross-match	2	Per product issued 9.3 (0.4)	3.56	1.80
5 Manual cross-match	1	Per product issued 15.0*	5.74	2.67
6 Stock control	3	Per day 57.7 (16.0)	22.10	0
7 Blood orders	2	Per day 40.5 (4.9)	15.51	0
8 Audit trail for blood products	5	Per day 9.4 (3.4)	3.60	0

* No standard deviation reported since only one form completed.

Figure 4.2: Number of group and screens performed at each hospital



Group and screens are performed during pregnancy to provide a record of a mother's grouping in case blood is required for maternal transfusion (due to blood loss), and to check for any new antibodies (for example due to mismatches with paternal derived antigens on red blood cells).

Figure 4.3: Number of units of blood products managed at each hospital



Key: Rec, Received; Iss, Issued; Tra, Transfused

Based on 2014/15 data, the vast majority of cross-matches (for RBC issue) were performed electronically (92% at Oxford and 94% at Reading). On average 1.4 and 3.1 group and screens were performed per unit of blood transfused at Oxford and Reading respectively (only taking into account group and screens performed for transfusion). For every unit of RBCs transfused, on average 1.4 cross-matches were performed at Oxford and 1.3 at Reading.

Analysis of the 20 daily records of time spent on bench and non-bench activities by the transfusion laboratory managers and senior staff showed that on average the laboratory managers at Oxford and Reading spent 100% and 98% of their time on non-bench work, and the senior staff spent 66% and 13% of their time on non-bench work respectively. Apportioning 100% of the salary costs for the laboratory manager, and 66% of the salary costs for 3.2 WTE Senior BMS across the total activity of the transfusion laboratory added an additional £1.30 to the cost of each activity at Oxford. Apportioning 98% of the salary costs for the laboratory manager, and 13% of two WTE Senior BMS across the total activity at Reading added an additional £1.05 to the cost of each activity.

Cost per group and screen

The costs per group and screen are presented in **Table 4.3**. This incorporates the direct inputs of booking in a blood sample, and processing the group and screen (the direct inputs listed relate to the data collection forms, see **Appendix 6**). Costs of equipment are also included, a blood grouper and a centrifuge are required for processing a group and screen. On average 8% of patients at Oxford and 4% of patients at Reading require antibody investigations; 8% and 4% respectively of the staff and consumable costs associated with antibody investigations are therefore also included, as well as the costs of equipment. The cost per group and screen including overheads is estimated to be £9.94 at Oxford and £6.86 at Reading, giving an average cost across the two hospitals of £8.40. Each of the cost categories (equipment, consumables and staff) is higher at Oxford than Reading.

Table 4.3: Cost per group and screen at each transfusion laboratory

Inputs		Cost category			Total
		Equipment	Consumables	Staff	
Oxford	Book in sample	£0.00	£0.00	£0.65	£0.65
	Process group & screen (G&S)	£0.96	£2.37	£0.73	£4.06
	Antibody investigations	£0.08	£0.98	£0.98	£2.04
	Indirect inputs*	£0.23	£0.00	£1.30	£1.53
	Total (before overheads)	£1.27	£3.35	£3.66	£8.28
	TOTAL (including overheads)^	-	-	-	£9.94
Reading	Book in sample, process G&S	£0.46	£2.24	£1.00	£3.69
	Antibody investigations	£0.00	£0.45	£0.29	£0.74
	Indirect inputs*	£0.23	£0.00	£1.05	£1.28
	Total (before overheads)	£0.68	£2.69	£2.34	£5.72
	TOTAL (including overheads)^	-	-	-	£6.86
Average	TOTAL (including overheads)^	£1.17	£3.62	£3.60	£8.40

* Indirect inputs include senior staff time and IT equipment.

^ Overheads were calculated as 20% of the cost per activity.

Cost per RBC cross-match and issue

The costs per RBC cross-match and issue are presented in **Table 4.4**. Cross-matching can be conducted electronically if a patient does not have significant RBC antibodies, otherwise a serological cross-match needs to be performed; at Oxford this is done manually, Reading uses an automated process. (A data collection form for manual cross-matching was included for Reading, but this is only done very occasionally; inputs were estimated for one manual cross-match but this was done for the purpose of data collection rather than as per usual practice, manual cross-matching was therefore not used in the costing calculations for Reading). The direct inputs for cross-matching were weighted according to the annual activity of each type of cross-match: electronic or manual/automated cross-matching. For Oxford, 92% of cross-matches were performed electronically and 8% manually, for Reading 94% were performed electronically and 6% were automated.

The cost per cross-match and issue including overheads is estimated to be £8.69 at Oxford and £7.45 at Reading, giving an average of £8.07. The difference between the hospitals is largely driven by higher costs associated with storing RBCs at Oxford.

Table 4.4: Cost per RBC cross-match and issue at each transfusion laboratory

Inputs		Cost category			Total
		Equipment	Consumables	Staff	
Oxford	Electronic cross-match	£0.00	£0.00	£1.13	£1.13
	Manual cross-match	£0.08	£0.04	£0.29	£0.41
	Indirect inputs*	£3.95	£0.00	£1.75	£5.70
	Total (before overheads)	£4.03	£0.04	£3.17	£7.24
	TOTAL (including overheads)^	-	-	-	£8.69
Reading	Electronic cross-match	£0.00	£0.00	£1.01	£1.01
	Automated cross-match	£0.03	£0.11	£0.21	£0.35
	Indirect inputs*	£2.48	£0.00	£2.37	£4.86
	Total (before overheads)	£2.51	£0.11	£3.59	£6.21
	TOTAL (including overheads)^	-	-	-	£7.45
Average	TOTAL (including overheads)^	£3.92	£0.09	£4.06	£8.07

* Indirect inputs include senior staff time, IT equipment and maintaining a supply of blood products.

^ Overheads were calculated as 20% of the cost per activity.

Cost per non-RBC issue

The costs per non-RBC issue are presented in **Table 4.5**. Non-RBCs are issued electronically, and cross-matching is not required. Frozen products need to be thawed before issue. The cost per non-RBC unit issued including overheads is estimated to be £7.95 at Oxford and £8.56 at Reading, giving an average of £8.26.

Table 4.5: Cost per non-RBC issue at each transfusion laboratory

Inputs		Cost category			Total
		Equipment	Consumables	Staff	
Oxford	Electronic issue	£0.44	£0.00	£1.23	£1.67
	Indirect inputs*	£3.21	£0.00	£1.75	£4.96
	Total (before overheads)	£3.65	£0.00	£2.97	£6.62
	TOTAL (including overheads)^	-	-	-	£7.95
Reading	Electronic issue	£0.28	£0.00	£1.07	£1.35
	Indirect inputs*	£3.41	£0.00	£2.37	£5.78
	Total (before overheads)	£3.69	£0.00	£3.44	£7.13
	TOTAL (including overheads)^	-	-	-	£8.56
Average	TOTAL (including overheads)^	£4.40	£0.00	£3.85	£8.26

* Indirect inputs include senior staff time, IT equipment and maintaining a supply of blood products.

^ Overheads were calculated as 20% of the cost per activity.

Cost per RBC unit transfused

For every unit of blood transfused, on average 1.4 and 3.1 group and screens are performed, and for every unit of RBCs transfused on average 1.4 and 1.3 cross-matches are conducted at Oxford and Reading respectively (based on the activity of the transfusion laboratories in 2014/15 presented in **Figures 4.2** and **4.3**). These are factored into the cost per RBC unit transfused.

The estimated costs per RBC unit transfused are presented in **Table 4.6**. The direct costs associated with groups and screens, and cross-matches are taken from **Tables 4.3** and **4.4** above. The indirect costs are here apportioned over the total number of units transfused, rather than the number of units issued. The cost of laboratory inputs per unit of RBCs transfused is estimated to be £26.22 at Oxford and £30.90 at Reading, and on average £28.56.

Table 4.6: Cost per RBC unit transfused at each transfusion laboratory

Inputs		Cost category			Total
		Equipment	Consumables	Staff	
Oxford	Group and screen	£1.46	£4.69	£3.30	£9.45
	Cross-match	£0.11	£0.05	£1.99	£2.16
	Indirect inputs*	£5.99	£0.00	£4.26	£10.25
	Total (before overheads)	£7.56	£4.74	£9.55	£21.85
	TOTAL (including overheads)^	-	-	-	£26.22
Reading	Group and screen	£1.42	£8.35	£3.99	£13.76
	Cross-match	£0.03	£0.14	£1.59	£1.76
	Indirect inputs*	£3.93	£0.00	£6.30	£10.23
	Total (before overheads)	£5.38	£8.49	£11.88	£25.75
	TOTAL (including overheads)^	-	-	-	£30.90
Average	TOTAL (including overheads)^	£7.76	£7.94	£12.86	£28.56

* Indirect inputs include senior staff time, IT equipment and maintaining a supply of blood products.

^ Overheads were calculated as 20% of the cost per activity.

Cost per non-RBC unit transfused

For every unit of non-RBCs transfused, on average 1.2 and 1.1 units are issued at Oxford and Reading respectively. The estimated costs per non-RBC unit transfused are presented in **Table 4.7**. The cost of laboratory inputs per unit of non-RBCs transfused is estimated to be £23.51 at Oxford and £31.04 at Reading, and on average £27.28. As for RBC transfusions, it is the higher costs associated with a greater number of group and screens that makes Reading more expensive than Oxford.

Table 4.7: Cost per non-RBC unit transfused at each transfusion laboratory

Inputs		Cost category			Total
		Equipment	Consumables	Staff	
Oxford	Group and screen	£1.46	£4.69	£3.30	£9.45
	Electronic issue	£0.53	£0.00	£1.47	£2.00
	Indirect inputs*	£4.14	£0.00	£4.00	£8.14
	Total (before overheads)	£6.13	£4.69	£8.77	£19.59
	TOTAL (including overheads)^	-	-	-	£23.51
Reading	Group and screen	£1.42	£8.35	£3.99	£13.76
	Electronic issue	£0.31	£0.00	£1.18	£1.49
	Indirect inputs*	£4.53	£0.00	£6.09	£10.63
	Total (before overheads)	£6.26	£8.35	£11.26	£25.87
	TOTAL (including overheads)^	-	-	-	£31.04
Average	TOTAL (including overheads)^	£7.43	£7.82	£12.02	£27.28

* Indirect inputs include senior staff time, IT equipment and maintaining a supply of blood products.

^ Overheads were calculated as 20% of the cost per activity.

Summary of results

Table 4.8 summarises the cost estimates generated in the previous sections, based on activity data for 2014/15. Earlier in the chapter the latest activity data at the time of data collection were presented as well as 2014/15 data (**Figures 4.2 and 4.3**). The number of group and screens has increased slightly over this time, while the number of units managed has fallen, most significantly for RBC issues. Also included in **Table 4.8** are cost estimates based on activity at the time of data collection, to investigate whether the different levels of activity result in different cost estimates. All costs are presented in 2014/15 prices, so the differences all relate to differences in activity. Costs at the time of data collection and for 2014/15 are generally similar at each hospital. The largest difference is at Reading for the cost per unit transfused (for RBCs and non-RBCs), where, on average, 2.0 and 3.1 group and screens were performed per unit transfused in 2012/13 and 2014/15 respectively; the higher costs per unit transfused in 2014/15 are therefore largely attributable to the costs of an additional group and screen.

Table 4.8: Estimates of the costs of transfusion laboratory inputs based on activity at the time of data collection and 2014/15 activity

Activity	Oxford		Reading	
	2011/12	2014/15	2012/13	2014/15
Group and screen	£9.84	£9.94	£6.82	£6.86
RBC cross-match and issue	£8.01	£8.69	£6.19	£7.45
Non-RBC issue	£7.46	£7.95	£8.11	£8.56
RBC unit transfused	£25.18	£26.22	£21.24	£30.90
Non-RBC unit transfused	£20.32	£23.51	£23.03	£31.04

RBC, Red blood cell

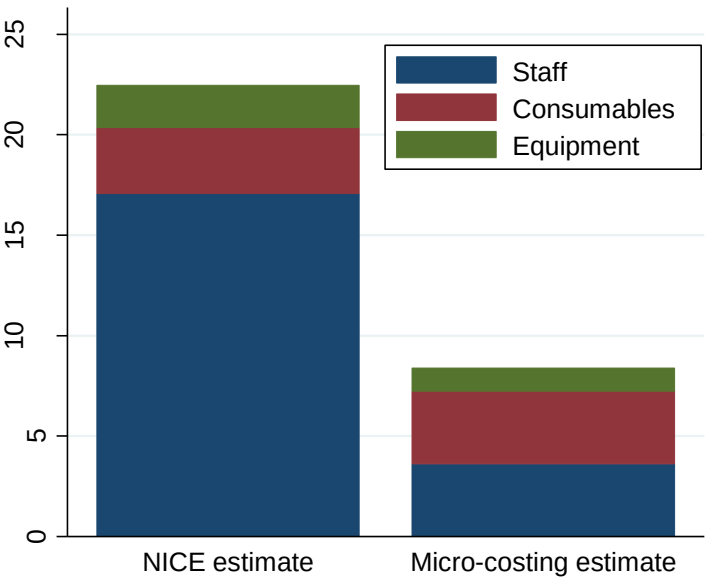
4.2.4 Discussion

This micro-costing study has estimated the cost of a group and screen, the cost per RBC and non-RBC unit issued and the cost of laboratory inputs per RBC and non-RBC unit transfused at two hospitals. Data collection was much more extensive than any previous UK study, a total of 232 data collection forms were completed by more than 40 different staff members. As described in Chapter 3, there has been little research into the costs of laboratory inputs into transfusion, recent NICE clinical guidelines on blood transfusion drew on the best evidence that is available (see **Section 3.4.1**) as inputs for their cost-effectiveness decision modelling.[83] It is helpful to compare the cost estimates for a group and screen and for laboratory inputs into administering RBCs that were used in that model with the findings of this study; NICE guidelines did not consider the costs of administering non-RBCs. Estimates from the NICE guidelines reported below have been inflated to 2014/15 prices using the hospital and community health services index,[63] so that direct comparisons can be made.

The estimated cost of a group and screen here (£8.40 on average across the estimates for Oxford and Reading) was considerably lower than the cost estimate of £22.46 in the NICE clinical guidelines on blood transfusion,[83] as shown in **Figure 4.4**. While the consumable and equipment costs are not dissimilar to those presented here, the difference lies in the staff cost, both in terms of the amount of time (21.35 minutes) and the unit cost used to

value the staff time (a band 6/7 at £48 per hour). The direct staff time associated with a group and screen was estimated to be 6.2 minutes at Oxford and 3.4 minutes at Reading, this was costed at a Band 6 (£23 per hour) with 20% added for overheads (indirect senior staff time was also added but this equated to just a couple of minutes). The direct staff time estimate generated here was based on more than 30 estimates of all the component parts of a group and screen (from more than 100 data collection forms). This is three times more observations than the NICE estimates were based on, which were also nine years older; the estimate of staff time generated here is therefore considered more reliable than that used in the NICE estimates. It was not possible to compare what was included in the unit costs used to value staff time, the reference to this in the NICE estimates was not sufficiently detailed to identify the exact source within the publication. Given the lower staff costs here, consumable (and equipment) costs make up a greater proportion of the total costs compared to the NICE estimate.

Figure 4.4: Comparing cost estimates for transfusion laboratory inputs into a group and screen (in 2014/15 prices)



In terms of issuing RBCs, the staff time for processing a blood order and computer issue was estimated to be 6.4 minutes in the NICE guidelines, with an associated cost of £5.12.

While lower direct staff time estimates and unit costs were reported here, when the costs of indirect staff time, and consumables and equipment, (notably the costs of the storage of RBCs) were added, the estimated costs per RBC unit issued were higher than in the NICE guidelines (on average £8.07).

The estimated cost associated with transfusion laboratory inputs for a RBC transfusion in the NICE guidelines was the cost of a group and screen added to the cost of an issue (£27.59), and for subsequent units was the cost of the issue with additional elements for consumables and equipment (£10.53). The equivalent estimate generated here was £28.56 for each unit (whether first or subsequent). Given the much higher time estimates and unit costs used in the NICE estimates for group and screens, the figure for the first unit is more similar than might be expected. In the micro-costing estimates generated here, the costs of more than one group and screen and more than one issue were incorporated into the costs of transfusion to account for the greater number of both group and screens and issues, than units transfused. Only by incorporating this activity that does not lead to transfusion will all the costs of the transfusion laboratory be factored into the costs per transfusion, this is why the costs for first and subsequent units are the same. There is a legitimate concern that if these estimates are used to cost resource use for patient X in an economic evaluation, it is possible that patient X only had one group and screen and one issue, and therefore that the costs of laboratory inputs into transfusion are overestimated for that patient. However, unless this is the particular focus of a study, it is unlikely that the number of group and screens and units issued will be captured for a patient. On balance, it is more important to ensure that all the costs of the transfusion laboratory are accounted for.

Generalisability of findings

Extensive data collection was undertaken in this study to generate reliable estimates of transfusion laboratory inputs into blood administration at Oxford and Reading. However,

as the study was only conducted at two hospitals, consideration is now given to how generalisable findings might be to other hospitals.

As Oxford and Reading are different types of hospital (Oxford is a large teaching hospital, Reading is a district general hospital) results might be expected to differ between them, but in fact were broadly similar. Costs of group and screens were higher at Oxford than Reading but the costs of issuing blood products were very similar. Two factors that influence the costs per unit transfused are the number of group and screens and units issued, for every unit transfused. With hindsight, it would have been useful to obtain this information from a greater number of transfusion laboratories to enhance the generalisability of the findings.

In the results of a recent survey of transfusion laboratories, graphs were presented of the number of group and screens performed per year and the number of RBCs issued per year; for both workload measures, Reading was in the most numerous band and Oxford was in the highest band.[107] The estimates of inputs at Reading may reflect those at other district general hospitals, and similarly the estimates at Oxford may reflect other teaching hospitals or high usage transfusion laboratories, but without further data collection (which was beyond the scope of this study), this cannot be known.

As there are about 320 transfusion laboratories in the UK (although approximately 130 are small, private only laboratories and therefore of less interest here), it could be argued that less extensive data collection around fewer inputs could have been undertaken in a greater number of laboratories, and results would be more generalisable. Looking at the results in **Tables 4.3-4.7** however, it would be difficult to justify collecting data on fewer inputs. Total costs are made up of many small components, of direct and indirect inputs, and there is no dominating element. Staff time is always a key driver of costs, but in each table either equipment or consumables (or both) also make up a significant proportion of costs.

In summary, on average across the two hospitals a group and screen cost £8, the cost per unit issued was £8 (for RBCs or non-RBCs) and the cost per unit transfused was £29 for RBCs and £27 for non-RBCs. These laboratory inputs into transfusion are just one aspect of the costs of administering blood. In the next section, the nursing inputs to transfusion are considered and quantified. Later in this chapter the costs of laboratory inputs to transfusion will be added to the costs of nursing inputs, and the findings compared further to the costs of blood transfusion reported in the NICE guidelines.

4.3 Micro-costing study of nursing inputs to order and administer blood on a day unit

4.3.1 Introduction

As described in Section 4.2.1, for a patient who needs a (non-emergency) transfusion, a blood sample will be taken and sent to the transfusion laboratory in order to identify a patient's blood group, and ensure that compatible blood products are issued for them. These blood products then need to be administered to the patient. As described in Chapter 3, transfusion is not without risk and patients need to be carefully monitored. Identification checks are also vital, one of the risks associated with transfusion is giving the wrong products to a patient.[6] On a ward or day unit, nurses perform two key inputs into transfusion: taking blood samples and placing requests for blood, and administering transfusions of blood products. The costs associated with these two activities are rarely identified or included within economic evaluations. This micro-costing study aims to generate reliable estimates of the costs of nursing inputs (and consumables) associated with administering transfusions of blood products.

4.3.2 Methods

This micro-costing study was undertaken as part of the 'Trial of prophylactic versus no prophylactic platelet transfusions' (TOPPS) trial,[108] funded by NHSBT, and was therefore conducted at two hospitals participating in this trial. The study was carried out on the haematology day units at OUH NHS Foundation Trust, Oxford, and at Guy's and St Thomas' NHS Foundation Trust, London (hereafter referred to as Oxford and London). Building upon the work conducted by Turner *et al.* (2003) into the steps involved in administering blood products, two data collection forms were developed to capture the direct staff time and consumables associated with nursing inputs to transfusion.[109] Form 1 covered blood sample collection for blood grouping and transfusion, and Form 2 covered blood administration, each for a single patient. Data collection forms were developed first in Oxford, in consultation with nursing staff on the haematology day unit. These forms were then adapted for use in London, again in consultation with nursing staff there to reflect slightly different practices. Forms were piloted before the study began. The data collection forms can be found in **Appendix 9**.

On each form, the process was split into a series of tasks. Each data collection form captured the time associated with each task, and the consumables associated with the process as a whole. Nursing staff on the haematology day units were asked to complete a form each time they undertook either of these two transfusion related activities for a patient. Forms were used to capture the inputs into the transfusion of RBCs or platelets, and the aim was to capture data on 30 RBC and 30 platelet transfusions at each hospital. (It was beyond the scope of the study to capture information on FFP transfusions, these are rarely administered on haematology day units).

All nursing staff on the haematology day units were sent a letter inviting them to take part in the study. As for the laboratory inputs study, each letter contained a 'unique number' for

each member of staff so that they could complete forms anonymously. Ethical approval for this work was granted by Oxfordshire Research Ethics Committee C as a substantial amendment to the approval for the TOPPS trial. Data collection was undertaken between October 2011 and March 2012 in Oxford, and between November 2011 and September 2012 in London.

Data analysis

The data collected were entered into Microsoft Excel 2013,[101] and analysis conducted in Stata 14.[110] Missing data on the forms were summarised and explored, and handled using mean imputation. As for the micro-costing study of laboratory inputs (see section 4.2.2. under *Data analysis*), the limitations of mean imputation were recognised,[76, 77, 102, 103] but available variables (nurse identifier and other times) were not expected to be good predictors of missing times that could be used in multiple imputation regression models; time inputs were anticipated to vary more between patients than between staff members. The mean staff time associated with each task for each process was calculated.

Unit costs were sought to value resource use. Nursing time was costed based on the mid-point of the salary range for a Band 5, taken from Agenda for Change salary scales for England from April 2014.[104] In order to calculate an hourly rate, staff were assumed to work 42 weeks per year, and 37.5 hours per week.[105] Staff salaries were inflated by 20% to incorporate National Insurance and Superannuation. A London weighting was not incorporated into the staff costs for the London hospital, this issue is returned to later in the chapter. Consumable costs were taken from the NHS Supply Chain National Catalogue 2011 or provided by the hospitals.[111] Costs are presented in 2014/15 prices, any unit costs in earlier prices were inflated to 2014/15 prices using the HCHS inflation index.[105, 106] Overheads have not been included in cost estimates; it was assumed that these would be incorporated into the 'hotel' costs associated with the location in which the transfusion related activities took place, which were assumed to be added separately.

The information was used to calculate the total staff time and consumables required, and associated costs, for taking a blood sample and placing a request for blood, and for administering a transfusion. For the costs of blood administration, the costs were split into the cost of administering a first unit and the marginal (additional) cost of administering subsequent units. The staff time associated with administering a first unit of blood included all the elements listed on Form 2 from obtaining a prescription up to observations after transfusion begun, the end of transfusion time was taken from the final unit transfused rather than the first unit if more than one unit was administered. Similarly, the costs of subsequent units included generating the pick-up slip, identification checks, and observations after transfusion begun; the end time was taken from the end of the previous transfusion. Following input from nursing staff, the cost of all consumables used was attributed to the first unit of blood transfused, consumable costs were zero for subsequent units. Unit cost estimates were generated separately for Oxford and London and then an average of the two costs calculated.

While nursing inputs are a key component of the costs of administering blood, nurses conduct other tasks while caring for a patient, and in any economic evaluation where blood administration is costed, it is likely that the costs of nursing inputs will be included in other ways. There is a risk of double counting nursing inputs, if for example, length of stay is costed and incorporates nursing time. In practice it will be difficult to avoid such double counting as it is unlikely to be possible to separate nursing tasks related to transfusion from other tasks. On balance however, it is better to include both costs; total costs per patient will be overestimated, but the difference between treatment groups, which is of primary interest in an economic evaluation, should not be affected, and if there are differences in transfusion between the groups, these differences will be more accurately captured.

4.3.3 Results

A total of 58 Form 1s were returned capturing the inputs for blood sample collection (28 from Oxford, 30 from London), and 148 Form 2s capturing the inputs into blood administration (87 from Oxford, 61 from London). Forms were completed by 12 nurses in Oxford, and 18 nurses in London.

Missing data on Forms 1 and 2 were summarised. At each site, staff time on two of the Form 2s were not completed. Of the remaining Forms 1 and 2, 16% and 5% of the times were missing at Oxford and London respectively, and needed to be imputed. Times were therefore very well recorded at London, and the small amount of missing data were spread across the forms. The time associated with the end of transfusion was most frequently missing at Oxford, (this could easily be forgotten as it needed completing at a later time than the bulk of the form). In eyeballing the data, there was nothing to suggest that forms with missing data were very different to forms with complete data. Consumables were recorded on all Form 1s, but were missing on 10/87 (11%) and 2/61 (3%) of Form 2s at Oxford and London respectively. Consumables left blank were assumed not to have been used, so no information on consumables was imputed.

Table 4.9 summarises the total nursing time and associated costs of taking a blood sample and requesting blood (captured on data collection Form 1). The times recorded for each of the steps within this procedure were broadly consistent at each hospital and between hospitals (a detailed breakdown of the time inputs are shown in **Appendix 10, Table 1**). The higher cost of consumables at London reflects slightly different practices on the two haematology day units. In London, the cannula (if used) was inserted when the blood sample was taken and therefore its cost is captured here; in Oxford the cannula (if used) was not inserted until blood was administered. The estimated cost of taking a blood sample

and requesting blood was £6.29 in Oxford and £9.72 in London, giving an average cost across the two hospitals of £8.01.

Table 4.9: Nursing time and costs associated with taking a blood sample and requesting blood

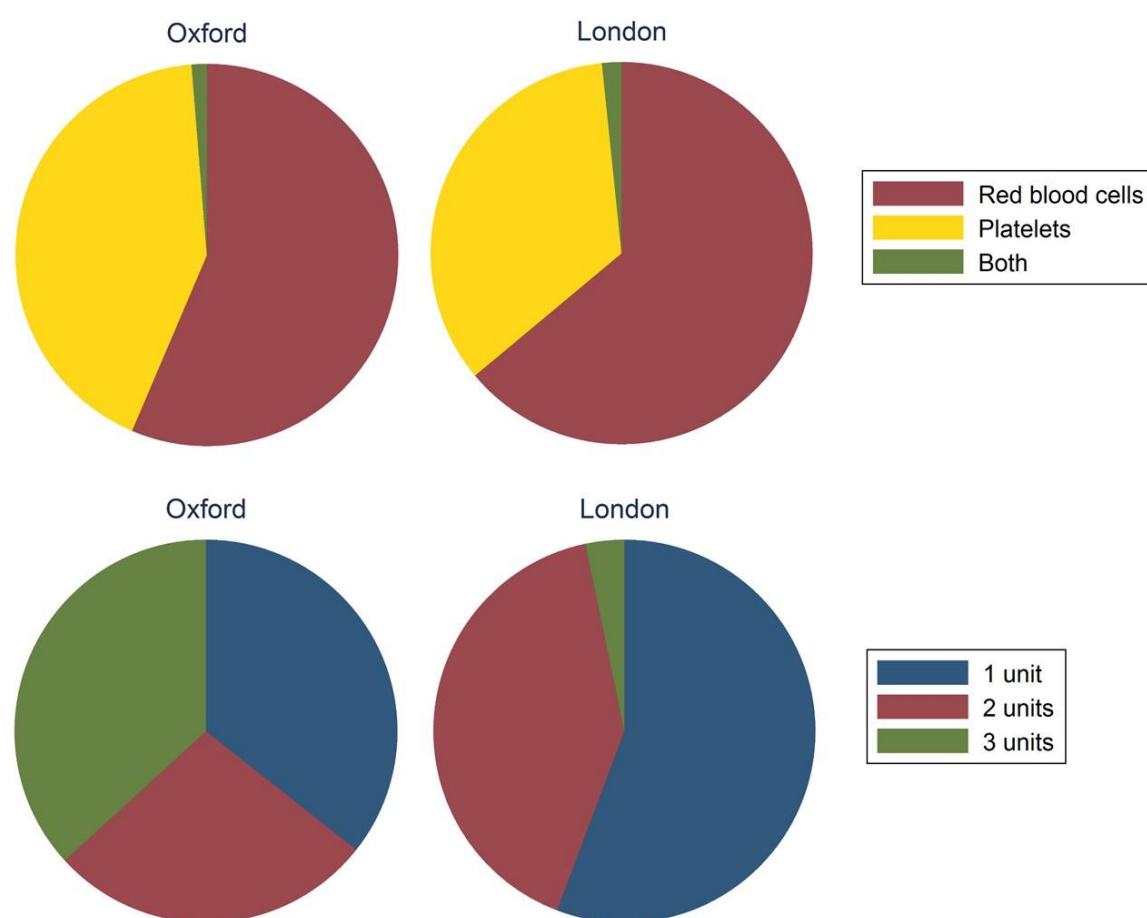
Hospital	n	Mean (SD) time (minutes)	Cost of mean time (£)	Cost of consumables (£)	Total cost (£)
Oxford	28	17.0 (6.1)	5.32	0.97	6.29
London	30	18.6 (14.5)	5.82	3.90	9.72

SD, Standard deviation

For the inputs into administering blood captured for 148 patients (on Form 2), **Figure 4.5** summarises the types of blood product that were given and the number of units transfused. Approximately 60% of transfusions were of RBCs. Data were captured on fewer patients having three units of blood at London than at Oxford. Sixty percent and 66% of transfusions were administered via a cannula at Oxford and London respectively, the others were administered via a central line.

Table 4.10 summarises the total nursing time and associated costs of administering a single unit of blood. A detailed breakdown of the time inputs for each of the steps within this procedure are shown in **Appendix 10, Table 2**. Time estimates and associated costs, and consumable costs are similar between the two hospitals; overall the cost estimates are £16.92 at Oxford and £18.33 at London, giving an average cost of £17.63. Consideration was given as to whether these findings differ depending on the type of blood product or the mode of administration of the transfusion. In fact the nursing staff time and cost of consumables is similar for RBCs and platelets, and whether administered via a cannula or a central line (further details are provided in **Appendix 10, Table 3**).

Figure 4.5: Characteristics of the transfusions captured by Forms 2s



*The type of blood product was missing for nine forms from Oxford.

Table 4.10: Nursing inputs into a single transfusion and associated costs

Hospital	n	Mean (SD) time (minutes)	Cost of mean time (£)	Cost of consumables* (£)	Total cost (£)
Oxford	85	37.2 (9.5)	11.64	5.28	16.92
London	59	41.1 (22.1)	12.86	5.47	18.33

SD, Standard deviation

* Cost of consumables is based on 77 forms from Oxford, and 59 forms from London.

For patients who had more than one unit of blood transfused at once, **Table 4.11** summarises the additional mean nursing time and associated costs for subsequent units of blood. Costs were slightly higher at London, partly because observations after transfusion begun were not done at Oxford, (a detailed breakdown of the time inputs for each step are shown in **Appendix 10, Table 4**). The average cost per subsequent unit across the two hospitals was £4.58.

Table 4.11: Nursing inputs into subsequent units transfused and associated costs

Hospital	n	Mean (SD) time (minutes)	Cost of mean time (£)
Oxford	79	11.2 (4.0)	3.50
London	29	18.1 (5.8)	5.66

SD, Standard deviation

4.3.4 Discussion

Table 4.12 summarises the findings of this micro-costing study of nursing inputs: on average it cost £8.01 to take a blood sample and request blood, £17.63 to administer a first unit of blood, giving a total cost for a one unit transfusion of £25.64. The additional cost of administering subsequent units of blood was on average £4.58. The percentage of each cost attributable to staff time has been included in **Table 4.12**, so that a London weighting could be applied to the costs if that was appropriate, (NHS staff are paid an extra 5-20% in high cost areas).[112]

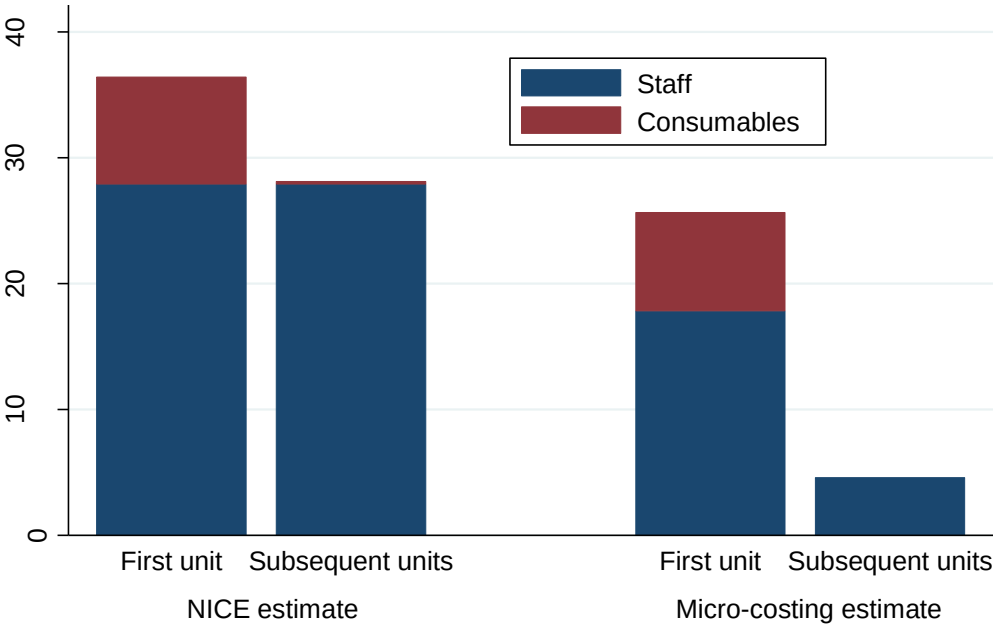
Table 4.12: Nursing and consumables costs of transfusion related activities

Activity	Average cost at Oxford (£)	Average cost at London (£)	Average cost across the two hospitals (£)	Average % of costs attributable to staff time
Blood sample and request blood	6.29	9.72	8.01	70
Administer first unit	16.92	18.33	17.63	69
Administer subsequent units	3.50	5.66	4.58	100

These cost estimates are now compared to those in the NICE clinical guidelines on blood transfusion, with NICE estimates inflated to 2014/15 prices (**Figure 4.6**).[63, 83] As was the case when transfusion laboratory inputs were compared, the costs associated with staff time are much higher in the NICE estimates than those presented here. Guideline Development Group expert opinion estimated the staff time on the ward to be 40 minutes,

15 minutes for blood collection and patient administration, and 25 minutes for observations (five observations taking five minutes each). This was also costed at a Band 5, but at a higher hourly rate than used here (£42 per hour), giving a cost of £27.88 for the 40 minutes. This staff time was applied to the first and, significantly, also to subsequent units. While the estimate of 40 minutes for the first transfusion is slightly lower than the times reported here (57 minutes on average across the two sites), the staff cost used in the model was significantly higher than those reported here as a higher unit cost was applied (staff costs presented here were on average £17.82 for requesting blood and administering the first unit). In the NICE model, consumables were estimated to cost £8.54 for patient assessment, transfusion preparation and the first unit, and just £0.24 for subsequent units; this is similar to the estimates here, (on average £7.81 for the first unit, £0 for subsequent units).

Figure 4.6: Comparing cost estimates for nursing inputs into administering RBCs (in 2014/15 prices)



This micro-costing study considered the nursing inputs into transfusions given on a haematology day unit, and the evidence reported in the NICE guidelines considered

transfusions given on a ward, these inputs and costs in these locations are likely to be similar. While many transfusions are given on a ward, transfusions may also be given in other settings in the hospital, and the inputs and costs associated with transfusions given elsewhere are considered next.

4.4 Exploring the generalisability of cost estimates of nursing inputs to transfusion on a day unit with other settings

The previous micro-costing study provides a baseline estimate of the nursing inputs required to administer blood, based on transfusions given on two haematology day units. Transfusions are given in other settings in a hospital; for example in the six months from April to September 2015, 25% of units transfused at Oxford were given in theatre, 9% in the emergency department (ED) and 66% on the ward or in ICU (data provided by the transfusion laboratory). While the costs of transfusions given on a ward are likely to be similar to the costs of transfusion on a haematology day unit, the costs in theatre or ED may be different. It is therefore helpful to explore the generalisability of the findings on the haematology day units with alternative settings to put that work into context, and to consider whether it would be appropriate to apply these new cost estimates to transfusions given elsewhere, or whether this would be very inaccurate. This was done in four semi-structured interviews with nurses working in theatre and ED. Based on Forms 1 and 2 used to collect data in the previous study (on the tasks of taking a blood sample and requesting blood, and administering a transfusion), nurses were asked whether each of the steps in the process on the haematology day unit would be done in their setting or how the process varied, and how long this might take. Detailed methods and results (and the interview schedule) are presented in **Appendices 11** and **12**, and a summary of the findings is provided here.

The costs of the staff inputs to take a blood sample for a group and screen in theatre or ED are likely to be similar to those reported on the haematology day unit. The time taken to

administer blood in these settings is less than on the day unit. Theatre and resuscitation in ED are higher cost settings than a ward or day unit, staff and equipment are on hand, ready for potentially emergency situations where timely intervention is critical; it is perhaps reasonable to think that activities in these environments are done more quickly. Consumable costs are similar, except where large volumes are transfused and blood warming sets are used. These interviews were exploratory however, and not designed to generate definitive quantitative estimates. They suggest that if further work were planned, it might be beneficial to focus on the costs of staff inputs to administering transfusions rather than on blood samples for group and screens in alternative settings. It is not possible to compare these findings to any other evidence, the literature review of the costs of administering blood in Chapter 3 did not identify any papers which considered the costs of transfusion specifically in theatre or the ED.

Having considered the wider applicability of the costs of nursing inputs to transfusion generated on a day unit with other settings, the findings from the two micro-costing studies are now combined.

4.5 Summary of the costs of administering a transfusion

In this chapter, estimates of the laboratory inputs into transfusion and nursing inputs into transfusion on a day unit have been quantified and consideration given to the nursing costs in alternative setting in which transfusions are given. The laboratory and nursing costs of a group and screen were estimated to be £16.41. **Table 4.13** summarises the costs of nursing and laboratory inputs generated to consider the total cost of administering blood, in addition to the cost of the blood products.

Wastage of blood products is also included in **Table 4.13**. According to the Blood Stock Management Scheme 2012-2014 Report, 2.4% of RBCs and 3.8% of platelets issued to

transfusion laboratories in England and North Wales were wasted.[99] The most common reason for RBC wastage was time-expiry, and for platelets was medically ordered but not used. These percentages and the number of units of RBCs and platelets delivered to the transfusion laboratories at Oxford and Reading (shown in **Figure 4.3**), were used to calculate the number of units of RBCs and platelets wasted at each hospital in 2014/15. The cost of this wastage was calculated based on the NHSBT 2014/15 price list,[113] and the cost apportioned across the number of RBC/ platelets units transfused at each hospital in 2014/15. Finally the cost of wastage of each type of blood product was averaged across the two hospitals. Given that platelets are more expensive than RBCs (£196.96 compared to £121.85 in 2014/15 prices)[113] and the proportion of platelets wasted was higher, the wastage costs for platelets are higher than for RBCs.

Table 4.13: Mean costs associated with administering a transfusion on a day unit

	RBCs		Platelets		Frozen products*	
	First unit	Subsequent units	First unit	Subsequent units	First unit	Subsequent units
Laboratory inputs	£28.56	£28.56	£27.28	£27.28	£27.28	£27.28
Nursing inputs	£25.64	£4.58	£25.64	£4.58	£25.64	£4.58
Wastage	£2.99	£2.99	£8.45	£8.45	£1.34	£1.34
Total	£57.19	£36.13	£61.37	£40.31	£54.26	£33.20

RBC, Red blood cell

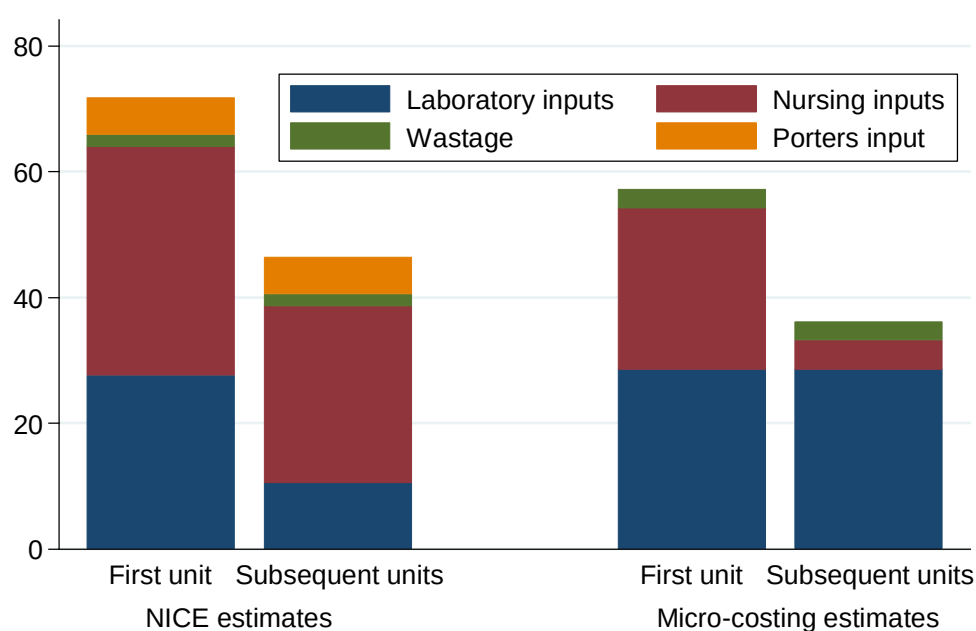
* Wastage costs assume the product is fresh frozen plasma.

The cost of administering RBCs on a day unit was estimated to be £57.19 for the first unit, and £36.13 for subsequent units. The cost of administering platelets was slightly higher, driven by the higher cost associated with wastage of platelets. These costs slightly underestimate the cost of administering blood: the cost of transporting blood samples, pick-up slips and blood products around the hospital by porters has not been estimated or included. This is thought to be the smallest component of the cost of administering blood (in terms of staff inputs) and was beyond the scope of this work; it was not felt that there were reliable secondary sources that could be used as an estimate.

Estimates of the costs of administering frozen products are also included in **Table 4.13**. These products were not included in the micro-costing study of nursing inputs into transfusion, but the products are administered in the same way as RBCs and platelets so there is no reason to think that the cost estimates generated are not applicable to these products. Estimates of wastage are not available for FFP and cryoprecipitate. Given that once these products have been thawed they have to be used quickly, the higher wastage rate of 3.8% for platelets was applied. As virtually all frozen products transfused are FFP rather than cryoprecipitate, wastage costs were calculated (as described above) assuming that all these products were FFP. Data were not available to calculate the cost of wastage for cryoprecipitate in the same way, but an approximate estimate would be £6.86 (3.8% of the unit cost for 2014/15, £180.54).[113]

The cost estimates for administering RBCs generated here are compared to the costs reported in the NICE guidelines on blood transfusion, inflated to 2014/15 prices (**Figure 4.7**).[63, 83] The NICE evidence estimated the costs of administering RBCs to be £71.74 for a first unit, and £46.38 for subsequent units. These figures are higher than those reported here. They do include 15 minutes of a porter's time to take pick up slips to the transfusion laboratory and return with blood products, but this only accounts for £5.75 of the additional cost. They do not include the costs associated with storing and maintaining a supply of blood products in the transfusion laboratory. Based on a rate reported in Agrawal *et al.* (2006),[98] wastage was assumed to be 1.5% of the cost of a unit of RBCs (£1.87), this was less than the costs reported above (based on more recent figures). Further comparisons are not possible, the NICE evidence did not consider non-RBCs, (nor transfusions given in locations other than a ward).

Figure 4.7: Comparing cost estimates for administering RBCs (in 2014/15 prices)



*Porters input not included in the micro-costing estimates

Having generated detailed estimates of the costs associated with administering blood, the next section considers how these estimates can be used in practice in an economic evaluation.

4.6 Using the costs of blood administration in an economic evaluation

In this chapter detailed and transparent estimates of the costs associated with administering a single unit transfusion and additional units (within the same transfusion episode) have been generated, however, depending on the resource use data collected as part of an economic evaluation, these unit costs may not be directly applicable. Consideration is now given to how to use these cost estimates in practice, and the resource use data that needs to be captured within an economic evaluation in order to incorporate the costs of blood administration. None of the papers included in the literature review of the costs of administering blood conducted in Chapter 3 discussed how to use the cost estimates in an

economic evaluation, nor did they highlight any particular considerations that might be required if patients receive multiple transfusions (of the same or different products).

If very detailed patient level data are collected on the number of group and screens, the number and timing of transfusion episodes, and the number of units transfused within each episode, then the unit costs generated in this chapter can be applied directly and very accurate estimates of the costs of blood administration can be included in the economic evaluation. However, this is unlikely to be the case. As will be seen in Chapter 5, even in an economic evaluation with very detailed data collection on trial participants and a focus on RBCs, this level of detail was not captured on the case report forms; no information on the number of group and screens was collected, and only the number of units of RBCs transfused each day was recorded. In this case, it would not be unreasonable to assume that all RBCs given on one day, were given in one transfusion episode. Therefore the cost of administering RBCs on any day would be the cost of a first unit given (£57.19) plus $(n-1)$ multiplied by the cost of subsequent units (£36.13), where n is the number of units of RBCs given on that day.

Frequently in an economic evaluation, it is only the number of units of each blood product that are transfused to a patient in a defined time period (for example during an inpatient stay) that are recorded, and therefore the number of transfusion episodes, and the number of units transfused within each episode are unknown. This is the case for non-RBC products in the case study reported in Chapter 5 and for all blood products in the case study in Chapter 6. One way to cost blood administration in this scenario would be to assume that all units of each blood product were given in the same transfusion episode, this is how the NICE estimates are used in practice.[83] This will underestimate administration costs however, if blood products are given over a number of transfusion episodes. Alternatively, and more appropriately, it would be useful to be able to apportion the costs of administration evenly across units, based on an average number of units of blood product given per

transfusion episode, and then apply a single cost of administration to every unit transfused. This can be calculated from the unit costs generated so far, but hinges on knowledge of the average number of units of blood product given per transfusion episode.

Number of units of blood product per transfusion episode

Initially, national estimates of the average number of blood products administered per transfusion episode were sought, however, this information is not reported in any of the large epidemiological studies that have been conducted in the UK,[17, 18, 24, 114, 115] indeed several papers clearly state that this information is not available in this country.[18, 116] Informally, opinions were sought at the South Central Regional Transfusion Committee meeting in September 2016, but members (who include a consultant haematologist, transfusion laboratory managers and transfusion practitioners) were not aware of any reliable data on this. Therefore the transfusion laboratory managers at the hospitals where the micro-costing work was undertaken were approached for any local data on the number of units given per transfusion episode.

The transfusion laboratory managers at Oxford and Reading were able to provide data for 2015 on the mean number of units transfused per request for RBCs, in both cases this was 1.3. This is the mean number of units transfused across all RBC requests, regardless of whether the requests resulted in any RBCs being transfused. Oxford were able to supply greater detail around these figures: the total number of RBCs transfused in 2015, the number of requests for RBCs made, and the number of requests made where no RBCs were given. It was therefore possible to calculate the mean number of RBC units transfused per request where blood products were actually given, this was 1.7. This is the best estimate available of the number of units of RBCs per transfusion episode. Similar data for 2015 were available from Oxford for platelets and FFP, a mean of 1.2 units of platelets and 4.4 units of FFP were transfused per request where blood was actually given. (Data were not available from Reading on non-RBCs).

While these are the best estimates available, it is important to recognise that they may underestimate the true mean number of units per episode. For example, if a patient's haemoglobin is retested after a single unit transfusion, and a second unit is ordered and transfused via the cannula or central line through which the first unit was given, this is really part of the first transfusion episode, but in these figures would be classed a separate episode. With the introduction of the single unit transfusion policy, this may have become more of an issue in recent years, but equally because of this shift in practice, recent data were sought to reflect these changes. These estimates of the number of units of blood per transfusion episode are now used to calculate the costs of administration per unit of blood product transfused.

Costs of blood administration per unit transfused

Costs in **Table 4.13** were combined with the mean units of blood products per transfusion episode and used to calculate the average costs of administering blood per unit transfused, shown in **Table 4.14**. The mean administration cost per transfusion episode was calculated by adding the cost per first unit transfused to $(n-1)$ times the cost per subsequent unit transfused, where n was the average number of units given in a transfusion episode. The mean cost per unit was then calculated by dividing the total cost per episode by the mean units per episode. For example, for RBCs the mean cost per episode was £57.19 + $(0.7 \times £36.13)$, and the mean cost per unit was the resulting cost of £82.48 divided by 1.7 units, £48.52. To this point, FFP and cryoprecipitate have been considered together as frozen products, however, since they are given in different quantities and have different wastage costs, they are reported separately here. The mean units per episode for cryoprecipitate is assumed to be two (personal communication with the Oxford transfusion laboratory manager, October 2016; this is also the dose recommended in the NICE guidelines).[83] The mean costs per unit for each blood product (**Table 4.14**) can be used to cost blood administration using resource use data which is frequently captured in an economic

evaluation (number of each type of blood product transfused), without information on transfusion episodes (which is less frequently available).

Table 4.14: Mean costs of administering blood per unit transfused

	Red blood cells	Platelets	Fresh frozen plasma	Cryoprecipitate
Mean units per episode	1.7	1.2	4.4	2.0
Mean cost per episode	£82.48	£69.43	£167.14	£98.50
Mean cost per unit	£48.52	£57.86	£37.99	£49.25

As presented earlier in this chapter, the administration costs are made up of the laboratory and nursing inputs into transfusions (group and screens and allocating and administering transfusions) and wastage of blood products. While the costs associated with laboratory inputs and wastage do not vary per first or subsequent unit transfused, the costs of nursing inputs do vary. In **Table 4.13**, the nursing costs of administration per first unit transfused incorporate the cost of taking a blood sample for a group and screen, and the staff and consumable costs of administering a single unit; the additional staff time of administering further units made up the subsequent unit cost. In **Table 4.14**, these three cost elements have been apportioned equally across the mean units per transfusion episode, to provide a cost per unit transfused. If patients have a number of transfusion episodes (either for the same blood product or for different blood products), then it is possible that one group and screen could be valid for more than one transfusion episode and the nursing costs of administration should be adjusted to reflect this, as described next.

Multiple transfusion episodes or types of blood products

If the costs of administering blood are calculated either by assuming that for each product all units given on one day are given in one transfusion episode, or by using the average costs per unit transfused just described, there is one adjustment to costs that might need to be considered in an economic evaluation. In the figures presented in **Tables 4.13** and **4.14**, every transfusion episode included the nursing costs of taking a blood sample for a

group and screen (£8.01). For the first transfusion episode, this will clearly be necessary, but there will be some variability about whether a second transfusion episode would require another group and screen. For RBCs, the British Committee for Standards in Haematology guidelines recommend that cross-matching (including electronic issue) is performed on samples that are taken no more than three days in advance of the transfusion (when the patient has been transfused RBCs or pregnant within the preceding three months).[117] Therefore if a blood sample is taken on day one, and a RBC transfusion is administered that day, then any RBC transfusions on days two or three can be matched for the patient using the blood sample taken on day one; from day four onwards a new sample would be required. For non-RBCs only one group and screen is required, blood products are issued based on a patient's blood group and a valid recent sample is not required. If the dates of transfusion episodes are recorded, then the exact number of group and screens conducted can be estimated. If this is not the case, and the time period over which transfusions occur is recorded, then a maximum number of group and screens required can be calculated and compared to the number of group and screens included in the costs of administration; costs associated with nursing inputs to group and screens can be capped if necessary.

An example of the costs of administering blood

The costs of administering multiple transfusions as may occur in clinical practice are now considered in an example. Suppose a patient had six units of RBCs, and one unit of platelets during a seven day hospital stay. Using the figures in **Table 4.14**, the administration costs are estimated to be £348.98, ($6 \times £48.52 + 1 \times £57.86$), and the number of transfusion episodes is estimated to be 4.4, ($6/1.7 + 1/1.2$), and therefore 4.4 group and screens are included in the costs. However the maximum number of group and screens a patient would need over seven days is three, (on days one, four and seven). Reducing the number of group and screens by 1.4, reduces administration costs by £11.21, ($1.4 \times £8.01$), and the costs of administering blood for this patient are £337.77. Administration costs may still be overestimated; if all blood products were administered by day three, then only one

group and screen would have been required and costs should be £16.02 less. Without information on exactly when blood products are transfused (or the number of group and screens performed), this cannot be determined, but at least capping the number of group and screens at the maximum required limits the overestimation. There is often a balance to strike between the burden of data collection and the accuracy of the costs generated.

4.7 Conclusions

The costs of administering blood on a day unit add substantially to the costs of the blood products themselves. For RBCs, costs are 40% (£49) higher when the costs of administration are included as well as the cost of the RBCs. While the costs of administration may seem small, these are frequently incurred costs. In 2014/15 24,313 units of RBCs were transfused at Oxford; considering only the 66% given on a ward or in ICU, the costs of administration exceed £750,000.

The estimates generated here add significantly to the limited existing literature on the costs of administering blood, which was reviewed in Chapter 3 (see section 3.4.1). The checklist used to assess the quality of included studies (**Appendix 3**) has been applied to the present study. The study scored 67% (full details in **Appendix 13**) which is higher than all of the previous studies conducted in the UK (see **Appendix 3**). It was an omission not to explicitly report the perspective of the study (that of the NHS), which would have improved the score to 75%.

Sharing more reliable estimates of the costs of transfusion with the clinical community will help to promote more appropriate use of blood; more effort is likely to be made to conserve resources if their true costs are not underestimated. Furthermore, detailed transparent cost estimates such as those generated here, which report costs separately for laboratory and nursing inputs, for first and subsequent units, and for wastage, enable the financial impact

of transfusion policies which might have different effects on different components of costs to be assessed. In addition, it is important that the costs of administering blood as well as the costs of the blood products themselves are taken into account in applied economic evaluations. If two alternative blood transfusion strategies are being compared, a failure to fully account for the costs of transfusion would bias the cost results in favour of the transfusion strategy with the greater blood use, and might even lead to incorrect conclusions on cost-effectiveness being made. The cost estimates summarised in **Table 4.14** (or **4.13**) could be used in future economic evaluations. These estimates can reasonably be applied to blood products administered on a ward, it is less certain how accurate they are for other settings, but they are the best estimates available. If these estimates are applied to the RBCs and platelets supplied by NHSBT to hospitals in England and North Wales in 2013/14,[99] the annual cost of blood administration, excluding the blood products themselves, is in excess of £97 million.

There are three potential areas where further work would be useful. Additional primary data collection could be undertaken to reliably estimate the costs of staff inputs to administering transfusions in alternative settings, particularly in theatre where 25% of transfusions were given at Oxford in 2014/15. Further work could also be used to quantify the inputs of porters to transfusion. In terms of using the costs in practice, further work to generate more reliable estimates of the average number of units of blood products given per transfusion episode would be very useful.

The cost estimates generated here are used in the economic evaluations described in the next two chapters.

Chapter 5: Cost-effectiveness of alternative transfusion thresholds in cardiac surgery

5.1 Introduction

In this chapter the cost-effectiveness of two alternative RBC transfusion thresholds in cardiac surgery is assessed, and the cost estimates generated in Chapter 4 are used to cost transfusions. Patients may require RBCs after cardiac surgery to improve oxygen delivery as a result of anaemia or blood loss, RBC requirements largely for anaemia are considered in this chapter. Peri-operative anaemia is common after cardiac surgery and is associated with adverse clinical outcomes, such as stroke, acute kidney injury and death.[118-120] Transfusion of allogeneic RBCs is a mainstay treatment for acute anaemia and, on average, over 50% of adult cardiac surgery patients in the UK and US receive a peri-operative blood transfusion.[90, 93] As described in Chapter 3, most decisions to transfuse are based on a haemoglobin (Hb) concentration falling to a level or threshold at which the clinician responsible for a patient's care feels uncomfortable, and this threshold varies between doctors and cardiac surgery units, resulting in wide variation in blood usage.[90, 91, 93, 94] A key reason for the threshold variation is the lack of evidence regarding what constitutes a 'safe' level of anaemia following cardiac surgery.

While RCTs of restrictive versus liberal transfusion thresholds in patients undergoing major surgery, or the critically ill, have demonstrated no significant differences in 30-day mortality or adverse outcomes,[121] observational studies in cardiac surgery (comparing transfused versus not transfused patients) suggest transfusion is associated with increased infection, low cardiac output, acute kidney injury and death.[120, 122, 123] RCTs rank more highly than observational studies in the hierarchy of evidence,[51] however, evidence exists from 37 times more patients in observational studies in cardiac surgery than RCTs in major surgery or the critically ill.[121, 124] Together these findings have been interpreted as

supportive of a restrictive transfusion practice,[125-127] and yet their applicability to a cardiac surgery population is unclear as the Hb concentration considered to be 'safe' in patients with heart disease is thought to be higher than for patients without heart disease. Humans can compensate for low Hb levels (as low as 5g/dL in healthy individuals)[128] by pumping blood more quickly around the body (increasing cardiac output) and by extracting a greater percentage of oxygen from the blood.[6] Patients with heart disease may be at the limit of their cardiovascular reserve (the heart may not be able to pump blood more quickly than it does ordinarily) and therefore may not be able to compensate physiologically for anaemia or tolerate Hb levels as low as patients without heart disease.[129] If the heart does not get enough oxygen, this can lead to organ failure.[6]

Despite cardiac surgery being the highest surgical user of RBCs in the UK, there is a paucity of evidence on the Hb level at which the clinical benefits outweigh the risks and transfusion is indicated. A recent review of the available evidence around RBC transfusion thresholds across all specialties, (based on RCTs and systematic reviews)[83] included just three RCTs of patients undergoing cardiac surgery (excluding one trial which relates to work later in this chapter).[130-132] In two single-centre RCTs,[130, 131] clinical outcomes were similar in both transfusion groups, and in the third, a pilot study,[132] there were more adverse events in the restrictive group. In each trial, restrictive and liberal thresholds were defined differently, and none of these studies were large enough to provide definitive results, indeed the most recent study highlighted the need for a large multi-centre RCT of transfusion thresholds in cardiac surgery.[132] Given the pressures on healthcare resources and the costs and scarcity of RBCs, it is important to consider the cost-effectiveness as well as the clinical effectiveness of alternative transfusion thresholds. Unfortunately, there is even less evidence available on the cost-effectiveness of alternative transfusion thresholds; none of the three RCTs in cardiac surgery included an economic evaluation, and across all other specialities the review included just one economic evaluation of a pilot trial of transfusion thresholds in critically ill patients.[83, 133] This was

described as an exploratory evaluation, and although patients were followed up beyond hospital discharge to 180 days, the only in-hospital resource use data collected and costed was length of stay by level of care.

Given the uncertainty around outcomes with restrictive or liberal transfusion thresholds after cardiac surgery and the paucity of cost-effectiveness information, there is an urgent need for further evidence on which to base transfusion decisions in cardiac surgery. The Transfusion Indication Threshold Reduction (TITRe2) trial (ISRCTN70923932) was conducted to address the uncertainty around the clinical and cost-effectiveness of alternative transfusion thresholds in cardiac surgery.

This chapter presents the cost-effectiveness analysis conducted alongside the TITRe2 trial. The trial and the clinical results are described first, before the health economic methods are presented, with a particular emphasis on the collection of detailed resource use data. The cost-effectiveness results are presented together with a number of sensitivity analyses to assess the impact on results of varying key parameters and cost drivers, and to investigate the impact of uncertainty on the results. The chapter concludes with a discussion of the findings in relation to other evidence, and the implications for clinical practice.

5.2 The Transfusion Indication Threshold Reduction (TITRe2) trial

In preparation for a larger definitive study, a pilot trial (TITRe1) was conducted at the Bristol Heart Institute in 2005-2006 to assess the efficacy of alternative transfusion thresholds in cardiac surgery.[134] TITRe2 was the following large trial, conducted across 17 specialist cardiac surgery centres in UK NHS hospitals between July 2009 and August 2013 and funded by the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (Project Number 06/402/94). Given that the direction of clinical thinking was moving towards less blood being better, this multi-centre superiority

RCT was designed to test the hypothesis that a restrictive threshold for RBC transfusion would reduce post-operative morbidity and healthcare costs compared to a liberal threshold. Patients aged over 16 years having non-emergency cardiac surgery were recruited between July 2009 and February 2013. Only patients whose Hb dropped to less than 9g/dL during the post-operative hospital stay were randomised, either to a restrictive threshold (transfuse if Hb falls below 7.5g/dL) or to a liberal threshold (transfuse if Hb falls below 9g/dL). The threshold was applied during patients' post-operative hospital stays, all other aspects of post-operative care were provided in accordance with each hospital's usual care. Very detailed data on patients were collected throughout their hospital stay on the trial case report forms (CRFs), and by post or telephone follow up three months after randomisation; this included detailed collection of resource use data. Patients also completed health outcome questionnaires pre-operatively, and six weeks and three months after randomisation.

The primary clinical outcome for TITRe2 was a composite of a serious infectious (sepsis or wound infection) or ischaemic event (permanent stroke, myocardial infarction, gut infarction or acute kidney injury) in the three months after randomisation. At the end of the trial, the main trial results reported no difference in the primary clinical outcome between the two alternative transfusion groups (the primary outcome was observed in 35.1% and 33.0% of patients in the restrictive and liberal groups respectively). This result suggested that neither transfusion threshold was better than the other in terms of the primary pre-specified clinical outcome evaluated in the trial. However, analyses also showed that more patients died within three months of surgery in the restrictive group than the liberal group (4.2% versus 2.6%) creating uncertainty about recommending restrictive transfusion after cardiac surgery. Moreover, sensitivity analyses of the primary outcome excluding patients who received transfusion prior to randomisation and using additional acute kidney injury data suggested a benefit from more liberal transfusion (due to a trend towards a higher risk of the primary outcome in the restrictive group in each case). These findings were also not

supportive of the emerging clinical view that less blood was better, and in fact suggest that more blood may be beneficial.

Further details of the TITRe2 trial methods and results have been reported in the New England Journal of Medicine.[135, 136] The economic evaluation conducted alongside the trial is described next.

5.3 Aim of the economic evaluation

The question the economic evaluation aimed to address was:

“What is the incremental cost and the incremental cost-effectiveness of a restrictive compared to a liberal haemoglobin transfusion threshold after cardiac surgery?”

5.4 Methods

5.4.1 Economic evaluation methods overview

For the TITRe2 economic evaluation, a cost-effectiveness analysis was conducted, with outcomes measured using the EuroQol EQ-5D-3L (the five level version was not available when the trial started). The base case analysis included all patients randomised into the trial except those randomised in error, which is consistent with the main effectiveness analyses. Analyses were performed on an intention-to-treat basis. Good practice guidelines on the conduct of economic evaluations were followed for the economic evaluation.[46, 47, 137] **Table 5.1** summarises the methods for the economic evaluation used in the base case analysis (the primary analysis), further details are provided next.

Table 5.1: Summary of methods used in the economic evaluation

Aspect of methodology	Strategy used in the base case cost-effectiveness analysis
Form of economic evaluation	Cost-effectiveness analysis for comparison between restrictive and liberal transfusion thresholds
Perspective	NHS and personal social services
Time horizon	A within-trial analysis, taking a three month time horizon
Population	All randomised patients were included, except those randomised in error
Costs included in analysis	<u>Index admission:</u> • Surgery • Blood products • Length of stay by ward type (including intensive care and high dependency units) • Medications • Re-operations • Investigations and treatments relating to complications, and serious adverse events <u>Post-discharge:</u> • Readmissions to hospital • Other hospital accident and emergency department and outpatient visits (e.g. warfarin clinics) • Community health and social care contacts
Utility measurement (primary economic outcome)	EQ-5D-3L (administered pre-operatively and at six weeks and three months post-operatively)
Quality-adjusted life-year calculations	Assume that patients' utility changes linearly between utility measurements
Adjustment for baseline utility	Regression used to adjust quality-adjusted life-year calculations for differences in baseline utility
Missing data	Multiple imputation

5.4.2 Form of analysis and primary outcome measure

A cost-effectiveness analysis (specifically a cost-utility analysis) using quality-adjusted life-years (QALYs) as the primary outcome measure was conducted, thus taking into account patients' quantity and quality of life. Incremental costs (the difference in mean costs between the two transfusion threshold groups) and incremental QALYs were considered together and presented as the incremental cost-effectiveness ratio, which quantifies the

incremental cost per QALY gained by switching from using a liberal threshold to using a restrictive threshold.

5.4.3 Perspective

The primary perspective of the evaluation was that of the UK NHS and personal social services, as recommended by NICE.[46] However, data were collected on some types of non-NHS costs including expenditure incurred by a patient when travelling to hospital. If resource use for these non-NHS costs differed between the trial groups, a sensitivity analysis taking a wider perspective and including these costs would be conducted. The perspective for outcomes comprised the patients undergoing treatment.

5.4.4 Time horizon

As described in Chapter 2, the time horizon is one of the most important methodological points to consider. A within-trial analysis, taking a three month time horizon was conducted. Surgical trials frequently only follow patients up until hospital discharge (which is often less than seven days), but it is important to capture complications or events that occur in the immediate post-discharge period and result in readmissions or additional resource use. It was anticipated that all major resource use (and outcomes) would occur within a three month timeframe, and therefore be captured. The start of the analysis was from the point of surgery. Surgery was chosen as the time origin, rather than the point of randomisation as was the case with the analysis of effectiveness, in order to capture the resources that would be required for the intervention from a decision-maker's perspective, that is, to include all relevant costs (and effects) involved in delivering an intervention. The time horizon continued until three months post-operatively. Ideally the time point for baseline costs and outcomes should be the same; however, the EQ-5D was collected pre-operatively, whereas detailed resource use collection began on the day of surgery.

5.4.5 Collection of resource use and cost data

Resource use data were collected on all significant health service resource inputs for the trial patients up to the point of the three month follow-up. Very detailed resource use data were captured on the trial CRFs and the three month follow up questionnaire, CRFs relevant to the economic evaluation can be seen in **Appendix 14**. The main resource use categories which were costed are listed in **Table 5.2**, along with the key sources of information for both the resource use and unit costs. Costing decisions (such as resource use assumed for complications) were made without knowledge of the allocation of patients to trial groups to avoid introducing bias.

Table 5.2: Resource use categories and sources of resource use and unit cost information

Resource use category	Sources for resource use information	Sources for unit cost information
Initial cardiac surgery	CRF C1	National Schedule of Reference Costs (2012-2013)[138]; NHSBT National Comparative Audit of Blood Transfusion[93]; NHSBT Price List[139]
Blood products	CRFs B1, B2	NHSBT price list[139]; costs of administering blood products from Chapter 4 (further details in Appendix 15, Table 1)
Initial stay in hospital post-surgery	CRFs D1, H5	National Schedule of Reference Costs (2012-2013)[138]
Medications	CRF D2	Electronic Marketing Information Tool[140]; British National Formulary[141]
Complications, including re-operations; serious adverse events	CRFs C1, C2-C4, C5, C6, C7, F1-F3, H5, X1	National Schedule of Reference Costs (2012-2013)[138]; Electronic Marketing Information Tool[140]; British National Formulary[141]
Hospital readmissions	CRF X1, 3 month follow up questionnaire - section 2a	National Schedule of Reference Costs (2012-2013)[138]
Outpatient attendances and visits to accident and emergency	3 month follow up questionnaire - sections 2b, 2c	National Schedule of Reference Costs (2012-2013)[138]
Community health and social care contacts	3 month follow up questionnaire - section 3	National Schedule of Reference Costs (2012-2013)[138]; Unit Costs of Health and Social Care[142]

CRF, Case Report Form; NHSBT, NHS Blood and Transplant

Initial cardiac surgery and blood products

Surgical procedures were split into four groups: coronary artery bypass grafting (CABG), valve, CABG and valve, and other (often a major aortic procedure). As the type of surgery itself was not the main factor being assessed within the trial, published cardiac surgery costs were used rather than performing a detailed micro-costing. Cost figures for the relevant cardiac surgery Healthcare Resource Group (HRG) codes from the elective inpatient spreadsheet of the National Schedule of Reference Costs were used;^[138] costs relating to length of stay (LOS) and blood products were subtracted to calculate the cost of the surgery itself.

LOS in hospital was removed by using the average LOS associated with each HRG and each speciality (cardiac surgery or cardiothoracic surgery) at a cost of £392 per day; this cost is a weighted average of elective inpatient excess bed days for relevant cardiac procedures (see **Appendix 15, Table 1** for further details). For valve surgery, there were HRG codes for single valve procedures and for procedures on more than one valve. The costs are higher for procedures involving more than one valve; 25% of the activity reported in NHS Reference Costs was for procedures involving multiple valves but in TITRe2 this proportion was only 10%. To reflect this, an average of the costs of single and multiple valve procedures was calculated, weighted according to the proportion of these types of patients in TITRe2.

The costs of blood products (RBCs, FFP and platelets) were removed from HRG costs by using the average numbers of products reported to be used by CABG, valve, and CABG and valve patients in the NHSBT national audit in 2011,^[93] and valued using published NHSBT prices.^[139] For the surgery category of 'Other', the costs of average blood products were removed by applying the information used for CABG and valve patients since the average operation time for 'Other' was lengthy, and most similar to the CABG and valve group.

The total number of units of RBCs transfused each day was recorded on the trial CRFs. RBC administration was costed using the unit cost estimates for first and subsequent units generated in Chapter 4 (**Table 4.13**), assuming that units given on the same day were given in one transfusion episode. The number of group and screens required for each patient based on the inpatient days transfusions were given was calculated, and any excess nursing costs associated with group and screens were subtracted (as described in Section 4.6). The total number of other blood products transfused were recorded on the CRFs, and the costs of blood administration in **Table 4.14** were applied, with additional adjustments for excess nursing costs associated with group and screens. Further details of the adjustments are provided in **Appendix 15, Table 1**.

Initial post-surgery hospital stay

In terms of hospital stay following the index surgery, LOS was collected for the cardiac intensive care unit (CICU) / high dependency unit (HDU), general intensive care unit (ICU) and ward during the trial. As time spent on CICU was not reported separately from time spent on HDU, and recognising that these activities probably require a different level of resources, the time of extubation was used to distinguish between time on CICU and time on HDU.

Patients had an initial extubation date and time recorded in the trial, along with the dates and times of any further intubations and extubations. If the exact time of extubation or movements between wards was unknown, there was provision on the CRFs to record an approximate time of AM, PM or overnight. If only an approximate time was available, the same assumptions as were made in the effectiveness analyses were used, which were based on discussions with the research nurses. For calculations involving the date and time of hospital discharge, a discharge time of 6pm was assumed (consistent with the effectiveness analyses). If data were missing on extubation date/time, it was assumed that

for those who died before discharge, that they were intubated until death. For one patient without a tracheostomy, and no indication that (s)he was not extubated, an average intubation duration was assumed, based on information from patients with available data. For patients who went on to have a tracheostomy, their time to tracheostomy and time to discharge were calculated and the average intubation time for patients with intubation durations between these two times was assumed. Similar assumptions were made for any re-intubations. CICU and HDU costs were taken from NHS Reference Costs.[138] To cost time on a cardiac ward, an average bed day cost was created by weighting the costs of excess bed days for relevant cardiac procedures according to activity from the elective inpatient spreadsheet in NHS Reference Costs (see **Appendix 15, Table 1** for further details).[138]

Medications and fluids

Medications and fluids given during surgery or intensive care, such as inotropes, were costed for each patient. Information on whether patients received these medications or not was collected on pre-specified yes/no tick boxes on the trial CRFs (Form D2). In order to cost these interventions, a cardiac surgeon on the trial research team provided an estimate of the likely quantity of fluids a patient would receive.

The costs of antibiotics administered after surgery for an infection were summed during the period of initial hospital stay post-surgery and during any hospital stay after discharge if patients were readmitted (up to three months). The names of specific antibiotics given during the index admission were reported on the trial CRF (Form C5) as free text with the route and duration of the course. The most likely dose was established with a cardiac surgeon on the TITRe2 research team. The costs of antibiotics were included in the costs of complications.

The regular medications which patients were taking at discharge from the cardiac surgery unit, such as beta-blockers and warfarin, were recorded on pre-specified yes/no tick boxes on CRF Form D2. A cardiac surgeon on the trial research team estimated the name, dose and mode of delivery (oral or intravenous) for these regular medications. Patients were assumed to take any medications recorded at discharge for the whole of the three month follow up and these medications were costed for three months.

Treatment of complications and serious adverse events

Cardiac surgery is a complex procedure and complications associated with surgery, many of which result in significant resource use, are common; information on complications was therefore collected in detail. Primary outcome complications which were costed included serious infection, permanent stroke, myocardial infarction (MI), gut infarction and acute kidney injury (AKI) stage 3. Details of these complications were recorded on CRF Forms C5 and C6. The costs of any procedures or tests required to verify these complications, such as computerised tomography (CT) or magnetic resonance imaging (MRI) scans for permanent stroke, laparotomy for gut infarction and electrocardiogram for suspected MIs, were also included. For all patients suspected to have had an MI, the costs of diagnostic investigations were included.

There are many different post-operative complications which may occur after cardiac surgery; indeed the study protocol listed 25 expected adverse events in addition to those that made up the primary clinical outcome and death.[135] These other post-operative complications (recorded on CRF C7) included pacing (both temporary and permanent), continuous positive airway pressure ventilation, tracheostomy and transient ischaemic attack. The costs of these complications were calculated and included. Cardiac surgery re-operations were also included in complication costs.

For each complication, a cardiac surgeon on the research team estimated the likely resource implications. Care was taken to avoid double counting of complication costs. For example, resource use associated with both acute respiratory distress syndrome (ARDS) and reintubation was assumed to be a transoesophageal echo and three chest x-rays. If a patient had both complications on the same day, only one echo and three chest x-rays were costed to avoid likely double counting. As well as capturing the types and numbers of complications patients experienced, the trial CRFs also captured details of any serious adverse events (SAEs), largely as free-text fields. For each patient with one or more SAE, the SAE fields in the trial database were individually reviewed, and resource use data were extracted. This resource use was costed if it was not already captured in complication costs, again to avoid double counting. **Tables 5, 6, 8 and 9 in Appendix 15** show all the complications, the corresponding diagnostic tests and treatments assumed, and their corresponding unit costs.

Hospital readmissions

The costs of hospital readmissions included all expected and unexpected cardiac surgery and transfusion complications, in terms of adverse events and SAEs, but excluded all unexpected unrelated complications. For example, the costs of readmissions for hypertension and angina were included, but the costs of readmissions for cancer treatment were excluded. Clinical opinion was sought to clarify whether unexpected complications were possibly related or were unrelated to the index surgery. A bed day cost for readmissions was created (from NHS Reference Costs) by weighting the costs of non-elective inpatient excess bed days across all specialties according to activity.[138] The cost of an accident and emergency (A&E) attendance was included if a patient was admitted via A&E or referred by their general practitioner (GP), and assumed to be admitted via A&E. If patients travelled to hospital via ambulance, this was also costed.

Outpatient attendances, Accident and Emergency visits and community health and social care contacts

The type of outpatient appointment was recorded by pre-specified tick boxes on the trial follow-up questionnaire (Section 2(c)) which included cardiac surgery, cardiology (non-surgical), renal/dialysis unit, stroke clinic or 'other'. If patients specified 'other', clinical opinion was sought as to whether these were likely to be linked to the surgery, in order to avoid costing any outpatient visits which were totally unlinked to the trial. Information on the number of A&E visits related to the surgery and the reasons for the visits was captured on the trial CRF (Section 2(b) of the follow up questionnaire). The reasons for visits recorded by patients were reviewed, and any unrelated activity excluded. Information was also collected on how the patient travelled to A&E to ensure any ambulance costs were captured. Primary care contacts with GPs and practice nurses, whether at the GP surgery or patient's home, were costed. Other NHS or social services visits at home or elsewhere, including any visits to cardiac rehabilitation clinics or warfarin clinics, were also costed using information collected on the trial follow-up questionnaire (Section 3).

5.4.6 Attaching unit costs to resource use

Unit costs for hospital and community healthcare resource use were largely obtained from national sources, for example, NHSBT price lists for blood products, the NHS Reference Costs for ICU, HDU and cardiac ward costs, MRI and CT scans and many complications, and Unit Costs of Health and Social Care for community costs.[138, 139, 142] Resources were valued in 2012/13 pounds sterling, any unit costs in earlier prices were inflated to 2012/13 using the Hospital and Community Health Services (HCHS) inflation index.[142] Costs of drugs given in hospital were taken from the Electronic Marketing Information Tool where possible,[140] which provides the reduced prices paid for generic drugs in hospital; other drug costs were taken from the British National Formulary (BNF).[141] **Tables 2-4** in

Appendix 15 list the medications used in the trial and their costs; further details on all unit costs and their sources can be found in **Appendix 15**.

5.4.7 Health-related quality of life (HRQoL) and QALYs

The EuroQol EQ-5D questionnaire, advocated for use in economic evaluations by NICE,[46] was used to measure HRQoL.[143] The EQ-5D is a generic measure of health outcome covering five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Responses recorded on the instrument were converted into a single index value using the UK valuation set, in which valuations from approximately 3,000 members of the UK general population were elicited using the time trade-off method;[144] scores were then used to facilitate the calculation of QALYs. Trial patients completed the EQ-5D questionnaire at three time points: in hospital pre-operatively and by post/telephone at six weeks and three months post-operatively (the questionnaire can be seen in **Appendix 14**). The pre-operative assessment of HRQoL provides a baseline utility for patients. HRQoL was assessed at an intermediate time point post-operatively (six weeks) as well as at the end of the time horizon to capture whether patients' HRQoL improved after surgery more quickly in one transfusion group than the other. HRQoL is often assessed in surgical patients six weeks post-operatively (partly as this may coincide with a follow up outpatient appointment and be captured there).

Total QALYs over the three month time horizon were calculated for each patient based on their EQ-5D scores at the three time points (pre-operatively, six weeks and three months post-operatively). **Appendix 16** describes how QALYs were calculated.

5.4.8 Missing data

The amount of missing data for both resource use and EQ-5D scores was first summarised descriptively, and exploratory analyses were conducted to explore the possible

mechanisms and patterns of missing data.[102] Logistic regressions were used to explore associations between missingness and baseline variables, and missingness and previously observed outcomes. Multiple imputation was used to handle missing data. This is a flexible approach, which is valid if data are assumed to be missing at random, (the probability that data are missing does not depend on the unobserved values, conditional on the observed data).[77, 102, 103] This assumption was found to be valid (as will be described in section 5.5.2). Details of the imputation methods are described in **Appendix 17**.

5.4.9 Within-trial statistical analysis of cost-effectiveness

Most of the cost-effectiveness analyses were conducted in Stata 14;[110] some of the graphs and unit cost calculations were conducted in Microsoft Excel 2010.[145]

Initially, resource use and HRQoL were summarised using means, standard deviations (SDs) and standard errors (SEs) of means. Since most of the results presented in this chapter are based on multiple imputation, uncertainty around mean estimates are presented using SEs, and 95% CIs are reported around mean differences. Costs and effects were not discounted as the time horizon was less than 12 months. The ICER (incremental cost-effectiveness ratio, described in Chapter 2) was derived from the average costs and QALYs gained in each trial group, producing an incremental cost per QALY gained by implementing a restrictive threshold in place of a liberal threshold. The restrictive threshold was considered as cost-effective if the ICER fell below £20,000, since this is the threshold at which NICE generally considers an intervention to be cost-effective.[42]

The ICER is the best estimate (point estimate) of cost-effectiveness, but it is important to investigate uncertainty around this estimate and the conclusions that are drawn from it. Non-parametric bootstrapping of costs and QALYs was used to quantify the degree of uncertainty around the ICER in the following three ways:[146]

- 1) To represent graphically the uncertainty around the ICER on the cost-effectiveness plane (described in Chapter 2);
- 2) To calculate SEs around the cost and QALY differences, and use these to calculate 95% confidence intervals (CIs) around the cost and QALY differences;
- 3) To generate a cost-effectiveness acceptability curve,[67] which indicates the likelihood that the restrictive threshold is cost-effective for different levels that healthcare decision-makers are willing to pay for health gain.

Since cost data are typically positively skewed and may contain a few extreme outliers, bootstrapping was used to avoid making parametric assumptions. **Appendix 18** describes how bootstrapping was performed, and further details of these three analyses.

5.4.10 Adjustment for baseline utility

A patient's HRQoL pre-operatively (their baseline utility) directly contributes to QALY calculations. It is important to control for any potential imbalances in baseline utility in the estimation of the mean difference in QALYs between treatment groups, to avoid introducing bias.[147] QALYs were therefore adjusted for baseline EQ-5D, and **Appendix 19** describes how this was done.

5.4.11 Sensitivity analysis

One-way sensitivity analysis was used to investigate the impact on the results of the cost and cost-effectiveness analyses of varying key parameters or major cost drivers, and also to investigate the impact of uncertainty on the cost-effectiveness results. Full details of all sensitivity analyses undertaken are provided in **Appendix 20**. In brief, sensitivity analyses for costing were conducted to investigate varying a number of unit costs (for example costs of complications, ward stays, re-operations and blood administration), moving the time

origin from surgery to the time of randomisation, and the impact of any high cost patients. Non-NHS costs were also considered as part of the sensitivity analyses. In terms of outcomes, assumptions for calculating QALYs were varied. A further sensitivity analysis examined life-years gained as a secondary outcome measure in the economic evaluation. This was not pre-planned at the outset of the within-trial cost-effectiveness analysis, but because the difference in mortality between the transfusion groups was not evident in the QALY results (see below), life-years were looked at separately.

5.4.12 Scenario analyses

A within-trial analysis was pre-planned for this study, but given the unexpected difference in mortality, some additional post hoc “what if” scenario analyses were undertaken to evaluate the effect on QALYs of propagating the difference in mortality to a longer, 12 month time horizon.

The survival status for all patients in the trial was known to three months, as were the dates of death, and the resulting survival curves to three months were estimated using the Kaplan-Meier product limit estimator.[67] Alternative scenarios assuming that the treatment effect on mortality remains the same, increases or decreases between three months and one year after surgery were considered. Parametric methods (specifically the exponential curve) were used to extrapolate survival from three to 12 months.[67] Survival probabilities and utility weights at baseline, six weeks, three months and one year were used to calculate quality adjusted survival, and estimate mean QALYs for each trial group to one year (no adjustment was made for baseline EQ-5D). Since no patients were censored, survival probabilities were straightforward to calculate for time points to three months. Utility weights at baseline, six weeks and three months were the mean EQ-5D scores in each trial group for patients alive at the time point. Patients’ utility was assumed to remain the same from

three to 12 months, and the mean EQ-5D scores were used at one year (last observation carried forward).

The effect on the ICER of alternative assumptions to extrapolate to a 12 month time horizon were also investigated. Mean costs from three to 12 months were assumed not to differ between the trial groups, and therefore the difference in costs was assumed to remain at £298, as per the base case analyses.

5.4.13 Subgroup analysis

Subgroup analyses were conducted to investigate whether cost-effectiveness results varied between patient subgroups. The pre-specified subgroups used for the effectiveness analyses, were used for the cost-effectiveness subgroup analyses:

- Operation type (isolated CABG versus other operation types);
- Age at operation (<75 years versus ≥75 years);
- Pre-operative diagnosis of diabetes (none versus diet, oral medication or insulin controlled);
- Pre-operative diagnosis of lung disease (none versus chronic pulmonary disease or asthma);
- Pre-operative renal impairment (estimated glomerular filtration rate ≤60ml/min versus >60ml/min);
- Sex (males versus females);
- Pre-operative ventricular function (good versus moderate or poor).

The impact of subgroups was evaluated using ordinary least squares regression separately for total costs and for QALYs, conditional on treatment group, subgroup and an interaction between treatment group and subgroup (and baseline EQ-5D for QALYs only). A Bonferroni adjustment was made to allow for the multiple tests conducted across the seven

subgroups and two variables, statistical significance was therefore evaluated at the 0.0036 level (0.05 divided by 14).[70]

5.5 Results

5.5.1 Analysis population

The TITRe2 trial randomised a total of 2,007 patients, four withdrew, leaving an analysis population consisting of 2,003 patients; 1,000 in the restrictive group and 1,003 in the liberal group. Patient characteristics, type of surgery and deaths within the three month follow up period are summarised in **Table 5.3**. Patients had a mean age of 69 years and 69% were male. Most patients underwent CABG (41%) or valve surgery (31%), and 95% of procedures were performed on cardiopulmonary bypass. There were significantly more deaths at three months in the restrictive group than in the liberal group ($p=0.045$).[136]

Table 5.3: Patient characteristics, type of surgery and deaths

	Restrictive threshold (n=1000)	Liberal threshold (n=1003)
Age – mean (standard deviation)		
Age at operation (years)	69 (10)	69 (10)
Gender – frequency (%)		
Male	693 (69%)	680 (68%)
Cardiac procedure – frequency (%)		
Coronary artery bypass grafting	408 (41%)	408 (41%)
Valve	307 (31%)	304 (30%)
Coronary artery bypass grafting and valve	195 (20%)	203 (20%)
Other	90 (9%)	88 (9%)
Death – frequency (%)		
Died in hospital	25 (2.5%)	17 (1.7%)
Died within three months of surgery*	42 (4.2%)	26 (2.6%)

*Includes deaths in hospital

5.5.2 Missing data

Summaries of the data collected showed that 2.5% of resource use data were completely missing, 2.4% in the restrictive group and 2.5% in the liberal group; and 10.7% of EQ-5D scores were missing across the three time points (pre-surgery, six weeks and three

months), 10.9% in the restrictive group and 10.5% in the liberal group. The low amounts of missing data reflect the high follow up rate (98.7% of patients were followed up at three months) and good completeness of data that was achieved in the trial.

Table 5.4 summarises the amount of missing resource use and outcome data for individual patients in each trial group. Although only 42% of cases were complete, in practice data were only missing for a small number of variables for each patient. For incomplete cases, patients in the restrictive and liberal groups were missing on average six and five values respectively (across more than 100 variables). Inpatient resource use was particularly well completed, incomplete cases were missing on average two and one values in the restrictive and liberal groups respectively. Missing data were non-monotonic, since individuals with missing EQ-5D data at six weeks may have complete data at three months.

Table 5.4: Number of patients with complete data by trial group

	Restrictive threshold (n=1000)	Liberal threshold (n=1003)
Resource use		
Index admission	906 (91%)	913 (91%)
Post discharge to three months	598 (60%)	609 (61%)
All	521 (52%)	549 (55%)
Outcomes		
EQ-5D at baseline	991 (99%)	992 (99%)
EQ-5D at six week follow up	813 (81%)	833 (83%)
EQ-5D at three month follow up	870 (87%)	867 (86%)
QALYs	754 (75%)	768 (77%)
All resource use and QALYs	414 (41%)	433 (43%)

QALY, Quality-adjusted life-year

Associations between missing resource use and QALY data and key baseline variables (age, sex, cardiac procedure, centre and baseline EQ-5D) were assessed using logistic regressions, and age was found to be a significant predictor of missing QALYs (odds ratio 0.98, 95% CI 0.97, 0.99, $p < 0.001$). Cardiac procedure and centre were significant predictors of missing costs and QALYs, but no associations were found between trial group or sex and missingness. Lower EQ-5D scores at baseline were not associated with missing cost

data, but were associated with missing QALYs (odds ratio 0.69, 95% CI 0.45, 1.05, $p=0.08$), although this was not statistically significant at the 5% level. This suggests that data might not be missing completely at random. Baseline variables (age, sex, cardiac procedure and centre) were all significant predictors of either costs or QALYs or both. Logistic regressions were also used to explore associations between missingness and previously observed outcomes. There was no association between missing post discharge costs and observed costs in the index admission, or between missing EQ-5D scores at three months, and observed scores at baseline or six weeks. Overall these findings support a missing at random assumption, and multiple imputation is a flexible and appropriate method for handling the missing data. When conducting the multiple imputation, baseline variables (age, sex, cardiac procedure and centre) were included in the regression models since missingness may depend on them. Since 58% of cases were incomplete, multiple imputation with $m=60$ was conducted.

5.5.3 Resource use and costs

Table 5.5 reports information on the main resource use items (surgery, blood products, LOS, complications and healthcare contacts post-discharge) for the trial groups to three months post-operatively. RBCs are the only resource item for which there is a clear difference between the groups, an expected finding given that the liberal group had more RBCs transfused. The average number of units of RBCs transfused in the restrictive group was 2.08 (SE 0.09) per patient, compared to 3.07 (SE 0.11) units per patient in the liberal group, leading to an average difference of 1.00 (SE 0.14) unit per patient. For most of the other categories of resource use the differences between the groups are very small. The differences are slightly larger for inpatient ward LOS, time in other hospitals and readmissions than for some other resource use items, but these are nevertheless small differences.

Table 5.5: Resource use per patient to three months from surgery

Resource use component	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold % or Mean difference (95% CI)
Frequency (%) or Mean (SE)	Frequency (%) or Mean (SE)		
Red blood cells – number of units/ patient	2.08 (0.09)	3.07 (0.11)	-0.99 (-1.27, -0.71)
Cardiac procedure – number (%) of patients			
Coronary artery bypass grafting	408 (41%)	408 (41%)	0%
Valve	307 (31%)	304 (30%)	1%
Coronary artery bypass grafting & valve	195 (20%)	203 (20%)	0%
Other	90 (9%)	88 (9%)	0%
Blood products – number of units/ patient			
Fresh frozen plasma	1.00 (0.06)	0.95 (0.06)	0.05 (-0.11, 0.21)
Platelets	0.65 (0.03)	0.64 (0.03)	0.01 (-0.09, 0.10)
Cryoprecipitate	0.23 (0.03)	0.21 (0.02)	0.02 (-0.05, 0.09)
Inpatient complications			
Primary outcome – number (%) of patients			
Antibiotics for infectious complication	341 (34%)	344 (34%)	0%
Stroke	14 (1%)	16 (2%)	-1%
Suspected myocardial infarction	3 (0%)	7 (1%)	-1%
Gut infarction	5 (1%)	1 (0%)	1%
Acute kidney injury - stage 3	60 (6%)	51 (5%)	1%
Other complications – number of events/ patient			
Reoperation	0.09 (0.01)	0.10 (0.01)	-0.01 (-0.04, 0.02)
Reintubation	0.07 (0.01)	0.07 (0.01)	0.00 (-0.03, 0.02)
Tracheostomy	0.03 (0.01)	0.03 (0.01)	0.00 (-0.01, 0.02)
Mask CPAP	0.13 (0.01)	0.12 (0.01)	0.01 (-0.03, 0.04)
Pneumothorax requiring chest drainage	0.01 (0.00)	0.01 (0.00)	0.00 (-0.01, 0.01)
Pleural effusion requiring drainage	0.06 (0.01)	0.06 (0.01)	0.00 (-0.02, 0.02)
Pacing	0.31 (0.02)	0.31 (0.02)	0.00 (-0.05, 0.04)
SVT/AF requiring treatment	0.41 (0.02)	0.39 (0.02)	0.02 (-0.03, 0.07)
VF/VT requiring intervention	0.02 (0.01)	0.01 (0.00)	0.01 (0.00, 0.03)
Low cardiac output	0.11 (0.01)	0.11 (0.01)	0.00 (-0.03, 0.02)
Inpatient length of stay – days/ patient			
Cardiac intensive care unit	1.14 (0.12)	1.12 (0.13)	0.02 (-0.32, 0.37)
High dependency unit	3.09 (0.12)	3.05 (0.12)	0.04 (-0.29, 0.37)
Ward	5.67 (0.15)	5.83 (0.17)	-0.17 (-0.62, 0.28)
Another unit / hospital	1.26 (0.20)	1.46 (0.23)	-0.20 (-0.79, 0.39)
Blood saving techniques – number (%) of patients			
Tranexamic acid	807 (81%)	810 (81%)	0%
Aprotinin	40 (4%)	33 (3%)	1%
Intra-operative cell salvage	481 (48%)	503 (50%)	-2%
Post-operative cell salvage	55 (6%)	45 (4%)	2%
Fluids - number (%) of patients			
Inotropes	623 (62%)	613 (61%)	1%
Gelofusine	842 (84%)	835 (83%)	1%
Hydroxyethyl starch	230 (23%)	233 (23%)	0%

Resource use component	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold % or Mean difference (95% CI)
Readmissions to hospital			
Length of stay – days/ patient	1.38 (0.16)	1.57 (0.18)	-0.19 (-0.66, 0.29)
A&E attendances			
Total A&E visits - number/ patient	0.09 (0.01)	0.08 (0.01)	0.01 (-0.02, 0.04)
Outpatient appointments - number/ patient			
Cardiac surgery outpatient visits	0.44 (0.02)	0.51 (0.02)	-0.07 (-0.12, -0.02)
Cardiology outpatient visits	0.28 (0.02)	0.25 (0.02)	0.03 (-0.02, 0.08)
Other outpatient visits	0.17 (0.02)	0.17 (0.02)	-0.01 (-0.06, 0.04)
Other healthcare contacts – number/ patient			
General practitioner at surgery	1.97 (0.07)	2.09 (0.08)	-0.11 (-0.32, 0.09)
General practitioner at home	0.43 (0.04)	0.41 (0.03)	0.03 (-0.08, 0.13)
Practice nurse	1.61 (0.12)	1.59 (0.14)	0.03 (-0.32, 0.38)
District nurse	2.44 (0.22)	2.35 (0.25)	0.09 (-0.57, 0.75)

A&E, Accident and Emergency; CI, Confidence interval; CPAP, Continuous positive airway pressure; SE, Standard error; SVT/AF, Supraventricular tachycardia/ Atrial fibrillation; VF/VT, Ventricular fibrillation/ Ventricular tachycardia

In terms of unit costs which were attached to resource use items, **Table 5.6** provides a summary of the key unit costs used and the source for the information, presented in 2012-13 prices. More detailed information on unit costs can be found in **Appendix 15**.

Table 5.6: Unit costs for key resources

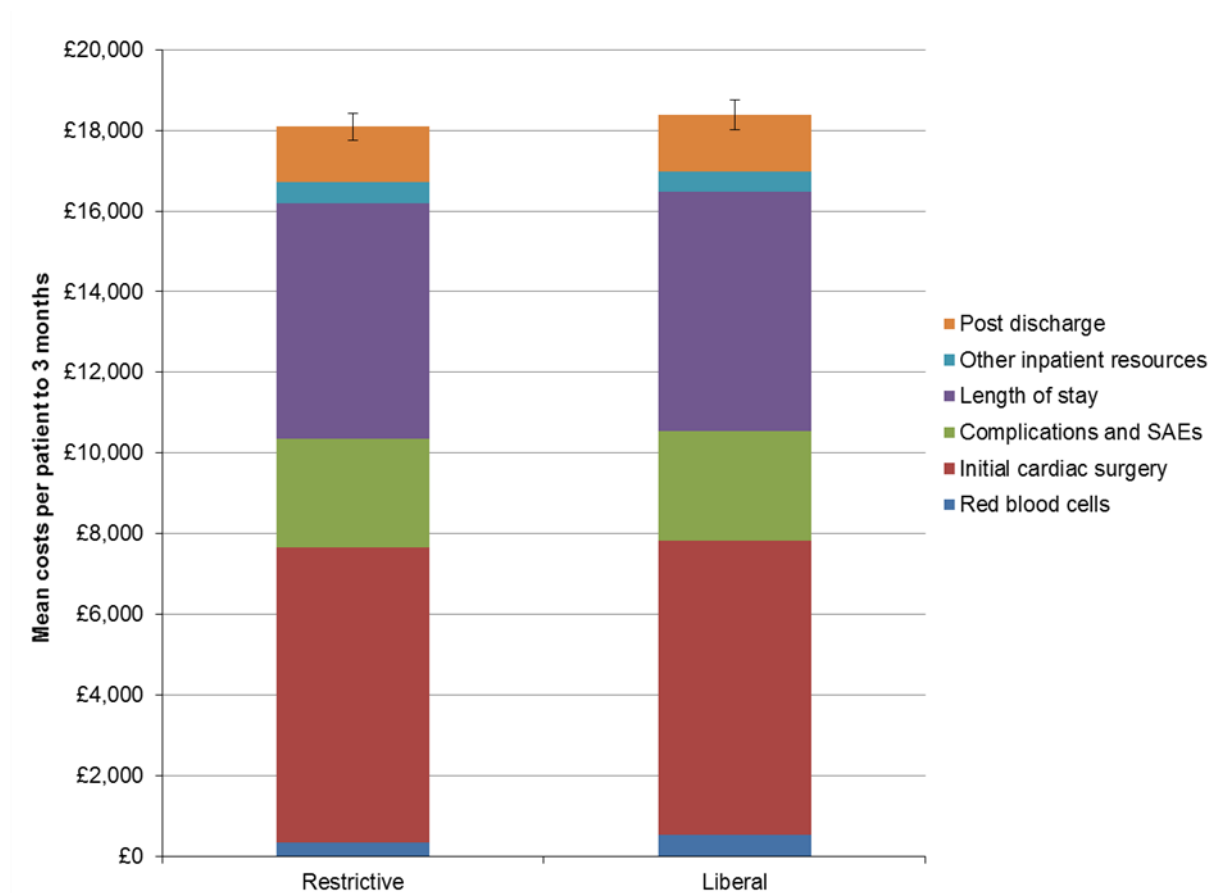
Resource use	Unit cost (£)	Source
Red blood cells (per unit of blood)	123.31	NHSBT Price List 2012/13[139]
Cardiac procedure		
Coronary artery bypass grafting	6714	See Appendix 15, Table 1
Valve	7336	See Appendix 15, Table 1
Coronary artery bypass grafting & valve	8054	See Appendix 15, Table 1
Other	8298	See Appendix 15, Table 1
Blood products (per unit)		
Fresh frozen plasma	27.46	NHSBT Price List 2012/13[139]
Platelets	209.30	NHSBT Price List 2012/13[139]
Cryoprecipitate	189.19	NHSBT Price List 2012/13[139]
Inpatient complications		
Primary outcome		
Antibiotics for infectious complication	See Appendix 15, Table 3	eMIT, 2014[140]; BNF 66, 2013[141]
Stroke	139	NHS Reference Costs 2012/13[138]
Confirmed by CT scan	62	NHS Reference Costs 2012/13[138]
Confirmed by MRI scan	248	NHS Reference Costs 2012/13[138]
Suspected myocardial infarction	1868	NHS Reference Costs 2012/13[138]
Gut infarction	62	NHS Reference Costs 2012/13[138]
Confirmed by laparotomy	2693	NHS Reference Costs 2012/13[138]
Acute kidney injury - stage 3	1438	NHS Reference Costs 2012/13[138]
Other complications		
Reoperation (duration <3 hours)	6608	NHS Reference Costs 2012/13[138]
Reoperation (duration ≥3 hours)	8298	NHS Reference Costs 2012/13[138]
Reintubation	395	NHS Reference Costs 2012/13[138]
Tracheostomy	5354	NHS Reference Costs 2012/13[138]
Mask CPAP	539	NHS Reference Costs 2012/13[138]
Pneumothorax requiring drainage	4218	NHS Reference Costs 2012/13[138]
Pleural effusion requiring drainage	4218	NHS Reference Costs 2012/13[138]
Pacing	3073	NHS Reference Costs 2012/13[138]
SVT/AF requiring treatment	4.79	eMIT, 2014[140]
VF/VT requiring treatment	2007	NHS Reference Costs 2012/13[138]
Low cardiac output	313	NHS Reference Costs 2012/13[138]
Inpatient length of stay		
Cardiac intensive care unit day	1190	NHS Reference Costs 2012/13[138]
High dependency unit day	619	NHS Reference Costs 2012/13[138]
Ward day	392	NHS Reference Costs 2012/13[138]
Another unit / hospital ICU day	1168	NHS Reference Costs 2012/13[138]
Another unit / hospital ward day	265	NHS Reference Costs 2012/13[138]
Blood saving techniques		
Tranexamic acid	15.50	BNF 66, 2013[141]
Aprotinin	316.83	Davies <i>et al.</i> , 2006[148]
Intra- or post-operative cell salvage	176	Davies <i>et al.</i> , 2006[148]

Resource use	Unit cost (£)	Source
Fluids		
Inotropes	57.30	eMIT, 2014[140]
Gelofusine	7.92	Teaching Hospital, South Central, 2013
Hydroxyethyl starch	40.60	BNF 58, 2009[149]
Readmissions to hospital		
Ward day	265	NHS Reference Costs 2012/13[138]
Intensive care unit day	1168	NHS Reference Costs 2012/13[138]
A&E attendances		
A&E visit (not leading to admission)	101	NHS Reference Costs 2012/13[138]
Outpatient appointments		
Cardiac surgery outpatient visit	299	NHS Reference Costs 2012/13[138]
Cardiology outpatient visit	131	NHS Reference Costs 2012/13[138]
Other outpatient visits	See Appendix 15, Tables 10 and 11	NHS Reference Costs 2012/13[138]
Other healthcare contacts		
General practitioner at surgery	34	Unit Costs of Health & Social Care 2013[142]
General practitioner at home	85	Unit Costs of Health & Social Care 2013[142]
Practice nurse	11.37	Unit Costs of Health & Social Care 2013[142]
District nurse	39	Unit Costs of Health & Social Care 2013[142]

A&E, Accident and Emergency; BNF, British National Formulary; CPAP, Continuous positive airway pressure; CT, Computed tomography; eMIT, electronic Marketing Information Tool; ICU, Intensive care unit; MRI, Magnetic resonance imaging; NHSBT, NHS Blood and Transplant; SVT/AF, Supraventricular tachycardia/ Atrial fibrillation; VF/VT, Ventricular fibrillation/ Ventricular tachycardia

Figure 5.1 presents a breakdown of total costs for each treatment group. This clearly shows that there is very little difference in costs between the groups apart from a difference in the average cost of RBCs, which is to be expected. Key drivers of total costs were surgery, complications and LOS. A breakdown of total costs is given in **Table 5.7**. The table is broken down into three cost categories: RBCs, inpatient episode and post hospital discharge. A more detailed breakdown of total costs is given in **Appendix 21**.

Figure 5.1: Breakdown of total costs for each trial group



SAEs, Serious adverse events

Error bars show standard errors around total costs.

The total cost of care from surgery up to three months is £18,092 in the restrictive group and £18,390 in the liberal group, creating a mean difference between the groups of -£298 (95%CI -£1276, £680). Most of this difference in cost is associated with the higher cost of RBCs in the liberal group (cost difference of -£170). The next main cost difference is in the complications and SAEs, and LOS costs, with the liberal group being more expensive than the restrictive group, but only slightly more. Post-discharge costs are similar between the groups.

Table 5.7: Breakdown of total average costs per patient for both trial groups

Cost component	Restrictive threshold (n=1000) Mean cost (£) (SE)	Liberal threshold (n=1003) Mean cost (£) (SE)	Restrictive versus liberal threshold Mean cost (£) difference (95% CI)
Red blood cells	352 (16)	522 (18)	-170 (-217, -124)
Inpatient episode			
Initial cardiac surgery	7309 (18)	7313 (18)	-4 (-55, 47)
Other blood products	283 (15)	273 (14)	11 (-30, 52)
Complications and SAEs	2687 (137)	2714 (146)	-27 (-420, 367)
Length of stay ^a	5842 (199)	5920 (225)	-78 (-667, 511)
Blood saving techniques	159 (9)	152 (8)	7 (-16, 30)
Regular medications	25 (2)	29 (2)	-3 (-8, 2)
Fluids	55 (1)	54 (1)	0 (-3, 3)
Total	16360 (309)	16454 (343)	-93 (-998, 812)
Post-discharge			
Readmissions	787 (93)	807 (89)	-20 (-274, 233)
Accident & Emergency visits	16 (2)	12 (2)	4 (-1, 9)
Outpatient appointments	201 (6)	217 (7)	-16 (-34, 3)
Other medical/ social care	375 (14)	378 (16)	-3 (-48, 42)
Total	1380 (95)	1415 (93)	-35 (-297, 227)
Total costs	18092 (338)	18390 (367)	-298 (-1276, 680)

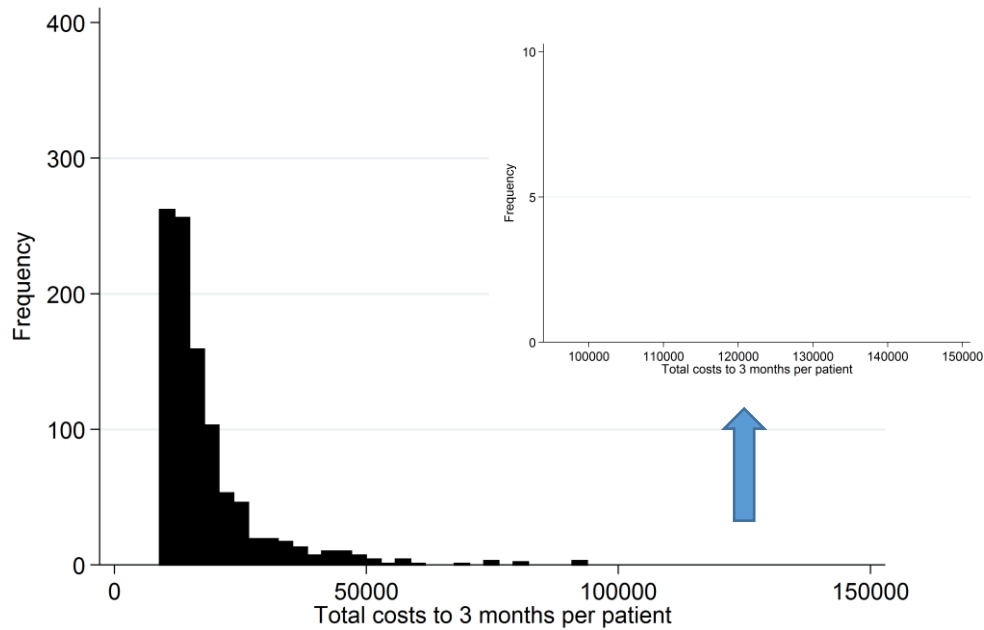
CI, Confidence interval; SAEs, Serious adverse events; SE, Standard error

Costs do not always sum to totals owing to rounding.

^a Includes days in another unit/hospital once transferred out of the cardiac unit

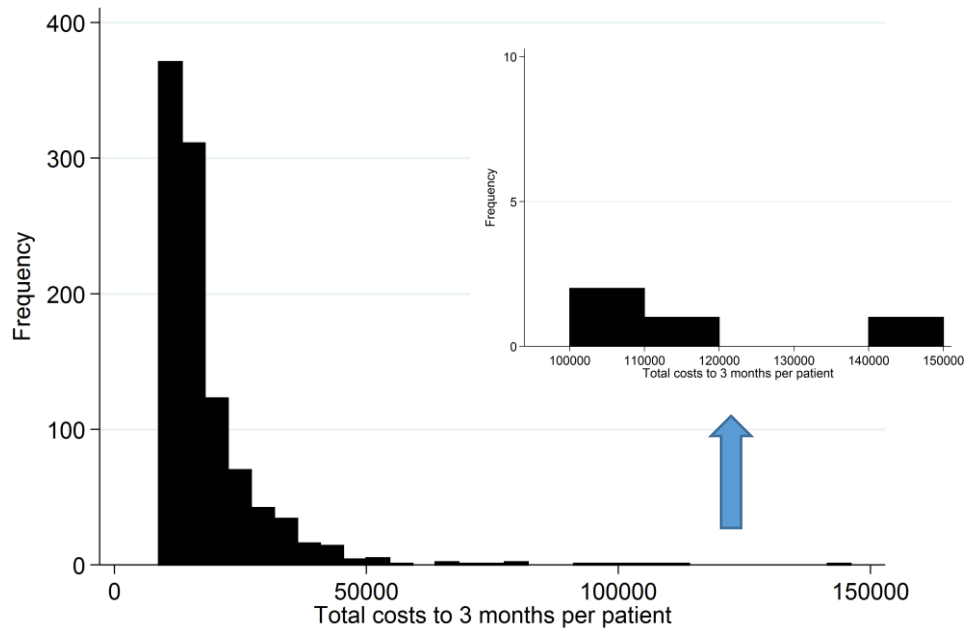
Apart from for RBCs, the differences in costs between the groups are small, although there is substantial uncertainty around these differences (as is evident from the 95% CIs in the final column in **Table 5.7**). In terms of the distribution of costs across the trial groups, the histograms presented in **Figures 5.2** and **5.3** show that the cost data were skewed for both groups, which is a common finding in economic evaluations. This skewness was enhanced by the existence of a few very high cost outliers, especially in the liberal group. There were four patients with costs over £100,000, who were all in the liberal group.

Figure 5.2: Mean total costs (£) per patient in the restrictive group



The inset graph shows that there were no extreme outliers in the restrictive group.

Figure 5.3: Mean total costs (£) per patient in the liberal group

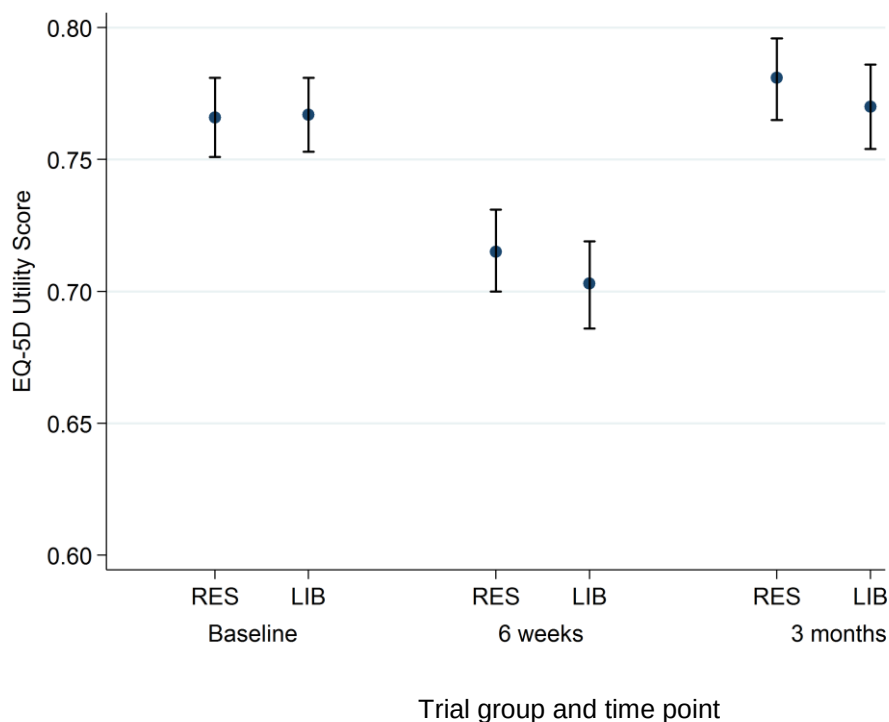


The inset graph shows that there were extreme outliers in the liberal group.

5.5.4 Quality-adjusted life-years (QALYs)

A summary of the mean EQ-5D scores at each of the time points and the QALYs gained in each group are shown in **Figure 5.4** and in **Table 5.8**. **Figure 5.4** only includes patients who were alive at each time point, whereas in **Table 5.8** patients who died are included with scores of zero from the date of death. On average, for patients who survive, their EQ-5D scores return to their pre-operative level, but on average across all patients EQ-5D scores did not quite return to their pre-operative level by three months in either treatment group.

Figure 5.4: Mean EQ-5D utility scores (and 95% CI) at each time point for each treatment group



Key: LIB = Liberal threshold; RES = Restrictive threshold

Table 5.8: Results for EQ-5D scores and QALYs

	Restrictive threshold (n=1000) Mean (SE)	Liberal threshold (n=1003) Mean (SE)	Restrictive versus liberal threshold Mean difference (95% CI)
EQ-5D time point ^a			
Baseline	0.766 (0.008)	0.767 (0.007)	-0.001 (-0.02, 0.02)
6 weeks	0.694 (0.009)	0.689 (0.009)	0.004 (-0.02, 0.03)
3 months	0.748 (0.009)	0.750 (0.009)	-0.002 (-0.03, 0.02)
QALYs to 3 months (adjusted for baseline EQ-5D)	0.1804 (0.0015)	0.1802 (0.0015)	0.0001 (-0.0041, 0.0043)

CI, Confidence interval; QALY, Quality-adjusted life-year; SE, Standard error

^a Deaths included as zero

As **Table 5.8** shows, there is very little difference between the groups for EQ-5D scores at any of the three time points, and a tiny (non-significant difference) in QALYs between the groups. Indeed, the QALYs to three months are 0.180 for both the restrictive and liberal groups, with a mean difference of only 0.0001. Given the significant difference in deaths between the groups (more deaths in the restrictive group), potential reasons for why the difference in deaths did not appear to translate into a difference in QALYs were explored. The exploratory plots of the QALY data conducted are described in **Appendix 22**. It was concluded that there could genuinely be no real difference in QALYs between the restrictive and liberal groups, despite the difference in deaths.

5.5.5 Base case cost-effectiveness results

Cost-effectiveness results are shown in **Table 5.9**. The differences in costs and QALYs between the groups are small and neither difference is statistically significant. The difference between the groups for QALYs, which is the denominator for the ICER, is particularly small. Dividing the difference in costs by a tiny number close to zero, results in a very large ICER. Based on the point estimate of the ICER (-£2,545,782), the restrictive threshold is considered cost-effective: the restrictive threshold is dominant over the liberal threshold as it is both more effective and less costly. However, there is great uncertainty

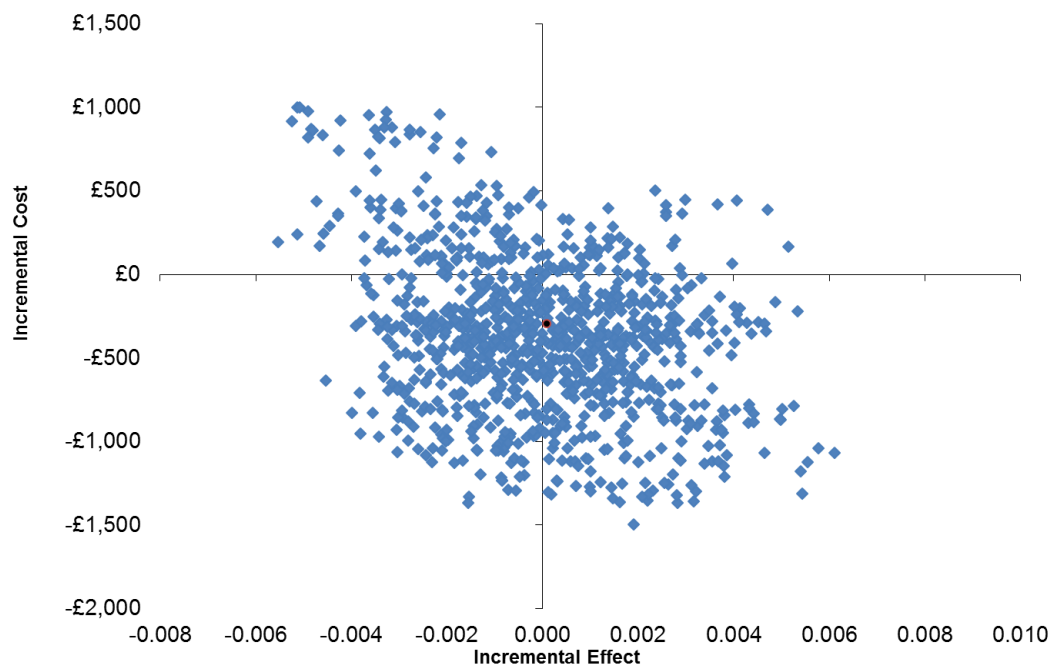
around this result, as shown on the cost-effectiveness plane in **Figure 5.5**. The black dot is the point estimate of the cost and QALY difference, and is close to the origin (the point where the axes cross and the incremental costs and effects are zero). The bootstrap replicates of the cost and QALY differences cover all four quadrants of the cost-effectiveness plane, which illustrates that there is actually very little difference between the two groups and much uncertainty. There is a 41% probability that the restrictive threshold dominates the liberal threshold, but also a 13% probability of the reverse scenario, that the liberal threshold dominates the restrictive threshold.

Table 5.9: Base case cost-effectiveness results

	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Difference
Total costs (95% CI)	£18092 (£17467, £18716)	£18390 (£17646, £19134)	-£298 (-£1212, £615)
QALYs (adjusted for baseline EQ-5D) (95% CI)	0.1804 (0.1772, 0.1836)	0.1802 (0.1773, 0.1832)	0.0001 (-0.0041, 0.0043)
		ICER (Cost/QALY)	Restrictive dominant (-£2,545,782)

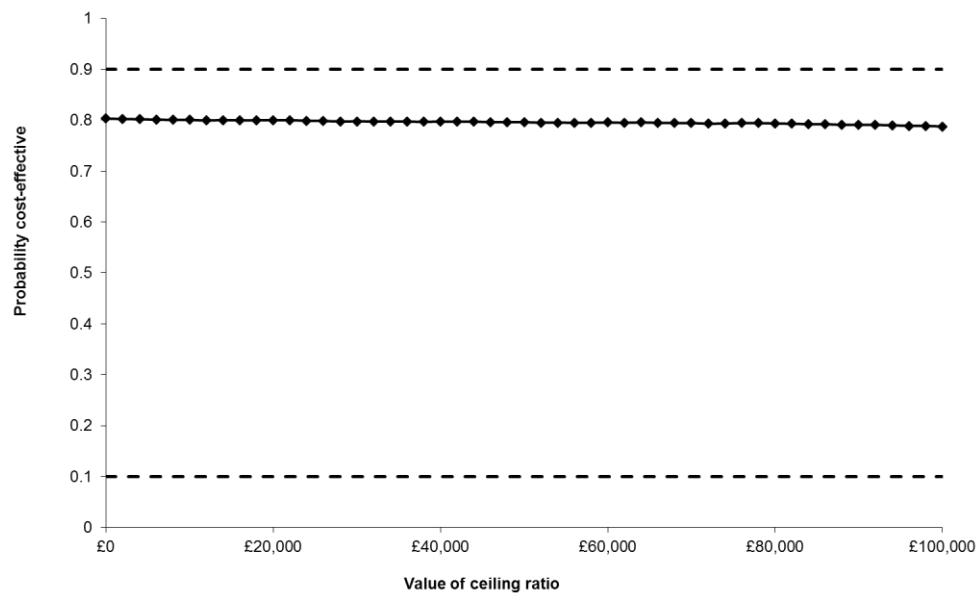
CI, Confidence interval; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life-year

Figure 5.5: Cost-effectiveness plane



The cost-effectiveness acceptability curve (CEAC) in **Figure 5.6** shows the probability that the restrictive threshold is cost-effective for a range of willingness-to-pay thresholds. If a decision-maker is willing to pay £20,000 for an additional QALY (the threshold at which NICE generally considers an intervention to be cost-effective), then the probability of restrictive being cost-effective is 80%. The probability that a restrictive threshold is cost-effective changes little across a broad range of willingness-to-pay thresholds, indicating that this probability is invariant to the willingness-to-pay threshold. Across ceiling ratios from £0 to £100,000, a restrictive threshold has a probability of being cost-effective of 0.79-0.80 and the liberal threshold has a probability of being cost-effective of 0.20-0.21. Clearly the restrictive threshold is more likely to be cost-effective, but there is much uncertainty around this. The dotted lines at 0.1 and 0.9 indicate the 80% confidence limits for the probability that a restrictive threshold is cost-effective. Since these horizontal lines do not cut the curve at any point, the 80% confidence limits on cost-effectiveness do not exist.

Figure 5.6: Cost-effectiveness acceptability curve



5.5.6 Sensitivity analyses

The results of the sensitivity analyses conducted around costs and QALYs are provided in full in **Appendix 23**, and key findings are summarised here. None of the sensitivity analyses around unit costs had a great impact on the cost difference between the groups, and findings reinforced how similar resource use was between the groups. Compared to the sensitivity analysis which excluded all blood administration costs, using the costs of administering blood (as in the base case analysis), costs increased by £173 in the restrictive group and £216 in the liberal group.

There were a few high cost outliers in both groups, and four patients with costs over £100,000 all of whom were in the liberal group. If these four patients are excluded, the liberal group becomes less expensive and more effective than the restrictive group, and conclusions are reversed (based on the point estimate). While there is much uncertainty around these findings, these four patients are clearly exerting a significant impact on the cost and cost-effectiveness results.

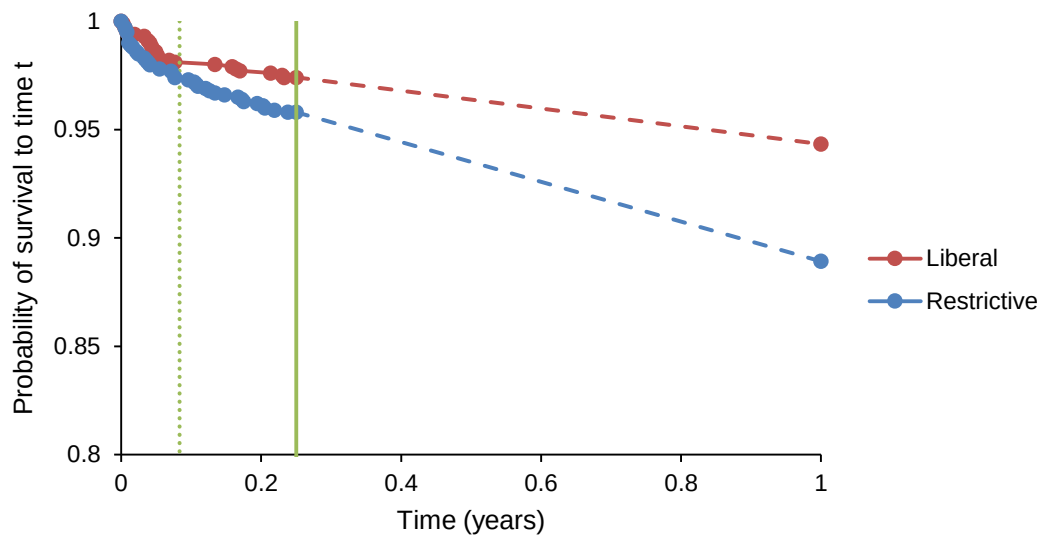
When life-years were considered as an alternative outcome measure, the restrictive threshold was less effective (given the greater number of deaths) and also less costly than the liberal threshold. This analysis generated a trade-off between effectiveness and cost; based on the point estimate of cost-effectiveness, if a decision-maker's willingness-to-accept compensation for the loss of one life-year were £20,000, then a restrictive threshold would be considered cost-effective, but there was considerable uncertainty around this.

One of the sensitivity analyses around outcomes considered not adjusting QALYs for baseline EQ-5D. While the groups appear well balanced at baseline suggesting this adjustment might not be necessary, there was concern that differences at three months were so small, that any imbalance at baseline could influence findings. Conservatively therefore, QALYs were adjusted for baseline EQ-5D. If QALYs are not adjusted, the mean difference between the groups is -0.00002 (compared to 0.001 in the base case). Although the sign of the difference changes, this does not alter cost-effectiveness conclusions. If QALYs are not adjusted the estimate of the ICER is in the order of £14.9 million; given that under this scenario the restrictive threshold is both less costly and less effective, a restrictive threshold would still be preferred on cost-effectiveness grounds.

5.5.7 Scenario analyses

Scenario analyses were undertaken to evaluate the effect on QALYs of propagating the difference in mortality to a longer, 12 month time horizon. The survival curves to three months are shown in **Figure 5.7**. Patients were more likely to die in the first month after surgery (one month is indicated by the green dashed line), than in months two and three. Alternative scenarios around the treatment effect on mortality were considered, these are listed in **Table 5.10**. The coloured dashed lines in **Figure 5.7** show one scenario (number two in **Table 5.10**), that mortality continues at the same rate as months two and three.

Figure 5.7: Survival curves for each trial group



The results of the scenario analyses are shown in **Table 5.10**. If the treatment effect on mortality increases or remains the same then marginally fewer QALYs are gained in the restrictive group than the liberal group. In these scenarios, given the restrictive threshold is also less costly, the ICER represents the incremental saving associated with the loss of one QALY by adopting a restrictive rather than a liberal threshold. In these scenarios, a restrictive threshold would be considered cost-effective (compared to a threshold of £20,000 per QALY), particularly for scenarios where the treatment effect remains the same. If the treatment effect on mortality decreases over the remaining months of the year, then QALYs are slightly higher in the restrictive group, and this policy dominates a liberal threshold. Propagating the difference in mortality to a longer time horizon does not alter the conclusions of the base case analyses.

Table 5.10: The effect on QALYs and cost-effectiveness results of alternative assumptions around extrapolating to a 12 month time horizon

Scenario for mortality from three to 12 months		QALYs		Difference	ICER (Cost/QALY)
		Restrictive threshold (n=1000)	Liberal threshold (n=1003)		
Treatment effect on mortality increasing					
1	Mortality in each group continues at the same rate as the first 3 months	0.708	0.722	-0.014	£21,579
2	Mortality in each group continues at the same rate as months 2 and 3	0.722	0.735	-0.013	£23,851
Treatment effect on mortality remains the same					
3	Mortality in each group continues at the mean rate for months 1-3 across all patients	0.715	0.716	-0.001	£252,559
4	Mortality in each group continues at the restrictive threshold rate in the first 3 months	0.721	0.722	-0.001	£266,866
5	Mortality in each group continues at the liberal threshold rate in the first 3 months	0.708	0.710	-0.001	£238,481
Treatment effect on mortality decreasing					
6	Mortality is calculated as per scenario 3, and then the two 12 month survival probabilities are averaged and applied to each group	0.717	0.714	0.003	Restrictive dominant (-£98,345)

QALY, Quality-adjusted life-year

5.5.8 Subgroup analyses

The results of the seven subgroup analyses conducted to investigate whether cost-effectiveness results varied between patient subgroups are presented in **Appendix 25**.

There were no significant subgroup interactions.

5.6 Discussion

In this chapter the cost-effectiveness of a restrictive compared to a liberal transfusion threshold after cardiac surgery has been assessed within an RCT. There was very little difference between the alternative transfusion groups in either costs or effects, and great uncertainty around the cost-effectiveness results. When a breakdown of total costs was considered, there was a clear difference in the costs associated with RBCs between the two groups, as expected because the liberal group were given more RBCs by definition; otherwise, cost components were very similar. The differences in cost between groups were about the same when considering only the RBC costs and when considering all costs; however, the former difference was estimated more precisely than the latter. Mean QALYs to three months were effectively identical in both groups. The point estimate of cost-effectiveness suggested that the restrictive group was more effective (very slightly greater QALY gain) and less costly than the liberal group (i.e. dominant), and therefore cost-effective. However, the extreme uncertainty around this result makes the point estimate less informative. The uncertainty was very evident on the cost-effectiveness plane; the point estimate was close to the origin, and the bootstrap replicates of the cost and QALY differences covered all four quadrants. Moreover, there were several outliers in the liberal group which exerted a substantial influence on the average costs of patients in that treatment group, reversing the direction of the results described above when they were excluded.

Given the higher mortality rate in the restrictive group, there was a clearer difference between the groups, favouring the liberal threshold, when life-years were considered as an alternative outcome measure; however the point estimate of cost-effectiveness still suggested that the restrictive threshold was cost-effective compared to the liberal threshold in this sensitivity analysis. This difference in mortality was not anticipated, and suggests that a longer time horizon would have been useful. Future studies might consider this, and

could make use of existing national datasets such as Hospital Episode Statistics to capture healthcare resource use over a longer time horizon.[150] Conclusions from post hoc scenario analyses assessing the impact on QALYs and cost-effectiveness results of propagating the difference in mortality to a longer time horizon did not differ from the base case results; in each scenario a restrictive threshold was favoured.

This economic evaluation was based on high quality cost and quality of life individual patient data collected in a large randomised trial, which achieved excellent completeness of follow-up. Four times more patients were randomised in TITRe2 than in the next largest trial comparing restrictive and liberal transfusion thresholds after cardiac surgery, and unlike previous studies only patients who breached the liberal transfusion threshold were randomised.[130-132] This avoided diluting the treatment effect, and cost and cost-effectiveness estimates, with similar numbers of patients in each group who were unlikely to be transfused. Very detailed data collection was undertaken, particularly around the occurrence of complications, which were one of the key drivers of total costs. Complications that made up the primary clinical outcome accounted for only 4% of the total costs of inpatient complications, it was therefore important to have collected detailed information on other complications. Despite all these strengths the economic evaluation did not find a difference between the groups. This is not an uncommon finding for within-trial economic evaluations, partly because sample size calculations rarely take into account economic endpoints, and may not be sufficiently powered to detect differences in these endpoints.[151] Retrospective sample size calculations suggest that this was not a major problem for this large trial however, at 80% power and with a two-sided test at the 5% level, there was sufficient power to detect a difference of £1500 in costs and 0.007 in QALYs. Differences in costs and QALYs between groups were much smaller than this, and therefore even with much large sample sizes a difference may well not have been found; in reality there may be very little difference between the groups. The very detailed data collection that was undertaken allows us to be more confident in this conclusion.

To the best of my knowledge this is the first trial-based economic evaluation assessing the cost-effectiveness of alternative transfusion thresholds after cardiac surgery. Indeed, apart from an exploratory economic evaluation of a pilot trial, this is the only trial-based economic evaluation assessing alternative transfusion thresholds in any clinical area. A recent review of observational studies that compared the effect of RBC transfusion with no transfusion in adult cardiac surgery patients identified 39 studies,[124] none of which included an economic evaluation, and only one of which reported any information on costs, which was limited to the costs of LOS and blood products.[120] There are no relevant studies with which to compare the results presented here.

Although the TITRe2 trial was a well-designed and rigorously conducted trial, the interpretation of its cost-effectiveness results is challenging because the differences in costs and quality of life between the groups were small and uncertain. Point estimates of cost-effectiveness (based on QALYs as the primary health economic outcome measure or life-years in a sensitivity analysis) suggested that a restrictive threshold was cost-effective, but there was extreme uncertainty around these results. From an economic perspective, it was concluded that there is no difference between the restrictive and liberal groups. While there was no difference in the primary clinical outcome, there was a borderline difference in mortality between the groups, favouring a liberal threshold. From a policy perspective, it is difficult to recommend restrictive transfusion after cardiac surgery, given that more patients died in the restrictive group.

A difference of approximately £300 between the groups is a modest cost difference (approximately 2% of total costs). However, since 36,134 cardiac surgery procedures were undertaken in the UK in 2013/14,[85] a difference of £300 in each procedure would have resulted in savings or additional costs of £10.8 million for the NHS. The effect of this cost difference, and whether it is a cost saving or additional cost, is clearly important for the

NHS; even small differences in individual costs can have a significant impact on overall budgets.

In summary, there is no health economic evidence to suggest a difference between the two alternative transfusion thresholds, as there was very little difference between the groups in either costs or effects, and great uncertainty around the cost-effectiveness results. While a restrictive threshold clearly saves blood (a scarce resource) and reduces costs associated with transfusion, there is no evidence to suggest such a policy reduces overall costs to the NHS. Studies to date comparing alternative transfusion thresholds have defined restrictive and liberal thresholds differently, further evidence is required to identify the most appropriate threshold. Given the clinical findings, future research might usefully investigate a different hypothesis that more liberal transfusion may be beneficial after cardiac surgery. A large RCT comparing restrictive and liberal thresholds in patients having cardiac surgery is underway in Canada and the US (the TRICS-III trial).[152] This will provide new evidence on this topic, and the results are likely to inform the direction of future research. To provide evidence of a difference in mortality associated with alternative transfusion thresholds would require a very large sample size, since mortality rates are low after cardiac surgery. This might lead us to consider alternative study designs, such as an observational study comparing the outcomes of patients who are and are not transfused. In practice however, it is difficult to collect information on all the factors that a clinician might weigh up when considering whether to prescribe a transfusion to a patient, and therefore adjusting for confounding factors is likely to be problematic, which may lead to biased results.[124] The issue of confounding does not arise in observational studies where the same patients are included in both arms of the study, as will be seen in the next chapter.

This chapter has considered the cost-effectiveness of alternative transfusion thresholds to treat anaemia after cardiac surgery. Patients are also given transfusions after cardiac

surgery to treat bleeding; the cost-effectiveness of alternative transfusion management strategies to guide treatment due to bleeding are investigated in the next chapter.

Chapter 6: Cost-effectiveness analysis of bedside clotting tests in cardiac surgery

6.1 Introduction

As described in Chapter 3, patients undergoing cardiac surgery are at risk of coagulopathy, which may result in major bleeding and the need for a re-operation, and is associated with significant mortality, morbidity and resource use.[153-155] A number of pre-operative and intra-operative factors are known to contribute to coagulopathy in these patients, such as renal impairment, anaemia, receiving platelet inhibitors within seven days of surgery and complex surgery that prolongs the duration of cardiopulmonary bypass. The resulting defects in clotting are poorly understood, leading to wide variation in treatment which is often non-specific. Early diagnosis of specific clotting defects would enable more timely and targeted treatments to be given to patients, and avoid unnecessary transfusions. Recent NICE guidance recommends the routine use of point-of-care (POC) diagnostic tests of coagulopathy for patients undergoing cardiac surgery.[155] However, there is uncertainty around the clinical effectiveness and cost-effectiveness of these tests,[156] reflected in the substantial variation in their use. Of the 17 cardiac centres who responded to a survey of transfusion practice, six centres reported using POC tests for 76-100% of patients, five centres used them for 26-75% of patients, four centres for 1-25% of patients, and two centres did not use them at all.[93] A few RCTs have assessed the introduction of POC tests, but a recent systematic review found many of these trials had methodological issues and a high risk of bias.[157]

In this chapter, the cost-effectiveness of introducing routine post-operative POC testing of clotting abnormalities in all patients undergoing cardiac surgery is assessed using decision-analytic modelling. The economic evaluation is based on the coagulation and platelet laboratory testing in cardiac surgery (COPTIC) observational study (ISRCTN20778544),

which was funded by the NIHR Programme Grants for Applied Research Programme. The COPTIC study is described first, before details of the economic model development and structure are presented. Cost-effectiveness results are presented together with a range of sensitivity analyses assessing the impact on results of variation in key uncertainties in the model. The results obtained using costs estimated in Chapter 4 are compared to results without costing blood administration, in order to explore whether cost-effectiveness decisions are altered by improvements in these cost estimates. The chapter concludes with a discussion of the findings and the limitations of the work, and overall their implications for patient blood management in cardiac surgery.

6.2 The coagulation and platelet laboratory testing in cardiac surgery (COPTIC) study

COPTIC was a prospective observational study conducted between March 2010 and September 2012 at a tertiary cardiac surgery centre in the UK; the Bristol Heart Institute, University Hospitals of Bristol NHS Foundation Trust. The study was designed to assess the benefits of routine use of POC tests for cardiac surgery patients. Specifically, the aim was to assess whether the predictive accuracy of a locally developed bleeding risk model based on age, comorbidity, treatment with dual anti-platelet therapy within seven days of surgery, and surgical complexity could be improved by adding the results of pre and/or post-operative POC test values. The POC tests under consideration were those in current use in theatres and/or intensive care units in UK cardiac centres: ROTEM (ROTEM® Delta, TEM International GmbH, Munich, Germany; www.rotem.de), Thromboelastography (TEG) (TEG® 5000 analyser, Haemonetics Corporation, Niles, IL, US; www.haemonetics.com), and Multiplate® analyser (Roche, Rotkreuz, Switzerland). Results of all three POC tests were considered post-operatively, only the Multiplate test was considered pre-operatively (Multiplate is designed to measure the degree of platelet inhibition by anti-platelets medications, which is the most important abnormality pre-operatively). Analysis of the

clinical data from COPTIC showed that pre-operative Multiplate test values did not improve predictive accuracy, so the focus here is on the post-operative tests.

Consecutive adult patients undergoing cardiac surgery were invited to participate in the study and 2495 patients were recruited between March 2010 and August 2012. Patients had two blood samples taken in theatre, the first pre-operatively immediately before the induction of anaesthesia, and the other once they had come off cardiopulmonary bypass and been given routine protamine to reverse the effects of heparin (which is given to prevent blood clotting during surgery). These blood samples were taken so that the POC tests could be conducted, but the results were not shared with any of the clinical team responsible for the patient. This was an observational study; patients received standard care, and decisions about transfusion were guided by standard laboratory investigations and ad hoc TEG analyses in accordance with routine practice.

The primary outcome of the study was post-operative Clinical Concern about Bleeding (CCB), a measure designed to capture bleeding that was likely to cause patient harm. Patients were defined as having post-operative CCB if they met any of three criteria:

- Post-operative blood loss from the chest drain of more than 600ml in the first six hours after admission to the cardiac intensive care unit (CICU);
- Intervention with a non-routine early pro-haemostatic treatment defined as additional protamine after initial heparin reversal, FFP, cryoprecipitate, platelets, anti-fibrinolytic drug, recombinant activated factor VII (rFVIIa) or fibrinogen concentrate in the first 12 hours after CICU admission;
- Reoperation for bleeding recorded during hospital stay for which no 'surgical' cause could be found.

Patients were followed-up until hospital discharge or death. Some clinical outcomes relating to CCB were captured on CRFs (**Appendix 26**), but most other data were collected from routine sources. Information on patients' baseline characteristics, operative and post-operative details (such as post-operative complications and length of stay) were obtained from two existing databases at Bristol Heart Institute: the Patient Analysis and Tracking System (PATS, Dendrite Clinical Systems Ltd, New Malden, UK) and the intensive care unit Innovian® data management system (Drager Medical Inc., Telford, PA, US). Transfusion data were obtained from the hospital blood bank. CRF, PATS and Innovian data were linked to the hospital's Clinical Biochemistry Database to obtain serum creatinine data for the estimation of acute kidney injury, and to the electronic laboratory databases to obtain the ROTEM, TEG and Multiplate test results. While the majority of the data came from existing sources, a considerable amount of work was undertaken by collaborators at the Clinical Trials and Evaluation Unit (University of Bristol) to link data from each of these sources based on pseudoanonymised patient identifiers (hospital number and date of operation).

For the clinical analyses, only patients with complete data for clinical outcomes, risk factors and test results were included. The analysis population for post-operative CCB included 1,833 of the 2,495 patients recruited. The differences between patients who were included and excluded were small, suggesting that the missing clinical outcomes, risk factors or test results were missing at random. Analyses first considered whether each POC test improved the predictive accuracy of the bleeding risk model, and then whether combinations of tests improved accuracy. The added value of POC tests was assessed by comparing the area under the Receiver Operating Characteristic (ROC) curve of the baseline bleeding risk model (a measure of the predictive accuracy of the logistic regression model), with the area under the ROC curve of the bleeding risk model with the POC test values. Individually, each of the tests improved the predictive accuracy of the clinical risk prediction model, the best performing test being TEG. The best performing combination of

tests was TEG and Multiplate. However, the differences in performance between any of the tests and no test, and between TEG and Multiplate and TEG alone were small. The ROC area was 0.72 for the baseline bleeding risk model, this was improved to 0.74 with the addition of TEG and 0.75 with the addition of TEG and Multiplate.

6.3 Aim of the cost-effectiveness analysis

The intention had been to identify the most effective test (or combination of tests) from the clinical analyses and to perform a cost-effectiveness analysis of the test(s). As the pre-operative Multiplate test showed little ability to predict CCB, the focus is on the post-operative tests and post-operative CCB. However, as the clinical results were similar for the different post-operative tests, the cost-effectiveness of all the tests was evaluated. Unlike TEG and ROTEM, the Multiplate test indicates the need for platelets only, rather than indicating the need for a range of blood products. It was therefore most clinically plausible to consider its introduction into routine practice in combination with either TEG or ROTEM, rather than on its own. The test options evaluated are shown in **Figure 6.1**.

Figure 6.1: Test options evaluated



For each of these four test options, the aim was to evaluate the routine use of POC testing in all patients. While current practice did not include the routine use of these tests (at the time of the study), the care of some patients may have been guided by the ad hoc use of a POC test, specifically a TEG test. The comparison was therefore between current practice (which may have included ad hoc use of a TEG test) versus routine post-operative POC testing in all patients undergoing cardiac surgery. The research question was therefore:

“Is it cost-effective to introduce routine post-operative point-of-care testing in all patients undergoing cardiac surgery?”

The clinical analyses evaluated the performance of the POC tests at predicting CCB, rather than evaluating how they would be used in practice and their effect on treatments given to patients. In order to evaluate the cost-effectiveness of the tests, it is necessary to consider how they would impact on a patient's care pathway (rather than an intermediary outcome such as predicting CCB) and how they would be used in practice: what test result cut-offs would indicate a positive test result, and what treatment this could result in. In the cost-effectiveness analyses, POC tests were considered to “rule in” treatments for patients but not to “rule out” treatment. If a POC test result was positive (or an ad hoc TEG test was positive), this was assumed to lead to a prophylactic treatment of protamine, platelets, FFP and/or cryoprecipitate. If a test result was negative this was assumed to have no impact on a patient's care pathway (based on advice from the study research team).

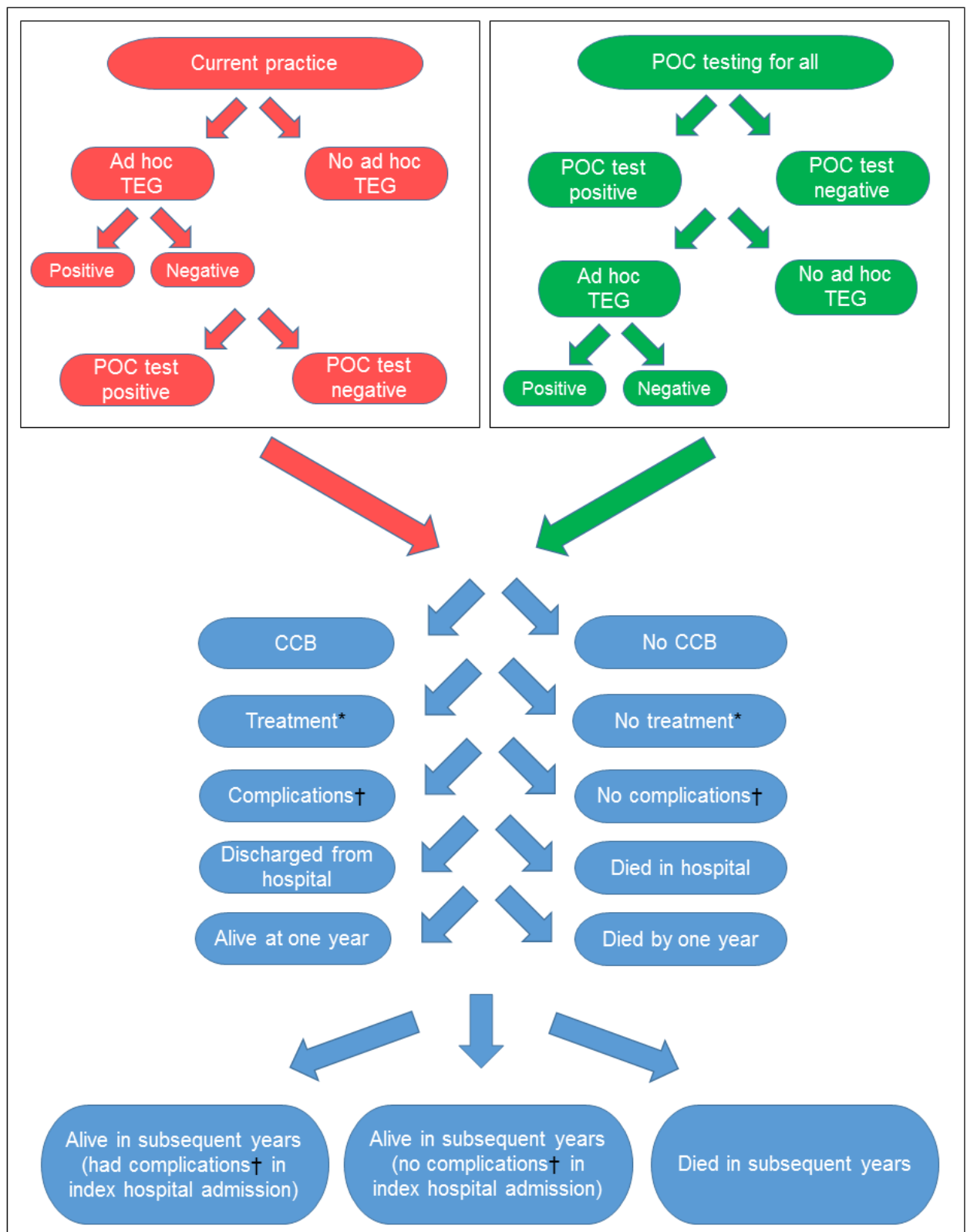
While introducing a test for all patients adds a cost to everyone in the short-term, the hypothesis was that this would provide better treatment guidance, and could reduce overall costs in the longer term. The aim of routine testing is to prevent severe blood loss, reopening of the chest for bleeding, large volume transfusion, further pro-haemostatic treatments (second line FFP, platelets, cryoprecipitate or rFVIIa) or shock and major morbidity (MI, stroke, sepsis or AKI) by prophylactic treatment.[154] Patients with a positive test result would receive timely and appropriate prophylactic treatment in order to prevent the development of CCB, and reduce the frequency of adverse events attributable to coagulopathic bleeding. This reduction in adverse events could lead to a reduction in total healthcare costs and improve outcomes.

The decision model used to address this research question is described next, the model structure is presented and then details are given of how the model parameters of probabilities, costs and outcomes were estimated.

6.4 Economic decision model methods

To address the question: *“Is it cost-effective to introduce routine post-operative point-of-care testing in all patients undergoing cardiac surgery?”*, an economic decision model was built to simulate the costs and effects of introducing a POC test for all patients compared to current practice. As uncertainty surrounds the performance of the POC tests in practice, a flexible framework was required to facilitate the assessment of uncertainty around parameter estimates. Models are a simplification of the real world, and will never capture every last possible scenario associated with an intervention, but the key consequences need to be included when the model is conceptualised and structured.[61] It is helpful if there are clinical events driving the model. The model was developed in consultation with clinical experts on the COPTIC study team, **Figure 6.2** highlights the model scenarios. The initial model scenarios are based on the test results, and are slightly different for current practice (shown in red) compared to post-operative POC testing for all (in green). Thereafter the model scenarios are the same for each arm of the model (in blue).

Figure 6.2: Cost-effectiveness model scenarios



CCB, Clinical concern about bleeding; POC, Point-of-care

* Treatment in the form of protamine, platelets, clotting factors, reoperation for bleeding, or five or more units of RBCs

† Complications defined as myocardial infarction, stroke, sepsis, or acute kidney injury.

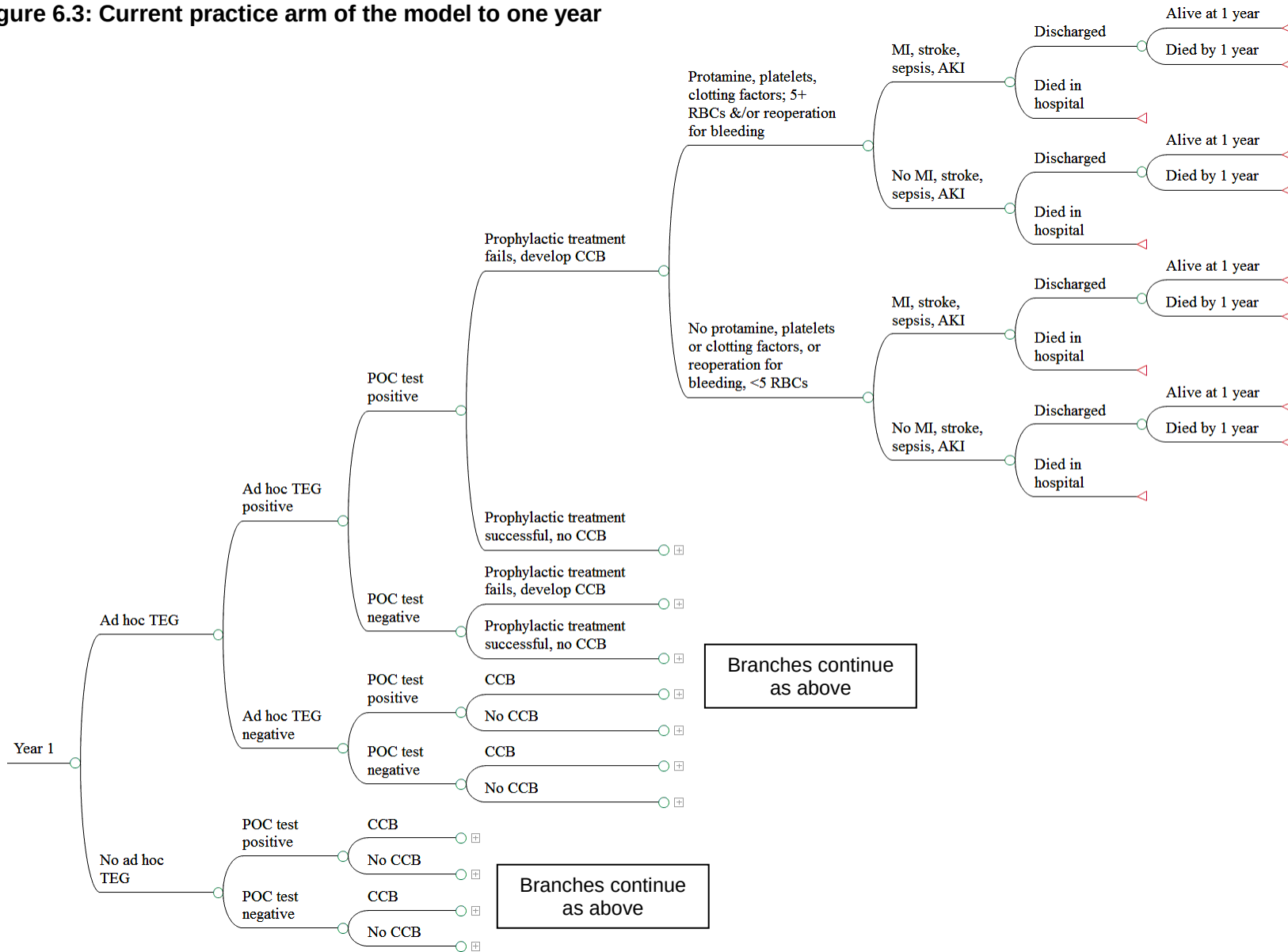
6.4.1 Cost-effectiveness model structure

The model combines the use of decision trees and Markov models and was developed in TreeAge Pro 2013.[158] All patients start in the 'Year 1' health state of the Markov model, and move through a decision tree which was used to model the patient pathway after leaving the operating theatre to one year post-surgery. At the end of the decision tree, patients move to one of three further health states in the Markov model (alive having had no complications during the index hospital admission, alive having had complications in hospital, and dead), which was then used to assess longer term consequences on an annual basis. The model structure was split into two main arms (branches): the top branch represents current practice and the bottom branch represents post-operative POC testing for all.

Current practice arm of model to one year

Figure 6.3 shows the current practice arm of the model for the first year. The decision tree subdivides the starting cohort of patients undergoing cardiac surgery into two, depending on whether patients have an ad hoc TEG test or not. Some patients in the current practice arm had a TEG test, and it was assumed the results were acted upon; it is therefore important to account for this in the current practice pathway.

Figure 6.3: Current practice arm of the model to one year



In the current practice arm, patients who have an ad hoc TEG test are then divided into those whose test is positive and those whose test is negative. The next branches in the tree divide patients into those whose POC test (whichever of the four options is being considered) is positive or negative. Although this information was not used clinically in current practice, it has been incorporated within the structure of the current practice arm to facilitate the population of the model using the COPTIC data, as will be described later. Patients with a positive ad hoc test will receive first line, prophylactic treatment on the basis of the test result; this is likely to be protamine, platelets and/or FFP. This prophylactic treatment may be successful and CCB prevented, or CCB may develop despite the prophylactic treatment. Patients with a negative ad hoc TEG test, and therefore no prophylactic treatment, may also go on to develop CCB or not. Patients are divided into those with and without CCB.

In the current practice arm, patients who do not have an ad hoc TEG are divided into those whose POC test is positive and those whose POC test is negative. As for those with an ad hoc test, this is for the purposes of subsequent ease when populating the tree with COPTIC data. The next branches in the tree for these patients divide them into those with CCB and those without CCB.

Regardless of whether patients had an ad hoc test or not (and whether this was positive or negative), the remaining branches in the tree are identical. After CCB or no CCB, patients are divided into those who receive treatment for clotting abnormalities or bleeding in the form of protamine, platelets, or clotting factors in the first 12 hours after surgery, a reoperation for bleeding or five or more units of RBCs; or not. By definition, the only treatment patients with no CCB would get is five or more units of RBCs. For patients with a negative ad hoc test or no ad hoc test, this includes any protamine, platelets or clotting factors received; for patients who had prophylactic treatment, the protamine, platelets and/or clotting factors are in addition to those received as prophylaxis. As RBCs may be

given for reasons other than bleeding, for example one or two units of RBCs may be given in response to a low haematocrit level or anaemia, it was considered more appropriate to regard large volume transfusions (five or more units of RBCs) than any RBC transfusions, as reliably reflecting clinically important bleeding,[159] hence the criteria set here.

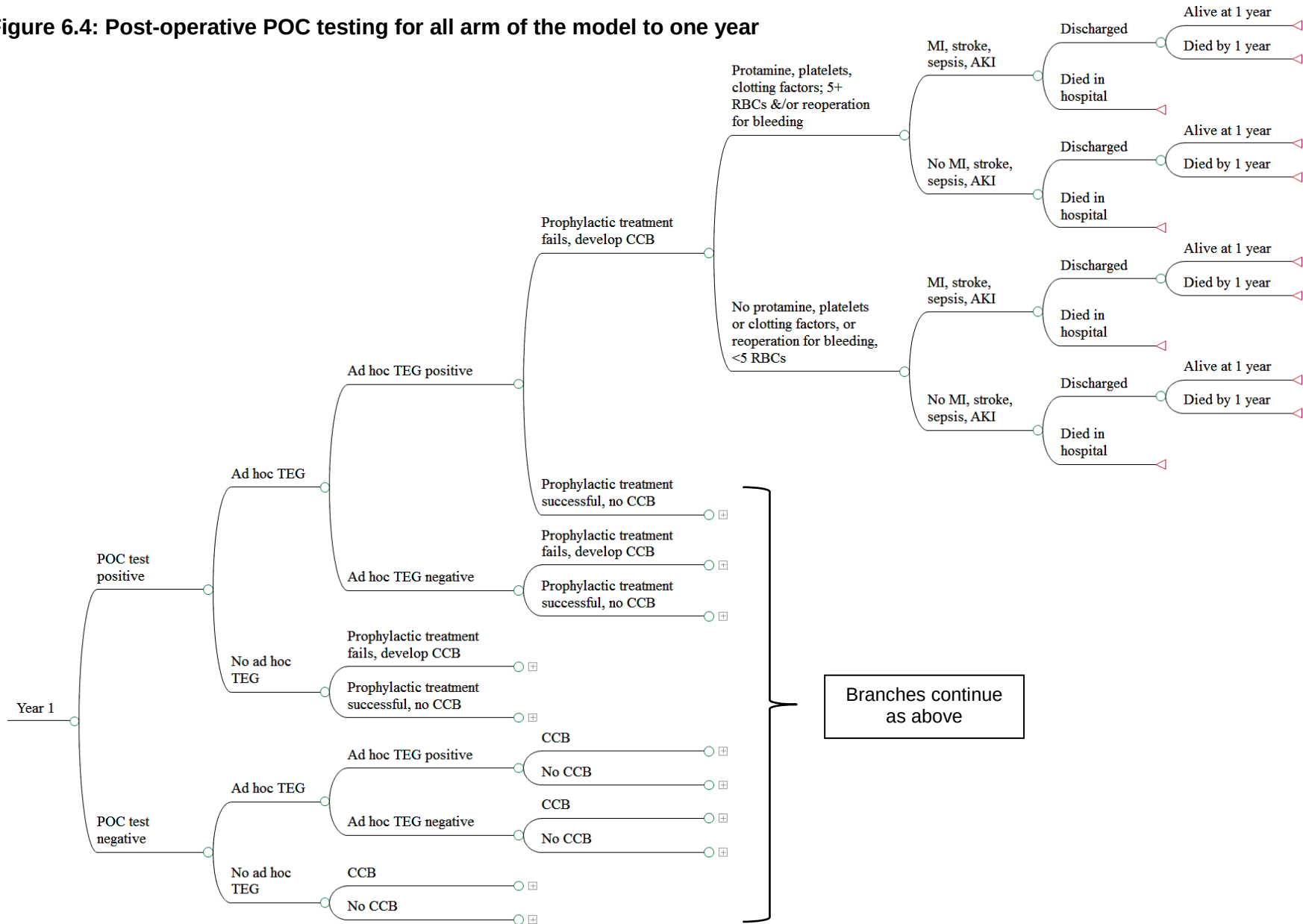
The remaining branches in the tree consider subsequent key events for patients: whether they develop any of four key complications in hospital (MI, stroke, sepsis or AKI), whether they survive to hospital discharge and whether they are alive at one year.

Post-operative POC testing for all

The lower half of the model is shown in **Figure 6.4** and illustrates the intervention arm and the routine use of a post-operative POC test for all patients. The structure of the model is the same regardless of whether the test introduced is TEG or ROTEM, or either test in combination with Multiplate. The post-operative POC test is conducted, and the cohort is split into two groups depending on whether the test result is positive or negative.

Regardless of whether the POC test is positive or negative, patients are then divided into whether they had an ad hoc TEG test or not under current practice. Those with an ad hoc test are further divided into whether this is positive or negative. Patients are divided into these additional groups for the purposes of populating the model, as will be described later.

Figure 6.4: Post-operative POC testing for all arm of the model to one year



If the POC test result is positive, then prophylactic treatment will be given to try to prevent the development of CCB. For patients with a positive POC test result, the following branches then indicate whether this prophylactic treatment is successful or not in preventing CCB. The branches then continue with whether they receive further pro-haemostatic treatments, five or more units of RBCs, or a reopening for bleeding, and thereafter as per this stage in the Current Practice arm, with whether they develop complications, and their survival status at hospital discharge and one year, and then the three health states in the Markov model, as described above.

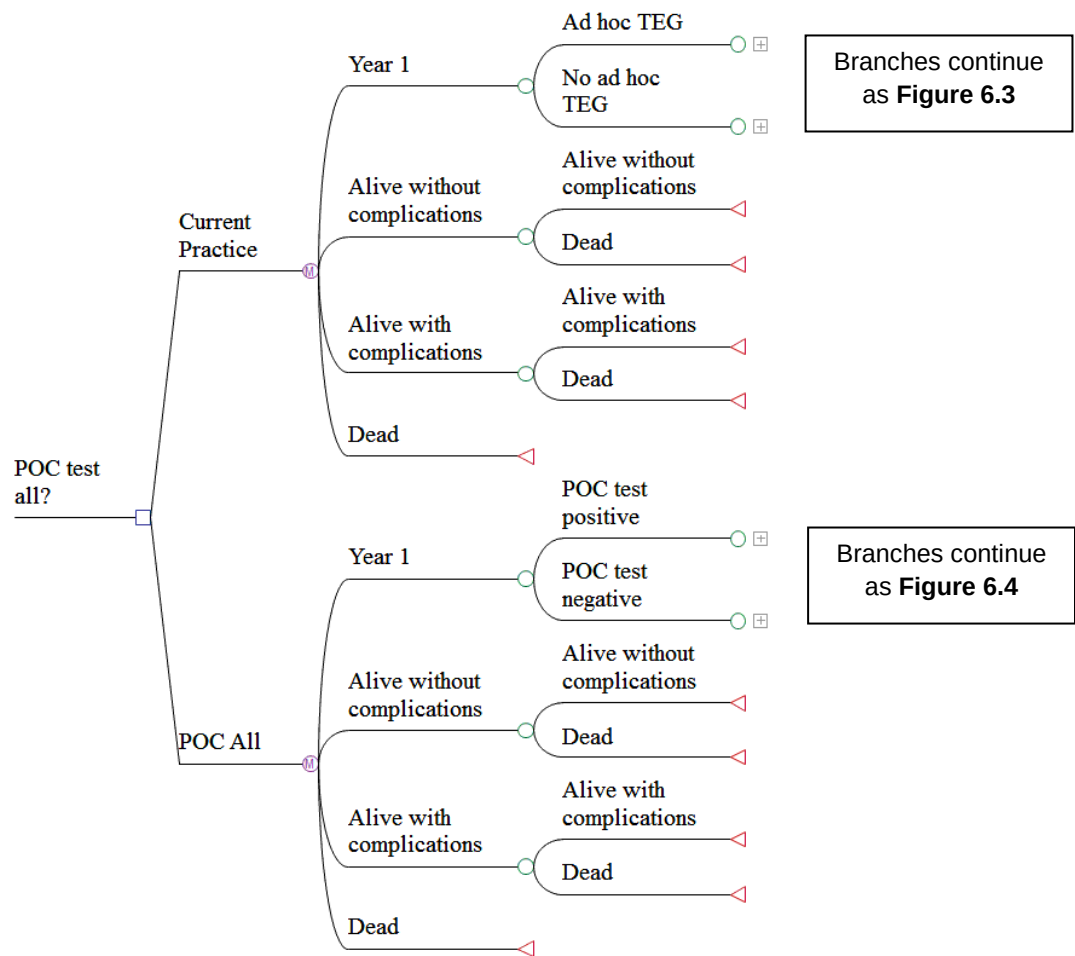
If the test result is negative, this has no impact on a patient's care pathway compared to Current Practice. The branches continue with whether patients develop CCB or not, and as above with whether they receive further treatments or not, develop complications, their survival status at hospital discharge and one year.

Both arms of the model beyond one year

Figure 6.5 shows the structure of the model beyond one year. In each arm, all patients start in 'Year 1' of the Markov model, and move through the decision tree which models the patient pathway to one year, and has just been described (shown in **Figures 6.3** and **6.4**). From one year, the structure of the model is the same in both arms. At one year, patients move into one of three health states in the Markov model: alive having had complications in their index hospital admission; alive having not had complications in their index hospital admission; and dead (**Figure 6.5**). In each of the annual cycles thereafter patients in the alive with complications health state can remain in that health state or die. Similarly patients in the alive without complications health state can remain in that health state or die. The death state is an absorbing state (i.e. patients remain there). The analysis took a five year time horizon, since it was anticipated that all major resource use (and outcomes) would

occur within this timeframe. It is recognised that bias could be introduced if a lifetime time horizon is not adopted. This was considered, but it was felt there were very limited data from which to extrapolate costs and outcomes for these patients to the longer term in a meaningful way, (indeed the extrapolation from hospital discharge to five years does not capture reoccurrence of complications and therefore has its limitations). To assess whether results would be influenced by a longer time horizon, the proportion of patients in each health state in each arm of the model at five years will be compared, and if this differs between arms, a longer time horizon will be implemented. A longer time horizon is also included as a sensitivity analysis.

Figure 6.5: Model structure for both arms beyond one year



6.4.2 Data for the model

The majority of parameters in the model were populated with estimates derived from patient level data from the COPTIC observational study, described earlier, which incorporated the collection of key health economic variables. Analyses of these data (including the POC test results and resource use data) were conducted in Stata 14.[110] From the 1,833 patients included in the clinical analyses of post-operative CCB in COPTIC, 31 patients were excluded from the cost-effectiveness analyses. These 31 patients had a reoperation with a surgical cause of their bleeding; they were not classed as having CCB, but unlike other patients without CCB, they may have had non-RBC products in the first 12 hours after surgery, or have had post-operative blood loss of greater than 600ml at six hours collected in the chest drain, but these were assumed to be related to the surgical cause of bleeding. The cohort for the cost-effectiveness analyses therefore included 1,802 patients. Patients had a mean age of 67 years and 76% were male. Most participants underwent CABG (59%) or valve surgery (22%), and 25% of patients were classed as having post-operative CCB (using the criteria outlined in **Section 6.2**).

The following sections describe how model transition probabilities, costs and outcomes were estimated to one year, largely based on the observational data. The final section describes how model inputs were estimated beyond one year. **Appendix 27** lists all the probabilities, costs and outcome estimates used to populate the base case models. The analysis was conducted from an NHS and personal social services perspective,[46] with costs expressed in 2013/14 UK pounds and outcomes as QALYs. Costs and effects were not discounted in the first year, thereafter a discount rate of 3.5% per year was applied.[68]

Model probabilities to one year – Current Practice arm

The probabilities for each branch of the model to one year were generated using the patient level data from the COPTIC study. Of the starting cohort of patients, 16% had an ad hoc

TEG (284/1802). The result of the ad hoc TEG was not captured in COPTIC, so the results from the POC TEG test were used to determine its result. The TEG test produces a number of results, which have published normal ranges.[160] In consultation with clinical experts on the study team, and based on 100% of the normal ranges, if any of the criteria in the list below were met, a patient was considered to have had a positive ad hoc TEG test result.

Criteria for a positive ad hoc TEG test result

- 1) If CK R (min) : CKH R (min) > 1.5 and if CK R (min) > 8
- 2) If CK R (min) > 8
- 3) If CK α -Angle < 47
- 4) If CK MA < 55
- 5) If CK LY60 > 15.

where CK: citrated kaolin; CKH: citrated kaolin with heparinise; R (min): reaction time (in minutes) to initial fibrin formation; α -Angle: measures the speed of fibrin build-up; MA: maximum amplitude of the fibrin clot; LY60: percent lysis 60 minutes after MA (percentage decrease in clot amplitude).

Patients are then divided according to whether their POC test was positive or negative. Details are given in the next section (Model probabilities to one year – Test All arm) on the criteria used to determine whether a POC test (or test combination) was considered positive or negative, and these criteria were also used to divide patients into POC test positive or negative in the current practice arm.

Patients are classed as having CCB or not, based on the outcomes reported in the COPTIC study (Section 6.2 above), with one adjustment for patients who had a positive ad hoc TEG. Any patient who had a positive ad hoc TEG, and only received quantities of protamine, FFP or platelets that could be considered first line prophylactic treatment, and no other element of the CCB outcome, was reclassified from CCB to no CCB. The protamine, FFP or platelets given which caused the patient to be counted as CCB are considered in this case to be prophylactic, and deemed to have prevented CCB. It was not known what treatments

were given to patients specifically as a result of the ad hoc test, but in-hospital treatment data were available. It was assumed that if a patient received additional protamine only, or up to one unit of platelets and two units of FFP but no additional protamine in the first 12 hours after surgery, and no cryoprecipitate in the first 12 hours, nor had CCB due to blood in the chest drain or a reoperation for bleeding, then they had successful prophylactic treatment. In the base case analysis, 16 patients were reclassified to 'No CCB' on this basis.

The subsequent probabilities of whether patients received treatment in the form of protamine, platelets, clotting factors (FFP, cryoprecipitate or rFVIIa), five or more units of RBCs and/or a reoperation for bleeding, and whether they developed complications (MI, stroke, sepsis or AKI) were straightforward to obtain from the COPTIC study. Only complications occurring in the index hospital admission before discharge were captured, it is not known whether additional events occurred after discharge.

It was known from the PATS (Patient Analysis and Tracking System) database whether patients were discharged from hospital or died in hospital, and survival status at one year was available for all 1,802 patients from the NHS Strategic Tracing Service (NSTS). Probabilities for being discharged from hospital, and for being alive at one year were therefore obtained from the COPTIC study. There were 73 deaths by one year, 31 in the index hospital admission and 42 between hospital discharge and one year.

Model probabilities to one year – Test All arm

Probability of a positive test result and treatments indicated by a positive test result

The TEG, ROTEM and Multiplate POC tests all produce a number of results, many of which have published normal ranges.[160-163] In consultation with clinical experts on the study team, and informed by the normal ranges and a published algorithm for ROTEM,[164] criteria were set to define positive test results and what treatments would be given as a

result. For TEG and ROTEM these values are approximately 80% of normal ranges. Details of the criteria for each POC test and combination of tests (and corresponding treatments) are provided in **Appendix 28**.

Probability prophylactic treatment is successful

For patients who had a positive test result (from TEG or ROTEM, or either TEG/ROTEM in combination with Multiplate) and who were given prophylactic treatment, an estimate of the probability that the prophylactic treatment was successful and the patient would not develop CCB was needed. This is one of the key parameters in the model, but also a major unknown. Although it was not possible to observe this probability, the observational data were used to estimate it. The proportion of patients with CCB who received more than first line treatment, and hence for whom it was assumed that first line treatment failed, was used as an estimate of the failure rate of prophylactic treatment. Primary treatment was assumed to have failed if a patient received more than one unit of platelets, or more than two units of FFP, any cryoprecipitate, rFVIIa or a reoperation for bleeding. There were 154/449 (34.3%) patients with CCB whose treatment failed according to this definition, the base case probability of prophylactic treatment failing was therefore 0.34 (with the complement of 0.66 signifying success). Alternative failure rates were explored in a sensitivity analysis.

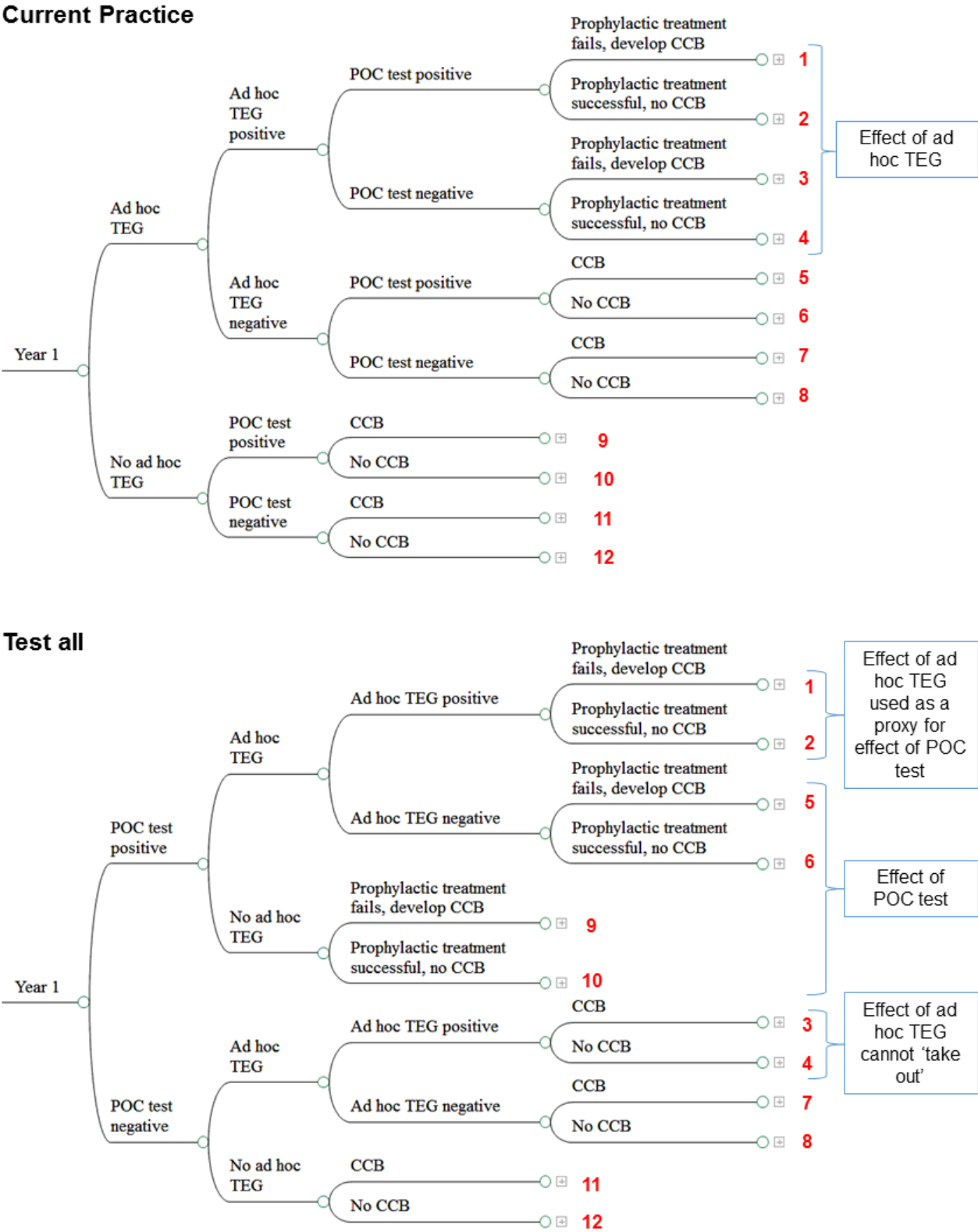
Other probabilities along the patient pathway

Once patients have been divided into whether their POC test is positive or negative based on the criteria in **Appendix 28**, it is then straightforward to use the COPTIC data to divide them into those who had an ad hoc TEG test, and those who did not. For those who had an ad hoc TEG, the POC TEG results were used to classify the ad hoc test as positive or negative, using the same criteria as in the Current Practice arm (and described in the earlier section, Model probabilities to one year – Current Practice arm).

As the POC tests conducted during the observational study were not used to guide treatment, it is not possible to directly observe the impact of the test results on patients' care pathways and on their treatments, costs and outcomes from this point forward in the model. However, at this point in the model, patients have been divided into the same 12 groups based on their POC test result, whether they had an ad hoc test, and its result (if applicable) and whether they had CCB or not, as this point in the Current Practice arm. This was the reason for structuring the model so as to divide patients in the Current Practice arm by whether their POC test was positive or negative, and in the Test All arm by whether they had an ad hoc test and its result. Patients in both arms of the model are divided into the same 12 groups, just in a different order, as can be seen in **Figure 6.6**. Branches labelled on **Figure 6.6** with the same number include the same patients in each arm. For example, patients in group one had an ad hoc test which was positive, a positive POC test and developed CCB – in both arms of the model. The probabilities going forward from these branches numbered one to 12 in the Test All arm can then be considered as per the Current Practice arm, but with some adjustments, which are described next. Costs and life-years which are described later will also be based on these 12 groups, again with some adjustments.

Looking at the POC Test All arm, patients in groups one and two, five and six, and nine and 10 all have a positive POC test. Under a Test All strategy, these patients would receive prophylactic treatment, with the aim of preventing CCB. Patients in groups one and two had a positive ad hoc test, it is therefore assumed that these patients had prophylactic treatment as a result of that test, which is already incorporated into the Current Practice arm. Therefore for groups one and two, no additional effects of the POC test are incorporated into the Test All arm.

Figure 6.6: Current Practice groups of patients used to populate the Test All arm



Patients in groups five and six had a negative ad hoc test, and in groups nine and 10 had no ad hoc test, so none of these patients would have received prophylactic treatment as a result of a test. The effect of the POC test therefore needs to be added here. The existing probabilities of CCB in groups five and nine need to be multiplied by the probability that prophylactic treatment fails, thus increasing the probability that patients are in groups six and 10, rather than five and nine, i.e. increasing the probability that they don't have CCB (compared to those groups under Current Practice).

In reality there were no patients in group six in any of the base case models, therefore it was not possible to switch patients from group five to group six. However, there were less than four patients in group five in each of the models, so this will not have had a significant impact on the results. Patients in groups five and six had a negative ad hoc TEG but a positive POC test; as less stringent criteria were used to determine whether the ad hoc TEG was positive compared to more stringent criteria to determine if the POC test was positive, there are very few patients in these groups. For some of the sensitivity analyses of less stringent criteria for positive POC test results, it was possible to switch patients from group five to group six. In the base case models there were 15-20 patients in group nine under Current Practice, these are the patients for whom the POC test could have a positive impact.

A limitation of not having observed data from which to estimate parameters in the Test All arm of the model is that it is not possible to 'undo' the effect of the ad hoc tests that are used in Current Practice. Above, it was not possible to 'take out' the effect of the ad hoc TEG in groups one and two and add back in the effect of the POC test result, the assumption is that care would be the same under both scenarios (a reasonable assumption if the POC test is a TEG like the ad hoc test, but less realistic if it is a different POC test). Additionally for patients in groups three and four in the Test All arm, who have a negative POC test but in reality have had the effect of a positive ad hoc test incorporated into their care; it is not

possible to take out the effect of any treatment as a result of the ad hoc test. There were between 95 and 107 patients in groups three and four in each of the base case models to whom this applies.

Cost data to one year

In the Current Practice arm, costs included were: healthcare costs to hospital discharge, healthcare costs from hospital discharge to one year and the cost of the ad hoc TEG (if applicable). In the Test arm, costs included were: healthcare costs to hospital discharge and to one year, the cost of the POC test and the cost of prophylactic treatment indicated by a positive test (for patients with positive results). Each of these cost categories are described next. Methods for costing resource use for patients in the COPTIC study are summarised first, before details of how these were used to populate the model with healthcare costs to hospital discharge are given.

Calculating observed healthcare costs to hospital discharge for patients in the COPTIC study

Costs from the end of surgery to hospital discharge were estimated for each patient in the COPTIC study using the resource use data collected. The majority of these data were obtained from two existing datasets, PATS and Innovian, but a considerable amount of additional work was undertaken by collaborators at the Clinical Trials and Evaluation Unit (University of Bristol) to address known limitations of these datasets. For example due to the amount of missing data in PATS for serious post-operative complications such as sepsis and AKI, Innovian data were also used to identify these complications, either by the event being recorded in Innovian or by review of five free-text fields, which were Intensivists review, Problems (Physician Daily Review and Plan), Progress note (Physician Daily Review and Plan), Surgical review, CICU ward round, and Plan of care on discharge. Data were available on the number of units of RBCs, platelets, FFP and cryoprecipitate given during CICU stay, any additional doses of protamine after initial heparin reversal, time spent

in critical care and on a ward, and the time of extubation, complications and use of rFVIIa. The time of extubation was used to differentiate between time spent in critical care that should be considered intensive care (CICU) and time spent in a high dependency unit (HDU). Complications captured and costed were stroke, MI, sepsis, and AKI (a cost was attached to stage 3 only). Any reoperations and use of an intra-aortic balloon pump were also recorded and costed. The PATS database included variables for gastrointestinal and pulmonary complications, haemodynamic support and arrhythmias, however more than 60% of these data were missing. These complications were not secondary clinical outcomes, and therefore additional work was not done to address this missing data. The decision was taken not to use these variables in the costings.

For the variables that were used, missing resource use data were assumed to be missing at random and were handled by applying multiple imputation using a series of chained regression equations.[77] Overall, less than 1% of resource use data were missing, and less than 2% of cases were incomplete. Twenty values were predicted for each missing data cell, essentially creating 20 different datasets. A method called Rubin's Rule (which acknowledges variability between as well as within imputed datasets) was used to summarise data across the 20 datasets.[78]

Appendix 29 summarises observed resource use to hospital discharge for patients in the cohort, and **Appendix 30** shows the unit costs (and their sources) used to value this resource use. The unit costs generated in Chapter 4 were used to cost blood administration. The resultant expected cost estimates for all patients, and separately for those with CCB and those without CCB, are shown in **Table 6.1**. The cost of any ad hoc TEG tests used are not included in these figures, since these costs were added into the model separately. The 16 patients who had a positive ad hoc TEG and were deemed to have had successful prophylactic treatment are classed as No CCB here.

Table 6.1: Breakdown of total average cost per patient in the COPTIC study

Cost component	Mean cost (£) (SE)			Mean cost (£) difference (95% CI)
	All patients (n=1802)	Patients with CCB (n=433)	Patients with no CCB (n=1369)	
Red blood cells	89 (5)	207 (16)	51 (4)	156 (133, 179)
Platelets	54 (3)	213 (10)	4 (1)	209 (198, 220)
Fresh frozen plasma	6 (0)	24 (2)	0 (0)	24 (22, 26)
Cryoprecipitate	11 (2)	46 (7)	0 (0)	46 (39, 53)
Blood product administration	60 (3)	182 (10)	22 (2)	160 (148, 173)
Protamine	0 (0)	1 (0)	0 (0)	1 (1, 1)
rFVIIa	7 (3)	29 (13)	0 (0)	29 (15, 43)
Time on CICU	825 (41)	1147 (123)	723 (37)	424 (236, 611)
Time on HDU	2393 (73)	3003 (198)	2201 (73)	803 (468, 1137)
Time on ward	2001 (46)	2142 (92)	1956 (53)	186 (-24, 396)
Re-operations	403 (42)	1273 (145)	129 (28)	1144 (957, 1332)
AKI stage 3	98 (9)	165 (22)	78 (9)	87 (48, 126)
Other complications†	30 (6)	49 (16)	24 (6)	25 (-1, 51)
Total costs	5980 (129)	8481 (359)	5188 (119)	3294 (2721, 3867)

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; CI, Confidence interval; CICU, Cardiac intensive care unit; HDU, High dependency unit; rFVIIa, Recombinant activated factor VII; SE, Standard error

†Other complications includes myocardial infarction, stroke, sepsis, use of an intra-aortic balloon pump.

Populating the model with observed healthcare costs to hospital discharge

Healthcare costs to hospital discharge for each of the different pathways from the end of surgery to discharge could have been estimated by simply averaging the costs to hospital discharge for patients in that pathway. There are many individual pathways however, therefore a large number of cost estimates would have been required (in excess of 35); the majority of which would have been based on just a few patients (less than 10). Cost estimates based only on a few patients may not be very accurate or reliable, and could be heavily influenced by any outliers occurring by chance. Regression analysis was therefore used to pool patients whose costs were not statistically significantly different, across

individual pathways, to increase the sample size for cost estimates; this also reduced the number of cost inputs required. **Appendix 31** describes these calculations.

Healthcare costs from hospital discharge to one year

Since resource use data were not collected beyond hospital discharge in the COPTIC study, estimates for healthcare costs beyond hospital discharge were sought from secondary sources. All patients who were discharged from hospital were assumed to incur healthcare costs between hospital discharge and one year. Patients who had complications during their index admission were assumed to incur higher healthcare costs in this time. Details of these unit costs and their sources are provided in **Appendix 32**.

Costs of the POC and ad hoc TEG tests

Pricing information was obtained from published sources for TEG and ROTEM,[165] and from the manufacturer for Multiplate (Roche). The price of capital equipment was converted into an equivalent annual cost to take account of depreciation and discounting, using a lifespan of seven years for the machine and a 3.5% discount rate. It was assumed that for any test introduced into routine practice at the Bristol Heart Institute, that two analysers would be required. In terms of throughput for the analysers, information was taken from the National Adult Cardiac Surgery Audit (NACSA). According to this audit 1,449 cardiac surgery operations were conducted in 2012/13 at the Bristol Heart Institute,[85] it was therefore assumed that each analyser would be used for 725 patients per year. Including both the capital and consumable elements, the cost of a TEG test per patient was estimated to be £37, the cost of a ROTEM test per patient to be £32 and the cost of a Multiplate test per patient to be £11.

The cost of an ad hoc TEG under current practice was estimated to be higher than the cost of a TEG if it were introduced for all patients. While the consumable costs were the same as per the POC TEG, the equipment costs were higher since the throughput for the

analysers was lower. Two TEG analysers were in use at the time of the study, and since only 16% of patients received an ad hoc TEG, each analyser was assumed to be used for 114 patients per year. The cost of the ad hoc TEG under current practice was estimated to be £64.

Cost of prophylactic treatment indicated by positive POC test results

Where blood products were indicated, the following number of units were assumed to be given: platelets – one unit, FFP – two units, cryoprecipitate – two units. A dose of protamine was assumed to be 50mg.

For each patient in the COPTIC study classified as having a positive POC test result, the cost of the prophylactic treatment that would have been indicated by the test result was calculated. For example, there were 65 patients with a positive TEG, of whom nine were indicated to need protamine, 29 FFP only, and 27 platelets and FFP. The average cost (and standard error (SE)) of prophylactic treatment for patients with a positive TEG was £224 (£19). Similarly, the average cost (SE) of treatment was £406 (£21) for patients with a positive ROTEM, £160 (£9) for patients with a positive TEG/Multiplate, and £362 (£16) for patients with a positive ROTEM/Multiplate.

Outcomes to one year

Outcomes for the cost-effectiveness model were measured in quality-adjusted life-years (QALYs). Individual patient data on survival was available from the observational study, but EQ-5D data were not collected, so utility weights from the literature were applied. LYs to one year were calculated for each patient in the COPTIC study and patients alive at one year accrued one LY in that time. For patients who died by one year, either in hospital or after discharge, the date of death was captured, and therefore it was possible to calculate the number of days to death from their operation date and divide by 365 days, to calculate the proportion of a LY accrued. To populate the model, LYs were pooled in a similar way

to costs to hospital discharge. Ordinary least squares (OLS) regression was used to determine whether there was any difference in the LYs accrued by the 12 groups of patients identified in **Figure 6.6**, for each combination of treatment/ no treatment, complications/ no complications, for patients who died at discharge, and similarly for those alive at discharge but who had died by one year. Frequently, LY estimates could be pooled across all the groups. The CEA Registry at Tufts University was searched for appropriate utility weights for patients 'with' and 'without complications',[166] further details on the weights applied during the first year are given in **Table 12** in **Appendix 27**.

Populating the model beyond one year

No data were available from the COPTIC study beyond one year (follow up was until hospital discharge or death, and survival data were captured from NSTS at one year), so secondary sources of information were sought to populate the model. For each annual cycle beyond one year, estimates of survival, utility and healthcare costs were required.

At one year, patients are split into three health states: alive having had no complications during the index hospital admission, alive having had complications in hospital, and dead. In terms of survival, age and gender adjusted population life tables are the starting point,[167] but these need to be adjusted to account for the increased risk of death in patients who have had cardiac surgery compared to the general population. A further adjustment is required for patients who experienced complications, since these patients are known to be at an increased risk of death compared to patients without complications. **Appendix 33** describes these two adjustments. Utility weights for patients with and without complications respectively from one year are given in **Table 12** in **Appendix 27**.

Healthcare costs beyond one year were calculated in the same way as the healthcare costs between hospital discharge and one year, details of these unit costs can also be found in **Appendix 33**.

6.4.3 Model analysis

For each model, once the structure had been set up in TreeAge, and all probabilities, costs and outcomes entered for current practice, the expected costs and QALYs associated with this arm were obtained for the first year, along with the probabilities of being in each of the three Markov states at the end of the first year. These costs, QALYs and probabilities had been separately calculated in Stata, and therefore provided a robust check that all the inputs had been entered correctly into TreeAge. Once the current practice arm of the model was set up, this could then be used to set up the Test All arm of the model. Separate calculations were conducted in Stata and Microsoft Excel 2013 to estimate the difference between the strategies at one year, again as a check that all inputs in TreeAge were correct.[101]

Costs and QALYs beyond one year were discounted at a rate of 3.5%,[68] and a half cycle correction was applied (which adjusts costs and deaths to occur half way through each annual cycle, rather than at the beginning of the year).[60] Cost-effectiveness analyses were run, and expected costs and QALYs associated with current practice and the test arm were calculated. The ICER (incremental cost-effectiveness ratio, described in Chapter 2) was derived from the differences in costs and QALYs between the test arm and current practice. The ICER is the cost per QALY gained of introducing a POC test compared to current practice. Analyses were conducted separately for TEG, ROTEM and each of TEG and ROTEM in combination with Multiplate.

6.4.4 Sensitivity analyses

Both one-way sensitivity analyses and probabilistic sensitivity analyses were conducted.

One-way sensitivity analyses were used to assess the sensitivity of the base case results to key uncertainties in the model. Two key uncertainties were the probability of a positive

POC test result, and the probability that prophylactic treatment indicated by a positive test result was successful and prevented the development of CCB. **Table 6.2** summarises the sensitivity analyses conducted, and further details are given in **Appendix 34**. An additional sensitivity analysis (SA) around the cost of complications is described in Chapter 7.

Table 6.2: Sensitivity analyses around key parameters

SA	Parameter varied	Base case	Alternative strategies for sensitivity analysis
1	Probability of a positive test result (which influences the cost of prophylactic treatment)	Approximately 80% of normal ranges	Approximately 100% of normal ranges. This also changes the average cost of prophylactic treatment.
2	Probability that prophylactic treatment is not successful in preventing CCB	0.343	Alter by +/-25%
3	Probability that prophylactic treatment is not successful in preventing CCB	0.343	Change to 0
4	Probability of CCB for patients in the Test All arm with a positive ad hoc TEG and a negative POC test	0.61-0.62 depending on the POC test	Multiply the probability of No CCB by the probability that prophylactic treatment fails
5	Cost of the ad hoc TEG	£64	Alter by +/-25%
6	Cost of the POC test	£32 - £48 (see Appendix 27, Table 10)	Alter by +/-25%
7	Cost of prophylactic treatment	£160 - £406 (see Appendix 27, Table 10)	Alter by +/-25%
8	Utilities from 1 year	0.69/ 0.85 with/ without complications	Alter by +/-25%
9	Utility from one year, with complications	0.69	Alter by -25%
10	Utilities excluded (life-years)	0.69-0.85 (see Appendix 27, Table 12)	Change to 1
11	Cost of blood product administration	See Appendix 30, Table 1	£0
12	Increased risk of death for patients who experienced complications compared to those who did not	Hazard ratios for patients with a 50-99% increase in serum creatinine since baseline from Ishani <i>et al.</i> (2011)[168]	Hazard ratios for patients with a ≥100% increase in serum creatinine since baseline from Ishani <i>et al.</i> (2011)[168]
13	Time horizon	5 years	10 years

CCB, Clinical concern about bleeding; CICU, Cardiac intensive care unit; FFP, Fresh frozen plasma; HDU, High dependency unit; RBC, Red blood cell; SA Sensitivity analysis

To quantify the uncertainty around these one-way SAs, parameters were assigned distributions (rather than fixed values) so that SEs and CIs could be estimated; this was done in the same way as the probabilistic sensitivity analyses that were conducted, details of which are provided in **Appendix 35**. Probabilistic sensitivity analysis (PSA) was used to investigate the joint impact on results of all uncertain parameters in the model simultaneously.

6.5 Results

6.5.1 Base case results

The expected costs and QALYs gained under Current Practice and each of the POC test options are shown in **Table 6.3**, together with the cost-effectiveness results for each POC test compared to Current Practice. For each of the POC test options, the mean differences in costs and QALYs compared to Current Practice are small and not statistically significant; the largest difference in costs is £35, approximately 0.2% of total costs; and the largest difference in QALYs is 0.0046, equivalent to 1.7 quality-adjusted days.

Based on the point estimates of the ICER, TEG and TEG and Multiplate are dominated by Current Practice as they are both more costly and less effective, but ROTEM and ROTEM and Multiplate are likely to be considered cost-effective. However, there is great uncertainty around all of these results, as shown in plots of the 1,000 simulated cost and QALY differences from the PSA for each POC test in **Figures 6.7a-d**. In each figure there are a large number of points in two or three quadrants of the cost-effectiveness plane. The black dot is the point estimate of the cost and QALY difference, and in each figure is close to the origin.

Table 6.3: Base-case results from the cost-effectiveness model assessing the introduction of POC tests for all patients

	Costs (£) Mean (SE)	QALYs Mean (SE)	Difference in costs to Current Practice Mean (95% CI)	Difference in QALYs to Current Practice Mean (95% CI)	ICER (£) – compared to Current Practice (CP)
Current practice	16108 (134)	3.5617 (0.4377)			
TEG	16134 (135)	3.5615 (0.4324)	26 (-34, 89)	-0.0002 (-0.0070, 0.0069)	CP dominant (-132153)
ROTEM	16118 (134)	3.5660 (0.4380)	10 (-58, 81)	0.0043 (-0.0030, 0.0149)	2318
TEG & Multiplate	16143 (135)	3.5617 (0.4398)	35 (-25, 102)	-0.00002 (-0.0079, 0.0090)	CP dominant (-2088098)
ROTEM & Multiplate	16127 (131)	3.5663 (0.4537)	19 (-50, 86)	0.0046 (-0.0042, 0.0149)	4251

ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SE, Standard error

Note: all costs and ICERs are rounded to nearest pound.

Figure 6.7a-d: Plots of 1000 simulated cost and LY differences from the PSA for Test All versus Current Practice for each of the POC test options

Figure 6.7a

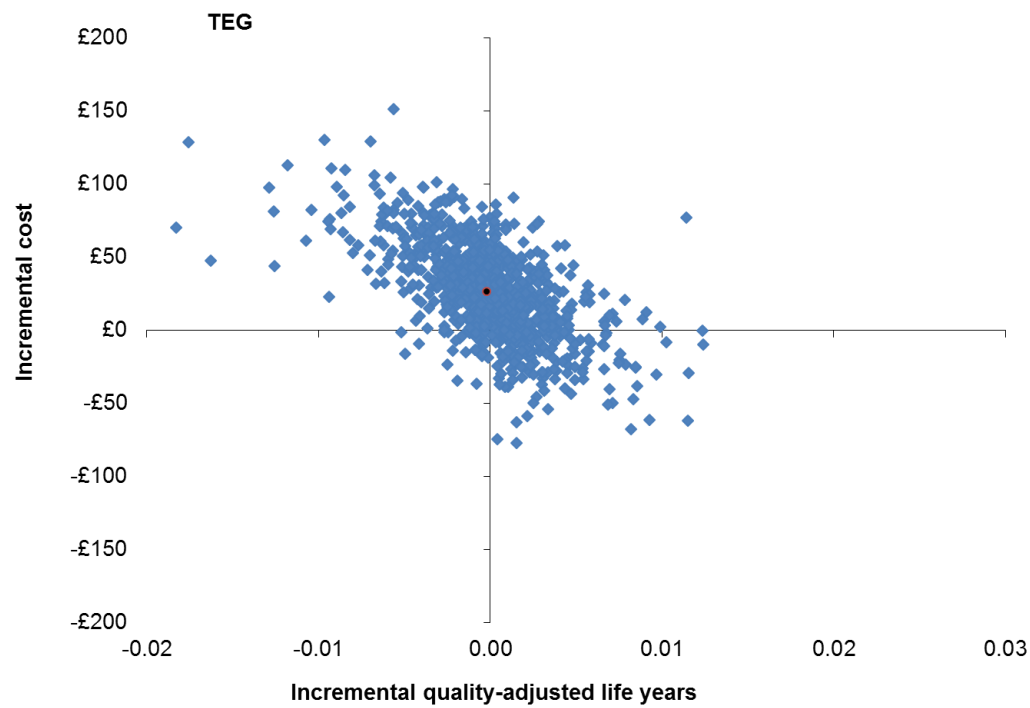


Figure 6.7b

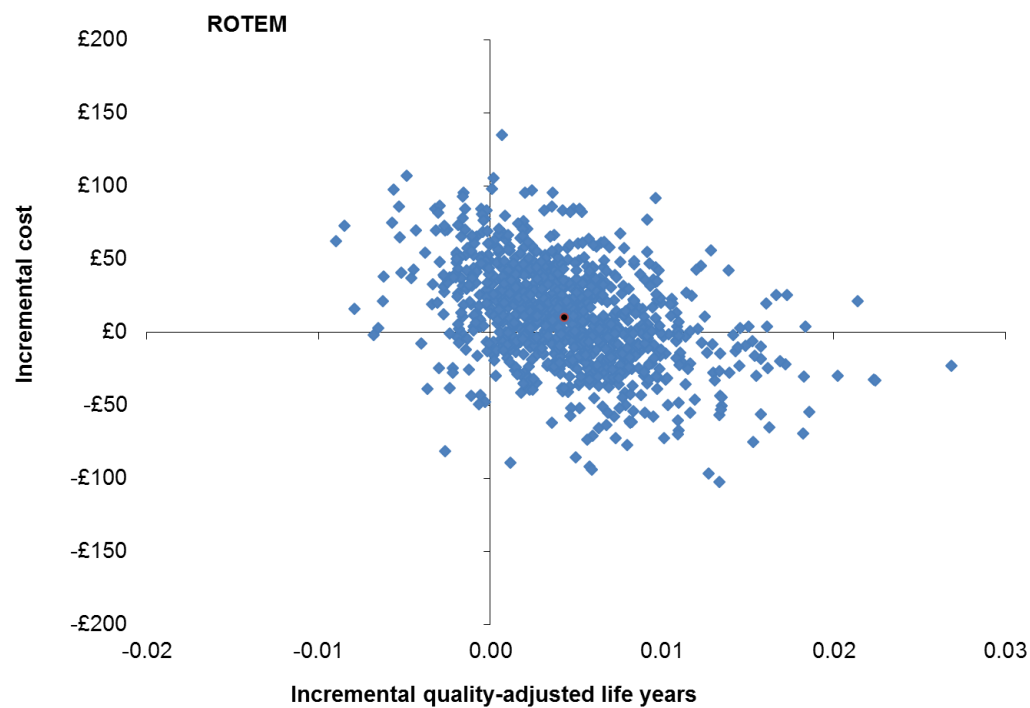


Figure 6.7c

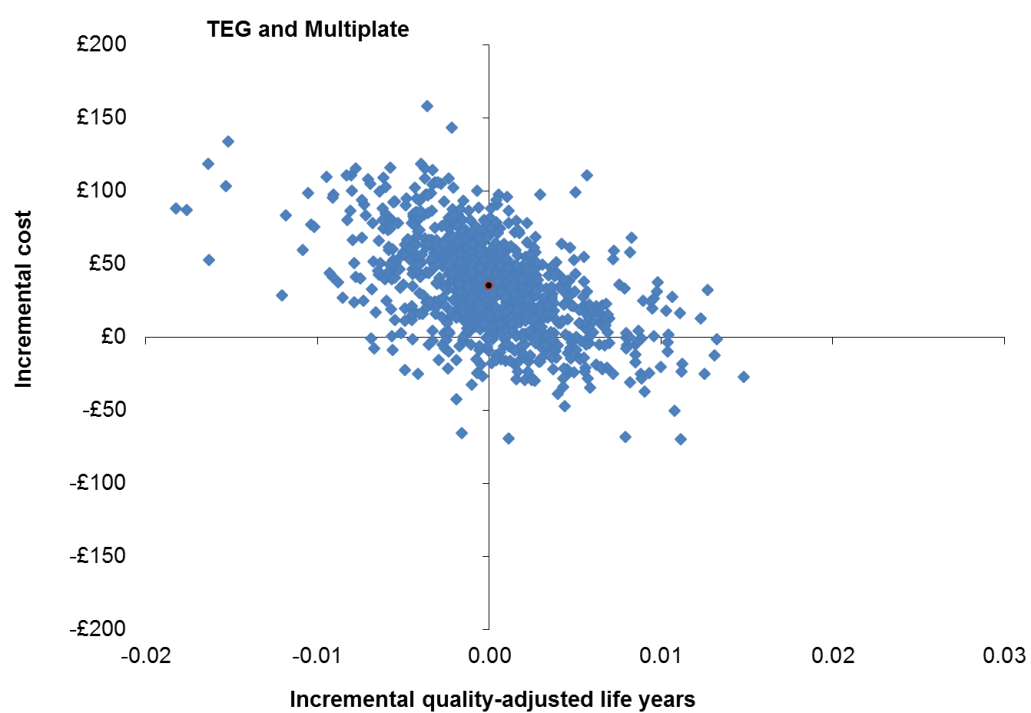
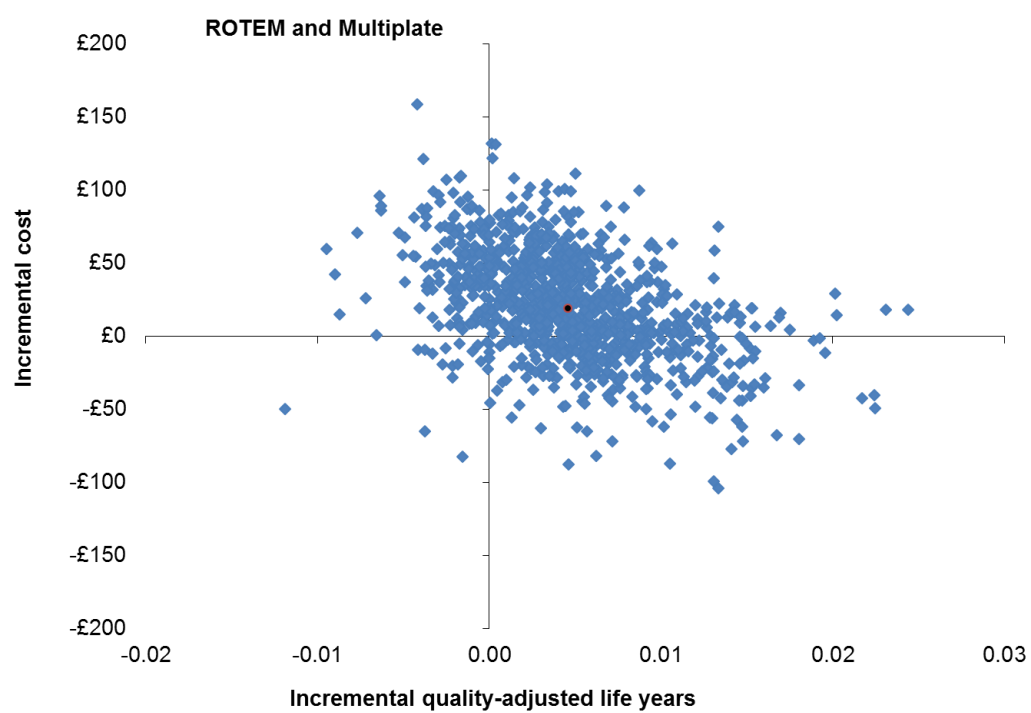


Figure 6.7d



The cost-effectiveness acceptability curves (CEACs) in **Figures 6.8a-d** show the probability that each POC test is cost-effective for a range of willingness-to-pay thresholds. If a decision-maker is willing-to-pay £20,000 for an additional QALY, then the probability of the Test All strategy being cost-effective is 0.35, 0.78, 0.34 or 0.71 for TEG, ROTEM, TEG and Multiplate, or ROTEM and Multiplate respectively. Across willingness-to-pay thresholds from £0 to £100,000, TEG and TEG and Multiplate are less likely to be cost-effective than Current Practice. As the willingness-to-pay threshold increases ROTEM and ROTEM and Multiplate are more likely to be cost-effective than Current Practice. There is however much uncertainty around these findings. The dotted lines at 0.1 and 0.9 indicate the 80% confidence limits for the probability that a POC test is cost-effective. Since these horizontal lines do not cut the curve at any point on any of the graphs, the 80% confidence limits on cost-effectiveness do not exist.

Figure 6.8a-d: Cost-effectiveness acceptability curves for Test All versus Current Practice for each of the POC test options

Figure 6.8a

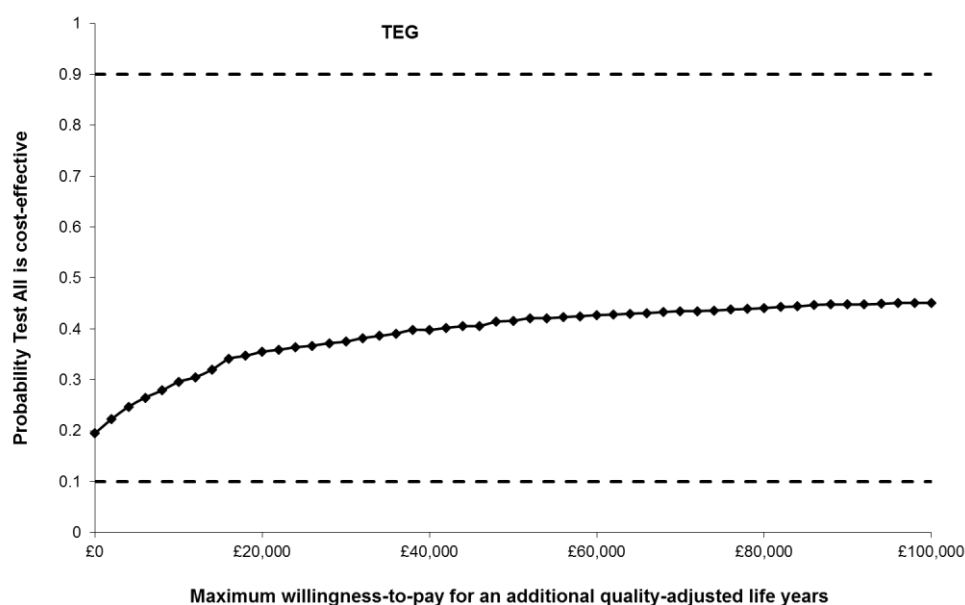


Figure 6.8b

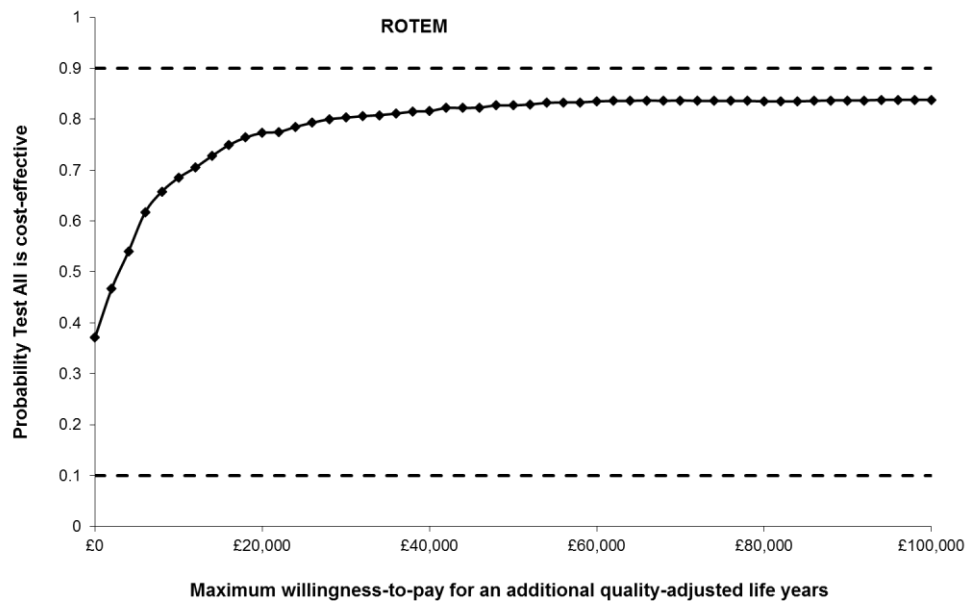


Figure 6.8c

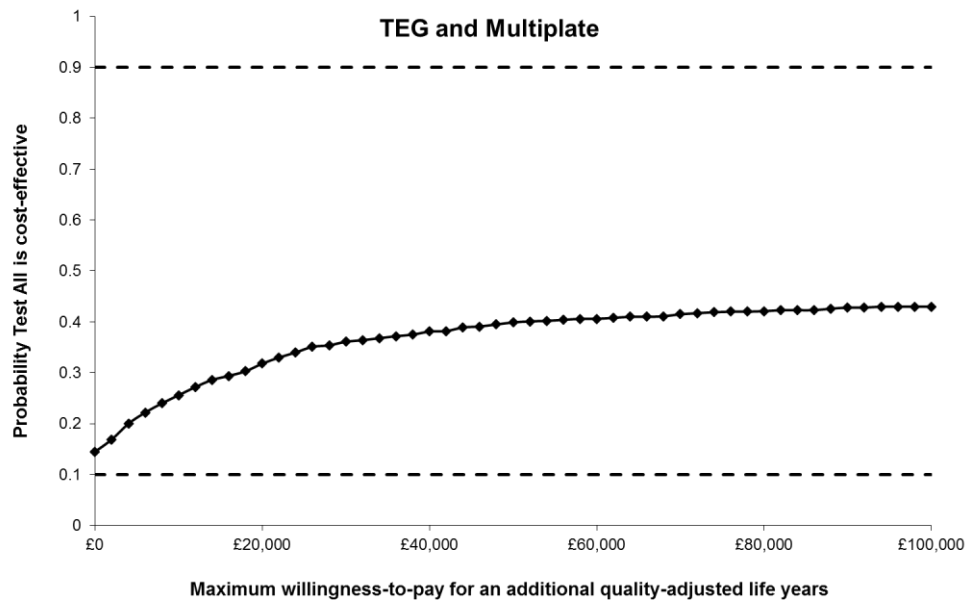
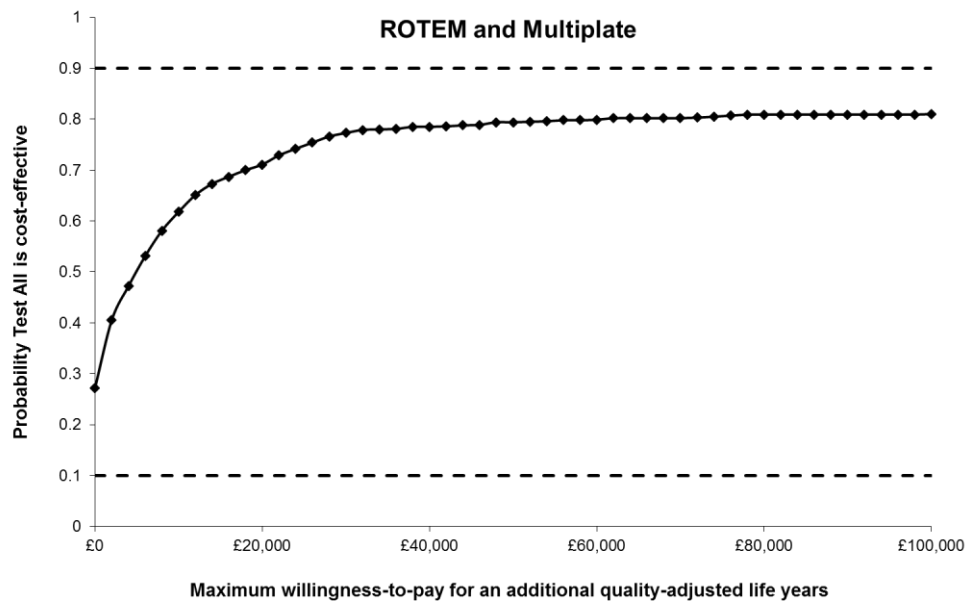


Figure 6.8d



There are clearly very small differences between the arms in each model. Under current practice, there were 433 patients classed as having CCB; the corresponding numbers in the Test All arm of the model were 423, 423, 420, 418 for TEG, ROTEM, TEG and Multiplate and ROTEM and Multiplate respectively. The models suggest the introduction of the test does not greatly reduce the number of patients with CCB.

To consider whether a shorter than lifetime time horizon has an impact on results, the proportion of patients in each health state at five years was compared between arms of the model. For current practice and each of the four test arms, 45% of patients were alive with complications, 34% were alive without complications, and 21% had died by five years. As there were no differences between the arms, it is unlikely that bias is being introduced, and the time horizon was not extended.

6.5.2 Sensitivity analyses

The results of the sensitivity analyses are shown in **Appendix 36**. In all cases, differences in costs and QALYs were very small, and the uncertainty around results remained.

6.6 Discussion

This is the first cost-effectiveness analysis of POC tests in cardiac surgery for which the majority of the model inputs (probabilities, costs and LYs) were estimated directly from an observational cohort of patients, rather than from published secondary sources.

There was very little difference between any of the POC tests and Current Practice in either costs or QALYs, and great uncertainty around the cost-effectiveness results. Mean QALYs to five years were 3.6 years for all strategies considered; the greatest difference in QALYs of 0.0046 is equivalent to 1.7 days. Costs were approximately £16,100 under each strategy, and the largest mean difference to Current Practice was £35. Point estimates suggested that TEG and TEG and Multiplate were more costly and less effective than Current Practice and therefore dominated by it, and that ROTEM and ROTEM and Multiplate were more costly and more effective than Current Practice and if a decision-maker was willing to pay £10,000 for an additional QALY, then they would be considered cost-effective, according to the base case and all point estimates in the sensitivity analyses (except one extreme SA). However, given the small differences in costs and QALYs, there was much uncertainty around these results. In the clinical analyses, TEG and TEG and Multiplate improved predictive accuracy of the bleeding risk model slightly more than ROTEM and ROTEM and Multiplate. These differences were small, and while statistically significant, they were not necessarily clinically significant, which is not at odds with the findings here.

In the base case analyses the results reflect that there were relatively few positive POC test results (compared to the number of patients with CCB in the COPTIC study), and therefore relatively few patients for whom the positive POC test could impact positively on their pathway (between 15-20 patients). Even if the POC tests have a significant impact for these few patients, it is perhaps not surprising that across a cohort of 1,802 patients, the

differences in resulting costs and QALYs between strategies were small. Recognising that there are only small differences between the strategies also explains why the majority of the sensitivity analyses (including those around the costs of blood administration) had very little impact on the cost and QALY differences between POC tests and Current Practice, to a very large extent the same changes were made to each strategy.

A recent Health Technology Assessment report considered the introduction of POC tests in several clinical areas, including cardiac surgery.[157] In their literature review of cost-effectiveness analyses of POC tests, only one study was identified, a model conducted for the Scottish NHS.[169] This study was largely based on a previous decision tree used to assess methods for minimising peri-operative allogeneic blood transfusion, and which considered the relationship between transfusion and subsequent complications and adverse events.[148] Whiting *et al.* (2015) also used a decision tree to assess the cost-effectiveness of POC tests in cardiac surgery, based on these previous studies but updating many of the parameter estimates with data from their clinical effectiveness review.[157]

Whiting *et al.* compared TEG and ROTEM to standard laboratory testing, and their cost-effectiveness results indicated that POC testing was dominant; each POC test was less costly and more effective than standard laboratory testing.[157] Conclusions were robust to various sensitivity analyses conducted. Across a broad range of willingness-to-pay thresholds, the probability of the POC tests being cost-effective was approximately 0.80. These results are different to those presented here, but there are some important differences between the studies, and some limitations to their work. The main outcome measure in the Whiting study was the proportion of patients having RBC transfusion under a POC testing strategy compared to standard laboratory tests. The difference in transfusion rates was based on the findings of a systematic review conducted by the authors, but they noted a high risk of bias in the trials identified in the review, and therefore the transfusion rates should be interpreted with caution. All other events were based on the transfusion

rates; patients were assumed not to have complications such as MI, stroke, and renal dysfunction if they did not have a transfusion. There were however COPTIC patients who experienced complications, but did not have a RBC transfusion. The model presented here benefited from the individual patient data available (albeit from one centre), which provided information on the blood products given and captured important clinical endpoints such as AKI and stroke, so it was not necessary to base outcomes on transfusion rates using secondary sources. In the Whiting study RBC transfusion was assumed to cause harm; more recent evidence (including from the TITRe2 trial) suggests however, that patients undergoing cardiac surgery benefit from more liberal RBC transfusion, and that mortality is reduced under such a strategy.[124, 136]

There were a number of interesting challenges and issues to consider when designing the economic model. While COPTIC aimed to improve the diagnosis and treatment of coagulopathic bleeding in cardiac surgery patients, there is no consensus definition of coagulopathic bleeding, and the outcome measure of CCB was developed by the clinical team to capture the different ways in which bleeding might be apparent. However it is not ideal to be defining a condition by its treatment, for example whether patients received early pro-haemostatic treatment. Given these difficulties in identifying patients with coagulopathic bleeding, there is uncertainty around the prevalence of the problem.

Linked to the difficulties of defining the problem is that there is no gold standard test of coagulopathic bleeding. In other screening programmes, for example for breast cancer, a patient with a positive screen would have a biopsy taken, and a definitive diagnosis would be obtained. Here, there is no gold standard test, and no time to wait for a definitive diagnosis. The aim of the POC tests is to provide information quickly on the particular form of a clotting abnormality, so that effective and directed treatment can be given promptly. It was therefore not possible to account for the diagnostic accuracy of the POC tests using sensitivities and specificities.

Careful consideration needed to be given to patients in the observational study who received an ad hoc TEG. It is likely that it was patients that clinicians were concerned about who received these tests, and therefore that there are systematic differences between patients who did and did not have ad hoc tests; it would introduce bias to exclude these patients. For patients who had a positive ad hoc TEG, it is likely that the effect of the test had already been incorporated into their pathway, and that pro-haemostatic treatment which would classify them as having CCB, was actually prophylactic treatment which may have prevented CCB. The impact of the ad hoc test on a patient's pathway and CCB outcome therefore needed to be incorporated into the model. For the POC test arm, it was necessary to estimate the impact of the POC tests on a patient's pathway, as it was not possible to directly observe this.

Limitations

There were a number of patients in the COPTIC cohort who had an ad hoc TEG and whose care pathway was assumed to have been influenced by a positive result. When these patients were considered in the POC test arm, particularly if they had a negative POC test result, it was not possible to 'take out' the effect of the ad hoc test. This may have biased results in favour of the POC tests; they were much less favourable in a sensitivity analysis which crudely attempted to take out the effect of positive ad hoc TEG. It is likely however that clinicians were concerned about patients who got these ad hoc tests; it is possible that under a Test All strategy, test results would be interpreted less stringently (as was assumed for the ad hoc tests in the Current Practice arm) for patients that clinicians were concerned about compared to the whole cardiac surgery population. If this were the case, then this is less of an issue.

The parameter inputs for this model were based on the cohort of adult cardiac surgery patients at Bristol Heart Institute (BHI) between March 2010 and August 2012. This cohort

should be reflective of the casemix of patients who receive surgery at the BHI, since all adult patients receiving cardiac surgery during this period were invited to participate. There is a limit to the generalisability of findings based on this cohort; the BHI receives referrals from other hospitals, and therefore is likely to have a different casemix compared to many other hospitals in England for example, which do not take referrals from elsewhere.

If a POC test were introduced in practice, it is likely that any patients who continued to bleed after a positive test result and initial prophylactic treatment, would be re-tested to identify whether further treatment was required. Re-testing patients was not taken into account in this model.

While data on the ad hoc use of TEGs in theatre and in CICU were collected in the COPTIC study, the results of these TEGs were not known, and nor was it known how or whether results were acted upon. With hindsight, it would have been helpful to capture further information here to more accurately reflect what happened to these patients.

There were limitations around the complications data available for patients in COPTIC. While Innovian data were used to supplement the PATS data for post-operative complications that were secondary clinical outcomes in the study to reduce the amount of missing data, there were additional complications (such as pulmonary and gastrointestinal complications) that were not included as secondary outcomes in the clinical analyses but which ideally would have been costed. Data from PATS for these complications was missing for more than 60% of patients, and this data was deemed not useable. This limitation will be investigated further in the next chapter.

There were some quality issues associated with the Innovian data, which records hourly records for patients in CICU/HDU. These data were used to estimate the amount of time spent on CICU/HDU, and the date and time of extubation was used to split a patient's time

between CICU and HDU. Some patients had overlapping periods of time on CICU/HDU, i.e. they appeared to have been readmitted back to CICU/HDU before the first or previous admission had finished. Approximately 50% of patients had five or more dates and times of extubation, which seems very high, again suggesting some inaccuracies in the data. Where an episode on CICU began before a previous episode had finished, the latter episode was ignored. Only the first date and time of extubation was used to differentiate between time on CICU and HDU, subsequent extubation dates and times were not used.

Although information was available on survival status at one year, resource use was only captured until hospital discharge. While secondary sources were used to make assumptions about resource use beyond hospital discharge, it would have been beneficial to have individual patient data on who had hospital readmissions for example or further healthcare resource use beyond hospital discharge to one year (and even beyond). It would also have been beneficial to have collected individual patient data on quality of life.

6.7 Conclusions

There was great uncertainty around the cost-effectiveness results, point estimates suggest that ROTEM and ROTEM and Multiplate may be cost-effective. Given the uncertainty around the cost-effectiveness (and clinical effectiveness) of POC testing in cardiac surgery, there is a need for further work in this area, and particularly for a rigorously conducted RCT. This would enable the impact of the POC tests on patients' care pathways to be directly observed, and individual patient data to be collected on clinical outcomes, resource use and health-related quality of life to assess the clinical effectiveness and cost-effectiveness of POC testing in cardiac surgery.

Chapter 7: Comparing resource use data from primary data collection and routine sources

7.1 Introduction

Alongside the push towards Big Data (introduced in Chapter 2), have been moves to make greater use of routine datasets within healthcare for research, including for economic evaluation. While in mainstream economics, much use has been made of routine datasets such as the British Household Panel Survey,[170] health economists have tended to make less use of routine data, and relied on primary data collection (alongside RCTs or cohort studies) or published sources. Sources do exist however, and there has been greater encouragement recently for researchers in England to make use of datasets such as the Clinical Practice Research Datalink (CPRD) of anonymised primary care records,[171] and Hospital Episode Statistics (HES),[150] which contain details of inpatient admissions (including critical care stays), outpatient appointments and emergency department attendances at NHS hospitals in England. The aim is to avoid the duplication of effort: if, for example, information on outcomes and resource use is collected on hospital administration systems, some of which may be collated nationally and available for England as a whole in HES, is it necessary or appropriate to collect large amounts of information on CRFs as part of patient-based studies? Evidence is needed to address this question: comparisons need to be made between resource use collected for the same patients from alternative sources to identify the scale of any differences, and to understand the reason for any differences to determine which are the more accurate and reliable data.

In the economic evaluation of the TITRe2 trial (Chapter 5), resource use data were collected on very detailed bespoke CRFs, whereas resource use data for the observational study (COPTIC, Chapter 6), were largely collected from existing hospital datasets. There are a subgroup of patients who were included in both the TITRe2 trial and the COPTIC

observational study. This presents an opportunity to compare the resource use and the costs of the resource use collected in COPTIC, largely from existing datasets, with the resource use and costs of the resource use collected for the same patients in TITRe2, from bespoke CRFs. Before comparisons between the two sources are made however, a literature review of existing evidence in this area is presented.

7.2 Literature review of studies comparing resource use from routine data with an alternative source

A literature review was undertaken to identify references which compare the validity of resource use collected from routine data with an alternative source to establish what is known in this field, and to place the empirical work presented later in this chapter into context. Papers were sought which compared resource use from routine or administrative datasets in the UK with an alternative source, for the purposes of economic evaluation. The electronic databases Medline and Embase were searched, and hand searching of papers discussed at the three most recent Health Economists' Study Group meetings (held between June 2015 and June 2016) was also conducted. The quality of included studies was assessed using a checklist, largely based on a previous quality assessment tool for comparing validation evidence from self-reported healthcare resource use data with administrative data.[172] Full details of the methods and results of the literature review are provided in **Appendices 37-41**. This section provides a short summary of the findings, and implications for future economic evaluations.

The literature review identified 14 studies in the UK which compared resource use from routine data with an alternative source. Nine (64%) studies compared patients' self-reported data from questionnaires or interviews with medical records. Two studies compared HES data to medical records, one study compared registry data to medical records, one study compared CRFs to medical records, and the final paper compared a

clinical database with HES. The assessment of study quality indicated that key information was generally well reported, overall studies met 84% of the quality criteria.

There were mixed findings among the studies comparing patient self-report data with medical records. While there was modest agreement between sources, there was also evidence of under-reporting by both patients and medical records in different studies, and a view that neither source can be treated as the gold standard or is necessarily more accurate. This needs to be investigated on a case-by-case basis. These papers highlighted another important issue, no data source is going to be reliable for the purposes of economic evaluation if it is frequently incomplete or very difficult to obtain. Five of these nine studies (56%) reported that data from at least one source was not obtained for 20% or more patients.

Only one study compared resource use data from CRFs to an alternative source.[173] There is little that can be concluded from this paper as it was a retrospective economic evaluation, the CRFs were designed for the clinical aspects of the trial and not for resource use data collection, it is perhaps not surprising therefore that resource use was lower from this source than patients' medical records.

In the two studies comparing HES data to medical records, HES inpatient and outpatient data was found to valid for the purposes of economic evaluation for the patient group studied (older men diagnosed with prostate cancer).[174, 175] Importantly though, in the study of outpatient data, the authors noted that the scope of the economic evaluation would need to include all resource use, and not just appointments relating to prostate cancer for example, since the reason for the appointment cannot be accurately identified from HES.[174]

In summary, this literature review has identified only limited previous work which explores the agreement and reliability of resource use from routine data with alternative sources. The findings suggest that no one source is always likely to be better than another, it is very dependent on the patient group, the nature of the study being conducted and the data sought. Before any economic evaluation, it would therefore be prudent to conduct some preliminary work testing out data collection methods to see if high completion rates can be achieved in practice, and if possible, to compare resource use from planned data collection methods for a sample of patients to data from a rigorously collected source.

This literature review has highlighted the lack of previous work in this area in the UK, and the lack of similar work to that being conducted next in this chapter. Only one (poor quality) study compared CRF data to an alternative source. The routine data source for many studies was case notes rather than electronic data, and no studies were conducted in the clinical area of heart surgery (or blood transfusion).

7.3 Bespoke data collection versus routine sources

The overlap of patients between the TITRe2 trial and the COPTIC observational study provides a rare opportunity to compare resource use collected from alternative sources for the same patients. The level of agreement between data can be investigated; if the two sources agree, then one source confirms the other, and there is greater confidence in the accuracy of the data collected (notwithstanding that both sources could be incorrect). If the sources do not agree, then there is some uncertainty about their accuracy. The magnitude of any differences can also be estimated. While it might be anticipated that data from CRFs would be more reliable than data from routine datasets because the data were collected to answer a specific research question, neither source can be treated as the gold standard, since no validation study of either source has been conducted. If there are differences, it

would be informative to look for any systematic patterns in the differences, which might help to explain them.

As well as assessing the level of agreement of the data collected, there is a second motivation for comparing resource use data between the alternative sources. In the analyses of the COPTIC study, there were concerns about data quality, particularly the complication data; undertaking this comparison enables this to be investigated further. There was much missing data for complication variables such as stroke and MI in the PATS database; for complications which were secondary endpoints, significant additional work (unplanned at the outset) was done by collaborators at Bristol to capture events reported in a second dataset, Innovian®, as well as in PATS. From an economic perspective however, there were other complications, such as gastrointestinal and pulmonary complications, which were recorded in PATS but were not secondary endpoints, which should have been costed. These variables had more than 60% missing data, and the decision was taken not to use them in the analysis of healthcare costs to hospital discharge. While it was known therefore that complications were under-costed in the COPTIC analyses, it was not possible to quantify this in any way. For the subgroup of patients in both studies, complications and their associated costs will be compared, and the differences quantified. It may be possible to extrapolate complication costs from this subgroup of patients to the entire COPTIC cohort, and identify some revised cost estimates which could be used in sensitivity analyses around the COPTIC health economic model. It is unlikely that there are sufficient numbers of patients in the subgroup to do this meaningfully for the 12 key groups of patients identified in the COPTIC analyses (see **Figure 6.6**), but it is hoped that it could be done for the cohort as a whole.

The next section of this chapter describes the methods used to compare resource use data collected from alternative sources in TITRe2 and COPTIC and associated costs for a subgroup of patients, and investigates the agreement between the data sources. Methods

for quantifying the under-reporting of complication costs in COPTIC are also described, and these estimates are used to inform a sensitivity analysis around the COPTIC health economic model presented in Chapter 6.

7.4 Methods for comparing resource use and associated costs

In both the COPTIC and TITRe2 studies resource use data were collected during and after cardiac surgery, but there were differences in terms of what was captured, and over what time period. In the COPTIC analyses, resource use was costed from the end of surgery until hospital discharge; additional data were also collected on surgery, and blood products given during surgery. In TITRe2, detailed resource use was captured from the beginning of surgery until discharge from the cardiac unit. If the patient was transferred to another unit in the same hospital, the LOS was also captured. Resource use from hospital discharge to three months post-surgery was also collected.

There were far fewer resource use items captured in COPTIC compared to TITRe2 (approximately 20 variables were costed in COPTIC, whereas more than 100 were costed in TITRe2). Therefore taking the COPTIC variables as the starting point, **Table 7.1** describes the resource use items that were captured in COPTIC, and the equivalent data that were captured in TITRe2. For each resource use item, **Table 7.1** summarises the level of detail of resource use captured in each study, and the time period over which data were collected. Where possible resource use is compared from the end of surgery until hospital discharge, the time period over which resource use was captured in COPTIC. Data on blood products were not available over this time period from both studies (further details provided in **Table 7.1**), so resource use is compared over alternative time periods for which more comparable data are available. RBCs were compared from the end of surgery until CICU/HDU discharge. While the number of units transfused each day were available from TITRe2, the number of days until CICU/HDU discharge was not readily available, so the

mean CICU/HDU LOS was calculated across all patients, and the number of units of RBCs given post-operatively to the end of that mean number of days calculated as the most comparable data to COPTIC. Other blood product use was compared intra- and post-operatively, but was not directly comparable; use was recorded to CICU/HDU discharge in COPTIC, and until hospital discharge in TITRe2. For complications, **Table 7.1** also specifies how these were defined, since there were some differences between studies. The final column of **Table 7.1** summarises which study had (on paper) the more comprehensive data for each variable. Where there was a difference in the level of detail available (in about half of the categories), the TITRe2 sources were frequently more detailed than the COPTIC sources. Although there were differences in definitions and/or time periods between sources, a pragmatic decision was made to continue to compare resource use and costs; these differences may relate to limitations around the data from one source or another, which is important to identify (notwithstanding that it may not have been required for a particular study).

The resource use items and complications listed in **Table 7.1** were all that were costed in COPTIC. In TITRe2 however, there was much more extensive data collection, particularly around complications. Three pages of the CRFs were devoted to post-operative complications, and more than 25 different complications were recorded, as well as free-text space for additional complications not listed on the CRF; these were all costed. Additional complications captured included pacing (temporary or permanent), mask continuous positive airway pressure, pleural effusion requiring drainage, and supraventricular tachycardia/ atrial fibrillation requiring treatment. The use of post-operative cell salvage was also collected and costed, as were the use of regular medications, and serious adverse events, which were recorded in great detail in free-text.

Table 7.1: Comparing resource use and complication data collected in each study

Resource use	COPTIC	TITRe2	Which study has the more comprehensive data?
Red blood cells	Number of units received from end of surgery to CICU/HDU discharge (not available from CICU/HDU discharge to hospital discharge)	Number of units received from beginning of surgery to cardiac unit discharge. This can be split into units received intra-operatively, and on each day post-operatively. The number of units given post-operatively to the mean number of days on CICU/HDU was calculated as the most comparable data to that available in COPTIC.	TITRe2
Other blood products – platelets, fresh frozen plasma, cryoprecipitate	Number of units received from end of surgery to CICU/HDU discharge (not available from CICU/HDU discharge to hospital discharge). Data also available on units received intra-operatively; these were summed to give the most comparable data to TITRe2.	Total number of units received intra-operatively and post-operatively during cardiac unit stay	Equal
Additional protamine	Number of additional doses	Not recorded	COPTIC
Activated Factor VII	Binary variable recorded. Data also available on whether received intra-operatively, so that direct comparisons with TITRe2 can be made.	Binary variable capturing if received intra-operatively/ post-operatively during cardiac unit stay	Equal
Length of stay by ward type	Time of arrival on CICU/HDU and discharge date recorded. Dates and times admitted and discharged from CICU/HDU recorded. Dates/times of extubation, and re-intubation/ re-extubation recorded. CICU/HDU time split by extubation time. NB data quality issues: overlapping CICU/HDU episodes ignored, and only first extubation date/time used.	Time of arrival on CICU/HDU and discharge date recorded. Dates and times admitted/ readmitted to CICU/HDU, general ICU, and a ward recorded. Dates/times of extubation, and re-intubation/ re-extubation recorded. CICU/HDU time split by extubation time.	Equal

Complications	COPTIC	TITRe2	Which study has the more comprehensive data?
Sepsis	Binary variable capturing any infective complication (chest infection, wound infection, mediastinitis, graft site infection, sternal wound infection, urinary tract infection, septic, sepsis, blood borne infection).	Binary variable recorded, defined by the following two conditions: antibiotic treatment for suspected infection, and the presence of systemic inflammatory response syndrome (SIRS) within 24 hours prior to the start of antibiotic treatment. SIRS was defined as two or more of the following conditions: temperature $>38^{\circ}\text{C}$ or $<36^{\circ}\text{C}$, heart rate >90 beats/minute, respiratory rate >20 breaths/min or partial pressure of carbon dioxide <32 mm Hg or <4.3 kPa, white blood cell count $>12,000/\text{mm}^3$ or $<4,000/\text{mm}^3$. Detailed information on antibiotics recorded.	TITRe2
Stroke	Binary variable capturing any peri- or post-operative neurological complication (stroke, transient ischaemic attack, hemiplegia, paralysis, paraplegia, dysphasia, cerebral/central nervous system infarct/ embolus).	Binary variable for permanent stroke recorded; captures new onset focal or generalised neurological deficit (defined as a deficit in motor, sensory or co-ordination function), with associated brain imaging (computerised tomography (CT) and/or magnetic resonance imaging (MRI)). Method of verification (CT or MRI) also recorded.	TITRe2
Myocardial infarction (MI)	Binary variable capturing any MI occurring before discharge or death from MI in hospital	Suspected MI recorded, with post-operative peak serum Troponin I or T. An adjudication committee classified each suspected MI as definite or not based on a patient's medical history, electrocardiograms (ECGs) (both pre-operatively and at the time of the suspected MI) and troponin levels at the time of the suspected MI.	Equal
Acute kidney injury stage (AKI) 3	Binary variable recorded. AKI stage 3 classed as present if serum creatinine increases ≥ 3.0 times the pre-operative value within 7 days of surgery, or serum creatinine increases by ≥ 353.6 $\mu\text{mol/l}$ from the pre-operative value within 48 hours of surgery, or renal replacement therapy (RRT) is initiated.	Binary variable recorded the highest AKI stage reached by the patient after randomisation. AKI stage 3 classed as present if serum creatinine increases >3.0 times the pre-operative value, or serum creatinine ≥ 4.0 mg/dl (≥ 354 $\mu\text{mol/l}$) with an acute increase of at least 0.5 mg/dl (44 $\mu\text{mol/l}$), or urine output <0.3 ml/kg per hour for 24 hours or anuria for 12 hours, or need for RRT.	Equal
Reoperation	Binary variable recorded	Number of reoperations recorded, and the duration of each reoperation	TITRe2
IABP (post-operatively)	Binary variable recorded	Low cardiac output requiring management (including IABP) recorded, but not comparable as IABP was not assumed to be used	COPTIC

CICU, Cardiac intensive care unit; HDU, High dependency unit; IABP, Intra-aortic balloon pump; ICU, Intensive care unit

Comparing resource use

To explore the degree of agreement between the data sources and the magnitude of any differences, individual resource use items and complications which were common to both datasets were compared at the population level and at the individual level. When resource use data is used in applied economic evaluations, interest is primarily in whether there are differences at the population level, however good agreement at the individual level is a more reliable indicator of whether the sources are providing the same information.

For counts of resource use such as the number of blood products given and continuous variables such as LOS, the mean resource use from each study is presented. For each resource item the difference in resource use between the studies was calculated for each patient. The level of agreement between sources was estimated using Lin's concordance correlation coefficient (CCC),[176] which quantifies the deviations from perfect agreement (defined as a 45 degree line) of one measure compared to the other. The CCC lies between minus one and one, where one indicates perfect agreement and minus one indicates perfect inverse agreement. Importantly this deviation takes into account both precision (how far observations are from the line of best fit) and accuracy (how far the line of best fit is from a 45 degree line). Alongside this the 95% limits of agreement are presented;[177] at the individual level, 95% of differences are expected to lie between these limits. To assess the difference between sources in the population as a whole, the systematic bias, the mean differences (and 95% CI) between studies are presented. Finally to consider the magnitude of the differences between sources for individual patients within the population, the mean absolute error (MAE), and the mean squared error (MSE) are reported.[178] The MAE is the average of the absolute value of the difference in resource use between the studies for each patient; the MSE is the average of the square of this difference (and like Lin's CCC, takes into account both precision and accuracy).[178]

For binary variables such as the use of recombinant Factor VIIa and complications, the number (and percentage) of patients having the event according to each study is presented, and the percentage difference between studies. To consider the agreement between individual patients within the population, the percentage of cases with agreement between the studies is presented, as well as the kappa statistic (and 95% CI). The kappa statistic is a measure of inter-rater agreement (here agreement between two data sources) for categorical data, which takes account of the agreement that would be expected to occur by chance.[70] It usually falls between zero, indicating agreement no better than chance, and one, complete agreement, but negative values (between zero and minus one) indicate agreement worse than expected by chance.

Comparing costs

The effect of these similarities and differences in resource use between studies is considered further by comparing the costs associated with each resource item or complication. Costs are presented in 2013/14 prices. The economic evaluation of TITRe2 presented costs in 2012/13 prices but these have been adjusted to 2013/2014 prices so that figures can be directly compared. Blood products have been re-costed using 2013/14 prices;[179] all other unit costs were inflated to 2013/14 prices using the Hospital and Community Health Services inflation index.[105] Unit costs in 2013/14 prices were the same in each study, except where there was a greater level of detail captured in TITRe2 which enabled resource use to be costed to a greater level of detail. For sepsis, detailed information on courses of antibiotics was captured in TITRe2, these were costed on an individual patient basis rather than assuming a particular antibiotic was given (as was done in the COPTIC analyses). The number and duration of reoperations was captured in TITRe2; a lower cost was attached to reoperations lasting less than three hours, compared to those of three hours or more. In COPTIC, the number of reoperations was not known nor was the duration; for those who had a reoperation, one reoperation of three hours or more was costed. In addition to time spent on a cardiac intensive care unit (CICU), high

dependency unit and a ward, any LOS on a general intensive care unit was captured in TITRe2 (but not in COPTIC); this was costed at a higher rate than CICU. For each resource use item and complication, the mean costs and standard error (SE) are presented for each study, and the mean difference (SE) between studies.

Quantifying the under-reporting of complication costs in COPTIC

For each patient, the total cost of all complications and SAEs captured in TITRe2 was compared to the total cost of complications captured in COPTIC (the former minus the latter). This difference provides an estimate of the amount by which complications are potentially under-costed in COPTIC (and for a few patients over-costed). This information was used to inform a sensitivity analysis for the health economic model for COPTIC (presented in Chapter 6). Patients were divided into several subgroups based on LOS and total cost of complications (both as captured in COPTIC), and the mean additional cost of complications calculated for each subgroup, for use in the sensitivity analysis. Patients who are in COPTIC and TITRe2 (and have been included in the analysis presented here) were compared to the COPTIC population as a whole; it was anticipated that patients in this subgroup would on average be sicker than patients in the COPTIC population as a whole, as to be randomised for TITRe2 a patient's haemoglobin needed to drop below 9g/dL. Adjustments were therefore considered when applying the estimates of the additional cost of complications generated here to the COPTIC analysis population in the sensitivity analysis. To conduct the sensitivity analysis, patients in the COPTIC cohort as a whole were divided into the same subgroups as the COPTIC and TITRe2 patients here, based on their LOS and total cost of complications. For each patient in each subgroup, the corresponding estimate of the additional costs of complications was added to their costs to hospital discharge. For each base case model for each POC test, the cost estimates for costs to hospital discharge were revised with these additional costs included and the models re-run, and compared to the base case results.

There was very little missing data for inpatient resource use in either study; if there is any missing data for the subgroup of patients being studied here, one dataset for each study will be created by averaging across the datasets generated by multiple imputation in the main analyses of these studies (described in Chapters 5 and 6). Analyses were conducted in Stata version 14,[110] TreeAge Pro 2013 and Microsoft Excel 2013 were also used for the sensitivity analysis around the health economic model.[101, 158]

7.5 Results

There were 256 patients in both COPTIC and TITRe2, 190 of these patients are in the final post-operative analysis dataset for COPTIC (n=1802). The analyses that follow are therefore based on these 190 patients.

Table 7.2 summarises some basic information on these 190 patients, using data from each study. There are only minor discrepancies between the data sources. The three patients classed as having 'Valve only' surgery in TITRe2, but 'Other' in COPTIC, had 'Valve and Other' according to additional COPTIC data. There were other patients in COPTIC who had 'Valve and Other' who were classed as 'Other' in TITRe2. From the size of the small discrepancies in age, there appeared to be differences of one day and of one month for these two patients. It is hugely reassuring that there is complete agreement on the number of patients who die in hospital and within three months of surgery (and agreement on who these patients are).

Table 7.2: Cardiac procedure, patient characteristics and deaths

	COPTIC data (n=190)	TITRe2 data (n=190)	Agreement between COPTIC and TITRe2 n (%)	Details of disagreement between sources for individual patients
	Frequency (%) or Mean (SE)			
Cardiac procedure				
CABG only	48 (25%)	48 (25%)	187 (98%)	3 'Valve only' in TITRe2 are 'Other' in COPTIC
Valve only	67 (35%)	70 (37%)		
CABG and valve	48 (25%)	48 (25%)		
Other	27 (14%)	24 (13%)		
Gender				
Male	123 (65%)	123 (65%)	190 (100%)	
Age				
Age at operation – years	70.2 (0.69)	70.2 (0.69)	188 (99%)	Small differences for 2 patients
Death*				
Died in hospital	5 (3%)	5 (3%)	190 (100%)	
Died within three months of surgery	7 (4%)	7 (4%)	190 (100%)	

CABG, Coronary artery bypass grafting; SE, Standard error

*Deaths within three months of surgery includes deaths in hospital

Tables 7.3 and 7.4 summarise resource use per patient from each study. There was no missing data for any of these variables in either study.

Table 7.3: Resource use per patient from each study: continuous variables

Resource	Mean resource use		Concordance correlation coefficient	95% limits of agreement	Mean difference	95% CI for mean difference	Mean absolute error	Mean squared error
	COPTIC	TITRe2						
Blood products (number of units)								
Red blood cells ^a	1.75	2.08	0.72	(-4.43, 3.77)	-0.33	(-0.63, -0.03) *	0.89	4.46
Platelets ^b	0.75	0.67	0.90	(-0.85, 1.02)	0.08	(0.02, 0.15) *	0.16	0.23
Fresh frozen plasma ^b	0.67	0.73	0.88	(-1.40, 1.30)	-0.05	(-0.15, 0.05)	0.21	0.47
Cryoprecipitate ^b	0.19	0.24	0.85	(-0.85, 0.75)	-0.05	(-0.11, 0.01)	0.09	0.17
Inpatient length of stay (days)								
(Cardiac) intensive care unit	0.75	1.48	0.05	(-12.70, 11.24)	-0.73	(-1.61, 0.14)	1.25	37.64
High dependency unit	5.00	4.27	0.49	(-10.55, 12.02)	0.73	(-0.09, 1.56)	1.29	33.54
Ward	6.11	6.09	0.99	(-1.50, 1.55)	0.03	(-0.09, 0.14)	0.28	0.60
Total	11.87	11.84	1.00	(-0.62, 0.68)	0.03	(-0.02, 0.07)	0.07	0.11

CI, Confidence interval

^a Post-operative red blood cell use to the end of day six after surgery are reported from TITRe2 to be as comparable as possible with the data from COPTIC.

^b Intra- and post-operative resource use is reported from COPTIC for these variables to be as comparable as possible with the data from TITRe2.

* p<0.05, Paired *t* test

Table 7.4: Resource use per patient from each study: binary variables

Resource / complication	Frequency (%)		Percentage difference	n (%) of cases with agreement	Kappa	95% CI for kappa
	COPTIC	TITRe2				
Activated Factor VII ^a	1 (1%)	1 (1%)	0%	188 (99%)	-0.01	(-0.02, -0.01)
Complications						
Sepsis	19 (10%)	49 (26%)	-16%	154 (81%)	0.38	(0.23, 0.53)
Stroke	5 (3%)	1 (1%)	2%	186 (98%)	0.33	(-0.16, 0.81)
Myocardial infarction	1 (1%)	0 (0%)	1%	189 (99%)	0	0
Acute kidney injury stage 3	19 (10%)	13 (7%)	3%	182 (96%)	0.73	(0.55, 0.91)
Reoperation	18 (9%)	19 (10%)	-1%	187 (98%)	0.91	(0.81, 1.00)

CI, Confidence interval

^a Intra- and post-operative resource use is reported from COPTIC for this variable to be as comparable as possible with the data from TITRe2.

Blood products

According to Lin's concordance correlation coefficient, there is very good agreement between the studies for the use of blood products. The limits of agreement for individuals are wider for RBCs than other blood products, partly as RBCs were more frequently given. There is a small but statistically significant systematic bias in the reported number of units of RBCs transfused between the studies, on average 0.33 less units of RBCs were reported in COPTIC sources compared to TITRe2 sources. The MAE is approaching one unit. However, it is difficult to draw any firm conclusions from this as the data are not quite comparable. Post-operative RBC use to the end of day six from TITRe2 was compared to RBC use post-operatively to CICU/HDU discharge from COPTIC. While patients were on average discharged from CICU/HDU on day six, there will have been variation around this, and this is likely to have led to discrepancies here. There is also a very small but statistically significant systematic bias in the reported number of units of platelets transfused between the studies, but again the data are not completely comparable and it is therefore difficult to draw meaningful conclusions.

Length of stay

There is perfect agreement between the studies for total LOS, narrow limits of agreement and a mean difference of just 0.03 days or 40 minutes. For individuals within the population, the MAE of 0.07 days (less than two hours) indicates that the magnitude of differences is very small. For LOS on different types of ward within the overall LOS, there are stark differences in the concordance correlation coefficient; there is virtually no agreement for LOS on ICU/CICU, moderate agreement for LOS on HDU and near perfect agreement for the time on a cardiac ward. For individuals, the limits of agreement are wide for time on ICU/CICU and HDU, but much narrower for time on a ward. The mean LOS on ICU/CICU is shorter from COPTIC sources compared to TITRe2 sources, but then the mean time on HDU is longer (by approximately the same amount); time on a cardiac ward is very similar between sources. The mean total combined number of days on ICU/CICU/HDU was 5.75

from both sources, with a mean difference (95% CI) of 0.002 (-0.10, 0.10). This mean difference is only three minutes. In both studies, time on CICU and HDU was recorded together, and the time on each type of ward was split by the time of extubation. It appears that the anomalies in LOS on different types of ward arise from anomalies in the extubation dates and times. As previously reported (Chapter 6), there were some concerns about the extubation data in COPTIC.

Complications

There are some differences in the reported number of patients with complications from each study (**Table 7.4**). Less patients were reported to have had sepsis from COPTIC sources compared to TITRe2 sources. Some of these differences are likely to be attributable to the different definitions used for some complications (see **Table 7.1**), particularly for sepsis and stroke. None of the four patients reported to have had a stroke in COPTIC but not TITRe2 sources, had a transient ischaemic attack reported in TITRe2 either. There are a high proportion of cases with agreement for each of the complications, but this is not surprising since many are rare events, and zero in both sources. It is therefore helpful to look at the kappa statistic, which assesses the agreement between sources for individuals, beyond what would be expected by chance. According to Altman's (1991)[70] suggested interpretations of kappa (largely based on those of Landis and Koch (1977)), [180] there is poor agreement between sources for MI, fair agreement for sepsis and stroke, good agreement for AKI stage 3, and very good agreement for reoperations.

Costs

The effect of the similarities and differences in resource use between studies is considered further by comparing their associated costs. **Table 7.5** presents mean costs of resource use items and complications from COPTIC and TITRe2 sources (from the end of surgery to hospital discharge unless otherwise indicated). The only costs for which there was missing data was for the use of an intra-aortic balloon pump from COPTIC sources (five

patients) and for the total costs of complications and serious adverse events from TITRe2 sources (one patient). The level of agreement for the costs of resource use measured continuously is the same as for the resource use itself (**Table 7.3**), since the resource use has just been multiplied by a constant factor (its cost); the exception to this is for total LOS, since several unit costs have been applied. The reported differences in the number of units of RBCs and platelets transfused translates into statistically significant differences in their costs between the studies. While there are much larger differences in the LOS costs, both for the different ward types and overall, these differences are not statistically significant. The differences in the number of patients reported to have experienced sepsis, stroke and AKI stage 3 translate into small but statistically significant differences in their costs between the studies.

Table 7.5: Mean costs for resource use items from COPTIC and TITRe2 sources (in £2013/14 prices)

Cost category	COPTIC (n=190) Mean (SE)	TITRe2 (n=190) Mean (SE)	Concordance correlation coefficient	95% limits of agreement	Mean difference (95% CI)
Red blood cells ^a	213 (28)	254 (21)	0.72	(-541, 460)	-40 (-77, -4) *
Platelets ^b	157 (16)	139 (16)	0.90	(-176, 211)	18 (3, 32) *
Fresh frozen plasma ^b	19 (3)	20 (3)	0.88	(-39, 36)	-1 (-4, 1)
Cryoprecipitate ^b	37 (10)	47 (12)	0.85	(-165, 145)	-10 (-21, 1)
Activated Factor VII ^b	13 (13)	13 (13)	-0.01	(-507, 507)	0 (-37, 37)
Additional protamine	0 (0)	Not available	-		
Length of stay:					
(Cardiac) intensive care unit	902 (115)	1795 (535)	0.05	(-15323, 13537)	-893 (-1947, 161)
High dependency unit	3131 (329)	2671 (164)	0.49	(-6606, 7527)	460 (-56, 976)
Ward	2421 (149)	2413 (151)	0.99	(-597, 613)	8 (-36, 52)
TOTAL	6454 (386)	6879 (600)	0.86	(-7518, 6668)	-425 (-943, 93)
Complications:					
Sepsis	3 (1)	15 (3)	0.17	(-93, 68)	-12 (-18, -6) **
Stroke	5 (2)	1 (1)	0.33	(-53, 62)	4 (0, 9) *
Myocardial infarction	10 (10)	0 (0)	-	(-259, 279)	10 (-10, 30)
AKI stage 3	145 (32)	99 (27)	0.73	(-533, 625)	46 (4, 88) *
Reoperation	795 (179)	712 (159)	0.89	(-2065, 2230)	83 (-74, 239)
IABP (post-operatively)	0 (0)	Not available	-		
All complications above	958 (190)	828 (166)	0.89	(-2152, 2413)	130 (-36, 297)
All inpatient complications and serious adverse events	958 (190)	2986 (392)	0.47	(-10184, 6130)	-2027 (-2623, -1432) **

CI, Confidence interval; IABP, Intra-aortic balloon pump; SE, Standard error

^a Costs for post-operative red blood cell use to the end of day six after surgery are reported from TITRe2 to be as comparable as possible with the data from COPTIC. Red blood cell costs from both sources exclude the costs of administering blood.

^b Costs for intra- and post-operative resource use is reported from COPTIC for these variables to be as comparable as possible with the data from TITRe2.

* p<0.05, ** p<0.001

Quantifying costs not captured in COPTIC, from TITRe2 sources

As well as comparing resource use data and associated costs that were collected for both studies, this subgroup of patients can also be used to consider what might not have been captured from COPTIC sources but can be estimated from TITRe2 sources. For example, RBC use was only available from COPTIC sources post-operatively to CICU/HDU discharge, whereas in TITRe2 this information was available post-operatively to hospital discharge. From TITRe2 sources, the mean (SE) costs of RBCs post-operatively to hospital discharge were £329 (35) (compared to £213 (28) from COPTIC sources); on average (SE) this is £116 (12) higher than from COPTIC sources. If the TITRe2 figures are reliable, this suggests that RBCs are under-costed in COPTIC (in resource use terms by approximately one unit).

The comparisons between these two sources enable the costs associated with complications not captured in COPTIC to be quantified. The mean costs associated with complications are £958 from COPTIC sources, and £2986 for all complications and SAEs from TITRe2 sources, a huge mean difference of more than £2,000. The costs associated with complications captured in COPTIC represent only 32% of the costs of all inpatient complications and SAEs captured from TITRe2 sources. This suggests that there is significant under-reporting of costs associated with complications based on COPTIC sources. While it was anticipated that there was under-reporting of these costs in COPTIC, there was no means of quantifying the under-reporting from COPTIC data sources alone. This additional analysis therefore provides valuable new information, and the TITRe2 complication cost estimates can very usefully be used to inform a sensitivity analysis around complication costs in the COPTIC health economic model, which is described next.

7.6 Alternative complication costs for the COPTIC health economic model

Given the results above suggest there is significant under-reporting of complication costs in COPTIC, the difference between the total cost of all complications and SAEs captured in TITRe2 and the total cost of complications captured in COPTIC is used to inform a sensitivity analysis around complication costs in the COPTIC health economic model.

While on average this difference was in the order of £2,000, it will vary significantly between patients. The aim was therefore to divide the 190 patients into several subgroups for whom this difference could be estimated and applied to similar patients in the COPTIC cohort as a whole. There were 143 patients whose complication costs from COPTIC sources were zero, patients were first divided into those with zero costs and those with greater than zero costs (n=47). The median LOS of the 190 patients was nine days; patients with zero complication costs according to COPTIC sources were further divided into those with a LOS of less than or equal to nine days (n=82), and those with a LOS longer than nine days (n=61). The mean additional costs of complications for these three groups of patients are shown in **Table 7.6**.

Table 7.6: Mean additional cost of complications

Subgroup	Number of patients in subgroup	Additional complication cost Mean £ (SE)	Cost used in the sensitivity analysis (£)
COPTIC complication cost of £0 and LOS ≤9 days	82	733 (161)	551
COPTIC complication cost of £0 and LOS >9 days	61	2279 (439)	1714
COPTIC complication cost > £0	47	3960 (980)	2977

LOS, Length of stay; SE, Standard error

As anticipated, there are indications that patients in COPTIC and TITRe2 (and included in the analysis presented thus far) are on average sicker than patients in the COPTIC population as a whole. The mean LOS for these 190 patients was 11.9 days compared to 9.6 days for COPTIC as a whole. The mean costs to hospital discharge for these patients were 33% higher than the COPTIC cohort (£7930 compared to £5980). There was also a greater proportion of these patients classed as having CCB (clinical concern about bleeding) than in the whole COPTIC cohort (42% compared to 25%). It is therefore appropriate to adjust these additional complication costs before applying them to the COPTIC cohort. As costs to hospital discharge were 33% higher for these patients, the additional complication costs were deflated by a factor of $1/1.33$ (0.75); the costs used in the sensitivity analysis are shown in the final column of **Table 7.6**. While these costs are an improvement, the variability between patients will have been underestimated since these costs were not available on an individual patient basis.

The results of the sensitivity analysis compared to the base case results are shown in **Table 7.7**. The average costs of each strategy rise by approximately £1211, but there is very little effect on the differences between POC tests compared to current practice, and conclusions are unchanged.

Table 7.7: Results of the sensitivity analysis around complication costs

		Costs £	QALYs	Difference in costs	Difference in QALYs	ICER £ – compared to
		Mean (SE)	Mean (SE)	to Current Practice	to Current Practice	Current Practice (CP)
				Mean (95% CI)	Mean (95% CI)	
Base case	Current practice	16108 (134)	3.5617 (0.4377)			
	TEG	16134 (135)	3.5615 (0.4324)	26 (-34, 89)	-0.0002 (-0.0070, 0.0069)	CP dominant (-132153)
	ROTEM	16118 (134)	3.5660 (0.4380)	10 (-58, 81)	0.0043 (-0.0030, 0.0149)	2318
	TEG & Multiplate	16143 (135)	3.5617 (0.4398)	35 (-25, 102)	-0.00002 (-0.0079, 0.0090)	CP dominant (-2088098)
	ROTEM & Multiplate	16127 (131)	3.5663 (0.4537)	19 (-50, 86)	0.0046 (-0.0042, 0.0149)	4251
SA	Current practice	17318 (146)	3.5617 (0.4377)			
	TEG	17343 (148)	3.5615 (0.4324)	25 (-45, 97)	-0.0002 (-0.0070, 0.0069)	CP dominant (-128004)
	ROTEM	17323 (146)	3.5660 (0.4380)	6 (-74, 87)	0.0043 (-0.0030, 0.0149)	1319
	TEG & Multiplate	17351 (148)	3.5617 (0.4398)	33 (-36, 110)	-0.00002 (-0.0079, 0.0090)	CP dominant (-1976858)
	ROTEM & Multiplate	17332 (149)	3.5663 (0.4537)	14 (-67, 98)	0.0046 (-0.0042, 0.0149)	3114

CI, Confidence interval; ICER, Incremental cost-effectiveness ratio; SA, Sensitivity analysis; SE, Standard error

7.7 Discussion

In this chapter resource use data collected from alternative sources in TITRe2 and COPTIC have been compared to assess agreement between sources, and to explore the scale of any differences. Blood product use was broadly similar between the two sources, but differences in the time periods over which data were available limited the comparisons that could be made. There was very strong agreement between sources for overall LOS, but some differences in the split between CICU and HDU, due to differences in the extubation data rather than the LOS data. There were some differences in the numbers of patients reported to experience complications, but this is likely to be partly explained by the different definitions of complications used in the two studies. Overall there is nothing in the data presented to suggest that one source is any less valid than the other.

When comparing resource use data between the studies, it was the difference in what was available that was more significant than the differences between studies for the same resource use items. RBC use was only available in COPTIC until CICU/HDU discharge, information from TITRe2 sources suggests that for the subgroup of patients investigated here (and who are indicated to be sicker than the COPTIC cohort as a whole) approximately one unit of RBCs is missed per patient (presumably given once a patient has moved to a ward). The difference in what was available and the impact on costs was most striking for complications. Again for this more poorly subgroup, the comparisons suggest that only 32% of complications costs were captured by COPTIC variables, a huge under-reporting. Even if the pulmonary and gastrointestinal complications, haemodynamic support and arrhythmia variables in PATS had been costed as planned, the COPTIC analyses may well still have significantly under-costed complications compared to the information available in TITRe2.

The comparisons presented here enabled the complication costs not captured in COPTIC to be quantified, which was not possible until now, and results suggest that costs to hospital discharge for COPTIC patients are on average closer to £7190 than £5980, a significant increase of approximately £1210 (20%). Whilst fully recognising the caveats around this; it was calculated in a very simplistic way, and involved extrapolating from a subgroup with different characteristics to the whole COPTIC cohort, it is the best (only) estimate that is available. The increased costs to hospital discharge did not alter conclusions in the sensitivity analysis around the health economic model reported here, but it is plausible to think that in other situations increasing the main cost component by 20% (on average) could have altered cost-effectiveness conclusions. While conclusions were not altered here, the substantial differences in costs found in the sensitivity analysis does add further uncertainty to the model results.

The findings from the sensitivity analysis suggest that for patients at Bristol Heart Institute (BHI) the costs associated with complications were underestimated by approximately £1,210 per patient when routine data sources were used. This suggests that if all 36,134 cardiac surgery procedures undertaken in the UK in 2013/2014 were costed from routine sources (with similar levels of under-reporting),^[85] then costs associated with these procedures would be underestimated by more than £44 million. As the BHI is a tertiary referral centre, and is likely to see on average, sicker patients than many hospitals in the UK, this figure may overstate the underestimation of costs; nevertheless the underestimation based on routine data would be significant.

Given the use of routine data is being encouraged, it is timely to have undertaken this analysis which will add to the literature on whether routine datasets can reliably provide resource use data for the purposes of economic evaluation. Assessments of the use of routine data in health technology assessment highlight potential but also limitations of this approach.^[181-183] In a study which replicated four RCTs based on routine hospital data

rather than the data collected in the trials (in inflammatory bowel disease, obstructive sleep apnoea, female urinary incontinence, and total knee replacement), NHS resource use data required were generally available from routine sources, but there were concerns about the validity of the data available.[182] Difficulties in identifying, accessing and extracting data were found, and there were concerns about the lack of uniformity in coding systems and definitions. Interestingly the authors felt that better knowledge of the capabilities of local systems was essential, which is what has been investigated here. In case studies where attempts were made to evaluate interventions based on routine hospital data, insufficient scope and content was found to limit the potential of routine data.[183] This resonates with the findings here; while PATS should have been able to provide accessible data on a range of complications experienced by patients, in practice there was much missing data and the additional work undertaken to overcome this shortfall (searches of free-text fields of an additional database) rendered these data sources not so 'routine'. While there is much routine data available, Raftery *et al.* (2005) concluded that major problems exist,[181] and much work and investment is required to facilitate its potential for use in health technology assessment, particularly around coding which is often not sufficiently detailed. Routine data may be of limited use if the two interventions being compared have the same code for example. Since routine datasets have generally been designed for administrative rather than research purposes, it is perhaps not surprising that changes are required to make best use of them for research purposes. Greater clinical input into their design and coding would help to improve data quality and their applicability.

HES data have the potential to provide a wealth of information on resource use, and while they are increasingly being used (data were released to more than 100 organisations between July and September 2015),[184] only a few studies have compared events reported in HES to alternative sources. One such study concluded that surgical procedures were well recorded in HES but post-operative complications were not,[185] another that patient-reported stroke events could be validated efficiently using HES data.[186] These

studies considered clinical events which have resource implications, but not resource use *per se*. There is a small body of literature which compares the agreement of resource use from healthcare records (often GP records) and patient-reported events, Houweling *et al.* (2014) is one such example, and cites other similar studies.[187] By exploring agreement or discordance between sources, datasets and their limitations can be better understood, which can inform future research. If routine data are to be more widely used, there is a need for further work in this area.

Any data collection is expensive, and while it might be hoped that using routine data would be less expensive than bespoke data collection, this should not be assumed and needs to be assessed on a case-by-case basis for research studies. Colleagues invested huge amounts of time in COPTIC to identify study patients from various databases, and to link the data and provide it in a useable format. The poor quality of some of the data led to additional work in searching free-text fields. Quality issues such as these are perhaps less of an issue in datasets such as HES which is increasingly being used for research; however in recent years there have been considerable difficulties in accessing HES data. In any study the costs of alternative methods of collecting data need to be considered, and value of information analyses could be undertaken to inform efficient design.[188]

Routine data do have potential for use in economic evaluations, but there are concerns about their validity.[182] Before undertaking an evaluation which relies on these sources, it would be prudent to exploration their agreement with other data sources or undertake formal validation work to ensure that the results of the study are not undermined by the quality of the data available.

This work has identified some areas for consideration for researchers using routine datasets to obtain resource use data. To be clear about what routine sources can and cannot provide, it is helpful to devise a wish list of data once a research question has been

defined, and compare this to the fields available in routine sources. If the data fields of an existing resource are reviewed to determine whether they contain all the required information, it is easy to be misled into thinking it is all there. For the datasets compared here to CRF data, it was the breadth of what was included in the routine datasets that was unavailable that led to systematically missing some information on complications; in other studies it might be the level of detail that may not always be available. Where there is less control over data, as is often the case for routine datasets designed for purposes other than research, it is helpful to get an early data extract to establish that what is listed in the data fields is in practice available. If routine sources cannot provide all the information sought for a study, the value of additional information could be estimated and used to determine whether it is worthwhile to find other ways of collecting the unavailable data from an alternative source.

The evidence presented in this and previous chapters is considered next in the final chapter of this thesis.

Chapter 8: Discussion and conclusions

8.1 Introduction

This final chapter provides an overview of the research findings, the interesting challenges which arose during the research and the limitations of the research. The contribution to the literature of the work presented and the generalisability of the findings and their policy implications are also described. The chapter concludes by identifying areas for further research.

8.2 Overview of thesis findings

This thesis has explored in detail several aspects of the costs of transfusion management strategies in cardiac surgery. The overall thesis aim was to provide reliable and comprehensive estimates of the costs of administering blood in the UK NHS, and to illustrate their usefulness in applied economic evaluations involving transfusion, by assessing the cost-effectiveness of two transfusion management strategies in cardiac surgery.

A literature review of the costs of administering blood was undertaken and concluded that there was limited evidence available from the 10 studies identified (Chapter 3), and considerable variation in the estimated costs of administration (£48 to £482 per unit of RBCs transfused). This lack of available and reliable unit cost information perhaps partly explains why the costs of blood transfusion in many economic evaluations are limited to the costs of the blood products only, which undoubtedly underestimates the costs of transfusion.

The first empirical study of this thesis filled this information gap by estimating the costs of administering blood using two detailed micro-costing studies. Results showed that the cost of administering a first unit of blood was £57 for RBCs, £61 for platelets and £54 for FFP.

Costs for subsequent units of blood were considerably lower, £33 to £40 for the different components. As anticipated, the costs of administering blood add substantially to the costs of the blood products themselves; for RBCs costs are 47% (£57) higher for the first unit and 29% (£36) higher for subsequent units of blood when the costs of administration are added to the costs of the RBCs. While the costs of administration per patient may seem small compared with other medical treatments, these are frequently incurred costs; more than 30,000 RBCs are transfused to patients in NHS hospitals every week.[14] If we assume that two units are given together, the annual cost of RBC administration exceeds £70,000,000. This is equivalent to the cost of 7,000 isolated CABG surgical procedures, nearly 40% of the number performed each year in the UK,[62, 85] or the cost of 90,000 cataract operations (over 25% of the number performed annually in the UK).[62, 189] When transfusions of platelets and FFP are considered as well as RBCs, and assuming that two units are given together, the annual cost of blood administration in the UK exceeds £90,000,000.[14]

Cardiac surgery patients often need blood transfusions after surgery to treat anaemia or blood loss. Two economic evaluations were presented in Chapters 5 and 6 which assessed the cost-effectiveness of transfusion management strategies, the first associated with anaemia and the second associated with blood loss. The first case study was a cost-effectiveness analysis of a restrictive compared to a liberal RBC transfusion threshold after cardiac surgery conducted as part of the TITRe2 trial. Costs from surgery to three months post-operatively for cardiac surgery patients at risk of needing a transfusion were very similar in the two trial groups, on average £18,000. When small differences in costs are found, it is really important that costs have been collected in great detail, so that we can be more certain that there really is not a difference. Resource use and costs were collected in great detail here, and the average cost difference was just 2% of total costs (£298). We can therefore be confident that there was not a large difference in costs between the alternative transfusion thresholds. There was also very little difference in QALYs between

the restrictive and liberal transfusion thresholds, and huge uncertainty around the cost-effectiveness results. From an economic perspective, it was concluded that there is no difference between the restrictive and liberal groups.

The second case study assessed the cost-effectiveness of introducing bedside testing devices of haemostatic function in cardiac surgery. A decision-analytic model was developed and implemented to compare current practice with introducing a POC test for all patients after surgery. The majority of the parameters for the model were estimated from an observational study (COPTIC). Cost-effectiveness results from this study were very uncertain, there was little difference between any of the POC test options assessed and current practice in either costs or QALYs.

The final piece of empirical work (Chapter 7), compared individual patient resource use collected from primary data and routine datasets, by taking advantage of a subgroup of patients who were in both the TITRe2 trial and the observational study (COPTIC). There was generally strong agreement between primary (clinical trial) data and routine datasets for data available from both sources, however, primary data captured post-operative complications more comprehensively than routine datasets. Findings were used to quantify the under-reporting of complication costs in the observational study, and suggest these may have been underestimated by on average £1,211 per patient. This is equivalent to the cost of 10 transthoracic echocardiograms. Including these additional costs of complications, increased the average total costs per patient in the observational study by 20%.

8.3 Challenges of this research

This thesis provided some interesting challenges to address. When estimating the transfusion laboratory inputs into administering blood, it was important to recognise that not all group and screens lead to requests for blood, and not all blood that is issued for patients

is actually transfused to them. In the micro-costing estimates, the costs of more than one group and screen and more than one issue were incorporated into the costs of transfusion to account for the greater number of group and screens and issues than units transfused. This ensured that all the costs of the transfusion laboratory were factored into the costs per unit transfused. It is recognised that if these unit costs are used in an economic evaluation, this may overestimate the costs of laboratory inputs into transfusion for some patients, however, unless this is the particular focus of a study, it is unlikely that the number of group and screens and units issued will be captured for each patient. On balance it was considered more important to ensure that all the costs of the transfusion laboratory were accounted for, something which was not considered in the cost estimates in the NICE guidelines on blood transfusion.[83] The detailed breakdown of the cost elements of administering blood presented in Chapter 4 allows researchers to tailor costs to their study.

While the hypothesis for the COPTIC decision-analytic model was that introducing a POC test for all patients would improve the diagnosis and treatment of coagulopathic bleeding in cardiac surgery patients, there is no consensus definition of coagulopathic bleeding. The outcome measure of CCB was developed by the clinical team to capture the different ways in which bleeding might be apparent, but it is not ideal to be defining a condition by its treatment, for example whether a patient received early pro-haemostatic treatment. Since it is not straightforward to identify patients with coagulopathic bleeding, there is uncertainty around the true prevalence of the condition. There is no gold standard test for coagulopathic bleeding (nor time to wait for a definitive diagnosis in this situation), it was therefore not possible to account for the diagnostic accuracy of the POC tests using sensitivities and specificities.

The comparison in COPTIC was between current practice and introducing a POC test for all patients. Under current practice some patients received an ad hoc TEG test, and careful consideration needed to be given to these patients in the model since information was not

available on the ad hoc TEG test result, or how this was acted upon. It would have introduced bias to exclude these patients, since it is likely that clinicians requested ad hoc tests for patients they were concerned about, and therefore that there were systematic differences between patients who did and did not receive an ad hoc test. It was reasonable to assume that patients who had a positive ad hoc TEG were given a pro-haemostatic treatment which would have classified them as having CCB, but in fact this was a prophylactic treatment which may have prevented CCB. For patients with an ad hoc TEG, its impact on their pathway and CCB outcome needed to be incorporated into the model. For the POC test all arm, it was necessary to estimate the impact of the POC tests on a patient's pathway, as it was not possible to directly observe this.

8.4 Limitations of this research

The two micro-costing studies assessing the costs of administering blood were each conducted at two hospitals. While we can be confident in the findings from each hospital, since a significant amount of primary data was collected, we would have more confidence in the overall findings if they had been conducted at several more hospitals. The study of nursing inputs was conducted on two haematology day units, and while the generalisability of the findings was explored in interviews with nursing staff in other clinical areas, primary data collection in theatre and the emergency department, and potentially the intensive care unit would have enabled the costs in different settings to be quantified. Less reliable estimates of the costs of administering FFP and cryoprecipitate were generated, since the study of nursing inputs did not consider these products, and wastage estimates were not available for these products either. Finally, primary data were not collected on the inputs by porters in conveying blood samples and blood products around the hospital, and these costs were not included.

The difference in mortality between the trial groups in the TITRe2 trial was not anticipated; the three month time horizon of the within-trial cost-effectiveness analysis may not have been sufficiently long to capture all the differences between the groups.

The limitations of the economic model for COPTIC were described in detail in Chapter 6. Data for the observational study were largely obtained from existing hospital datasets rather than being collected specifically for the study and this contributed to some information gaps. The results of ad hoc TEG tests were not available, nor was it known if (or what) treatments were given as a consequence, assumptions therefore had to be made. Although the hospital datasets contained a number of variables relating to complications, in reality the majority of data were missing for some complication variables, and the costs of complications were significantly under-estimated, as quantified in Chapter 7. For patients who had a negative POC test, but an ad hoc TEG which was assumed to be positive, it was not possible to 'take out' the effect of the treatment assumed to be given as a result of the ad hoc test when these patients were considered under a Test All strategy. Despite these limitations, the individual patient data directly captured important clinical endpoints such as AKI, thus avoiding the need to model the relationship between intermediary outcomes from secondary sources (for example transfusion rates) and subsequent complications, which has several drawbacks (described in more detail in Chapter 6).[157]

While the overlap of patients in the TITRe2 trial and the observational study provided an opportunity to compare resource use data collected from alternative sources, it was not possible to obtain data over exactly the same time period from each source for every resource use item (or complication), which limited the comparisons that could be made.

Having placed the findings of the analyses presented here into context by describing their limitations, the contribution this thesis makes to the literature is described next.

8.5 Contribution to the literature

This thesis has contributed to the literature in three ways:

- 1) By generating unit costs of administering transfusions;
- 2) By presenting some lessons learnt for future studies making use of routine data;
- 3) By providing health economic evidence around alternative transfusion strategies in cardiac surgery.

Blood transfusions may be given in virtually all secondary care specialties from gastroenterology and orthopaedics, to haematology and obstetrics and gynaecology, and therefore health economists conducting applied economic evaluations in a wide range of clinical areas may need unit costs of transfusion for use in their studies. Chapter 4 produced accurate estimates of the costs of administering blood on a day unit. The transparent breakdown of the costs of administering blood presented (for RBCs and other blood components), allows other researchers to apply specific costs to their own studies.

The comparisons between data collected from routine sources and CRFs identified some areas for consideration for researchers using routine datasets for the purposes of economic evaluation. To be clear about what routine sources can and cannot provide, it is helpful to start with a wish list of data, and compare this to the fields available in routine sources. If the data fields of an existing resource are reviewed to determine whether they contain all the required information, it is easy to be misled into thinking it is all there. For the datasets compared here to CRF data, it was the breadth of what was included in the routine datasets that was unavailable that led to systematically missing some information on complications; in other studies it might be the level of detail that may not always be available. Where there is less control over data, such as routine datasets designed for purposes other than research, it is helpful to get an early data extract to establish that what is listed in the data fields is in practice available.

The health economic evidence base around transfusion management strategies in cardiac surgery is very limited; this thesis includes the first economic evaluation of alternative transfusion thresholds after cardiac surgery and the first economic evaluation assessing the introduction of POC tests after cardiac surgery using individual patient data. As well as the cost-effectiveness results themselves, the studies add to the evidence in these areas by providing cost estimates and identifying key cost drivers and resources that require detailed measurement. In both studies there was little difference in costs and outcomes between the intervention groups, and considerable uncertainty around the cost-effectiveness results. In the economic evaluation of the TITRe2 trial, surgery, length of stay and complications were key cost drivers; the costs from surgery to three months post-operatively for cardiac surgery patients at risk of needing a transfusion were on average £18,000. Only 4% of inpatient complication costs were associated with complications that made up the primary clinical outcome, highlighting the need to comprehensively capture complications. Given the detailed data collection that was undertaken, we can be confident that there is not a large difference in costs between the transfusion groups. The resource use of patients in the COPTIC observational study was costed from the end of surgery to hospital discharge; the key cost driver was length of stay, and complication costs were also important. Costs to hospital discharge for the cohort of patients were on average £6,000; this is for a general cardiac surgery population as opposed to patients at risk of needing a transfusion. The health economic model structure developed for COPTIC, and the challenges and limitations could help to inform future studies.

8.6 Generalisability of the findings

The costs of administering blood on a day unit generated as part of this thesis can reasonably be applied to day units in other hospitals in the UK and to a ward setting. Although they remain the best cost estimates available for other settings such as theatre

and the emergency department, there is uncertainty about generalising to these alternative settings. There are, however, differences in practice to be aware of; an increasing number of hospitals require a patient to have two group and screens performed (if there is no historical record of their blood group on their patient records) before blood can be issued for them. This is an additional safety check that has been introduced to flag handling errors, such as mislabelled samples and to ensure that a patient's blood group has been correctly identified. The detailed breakdown of the costs of administering blood presented (Chapter 4) can be used to tailor costs to the setting in which unit costs are being applied.

The TITRe2 trial was a large multi-centre pragmatic UK trial, and the majority of the unit costs in the economic evaluation came from national sources. The results are therefore as generalisable as trial results can be to a UK cardiac surgery population at risk of needing transfusion, and may be relevant to other developed countries.

The findings of the other two analyses presented in this thesis may have limited relevance to alternative settings. The findings of the economic evaluation of the COPTIC study may not be generalisable to other centres in the UK, since the observational study was a single-centre study and the casemix of patients may not reflect those of other centres. There were also a number of limitations around this study (described above), which reduce the generalisability of findings. The comparison of data collected from routine sources and CRFs was based on two datasets in use at Bristol Heart Institute and not on national datasets from which findings would be more widely applicable. The specific findings in relation to the agreement between data sources is not widely generalisable, but the suggestions for consideration in future uses of routine data can reasonably be applied elsewhere.

In light of the findings and their limitations, their contribution to the literature and their generalisability, the policy implications of the analyses presented are considered next.

8.7 Policy implications

One of the objectives of the *Patient Blood Management* initiative (which aims to optimise care for patients who might need transfusion) is to reduce healthcare costs;[19] without accurate cost estimates it will not be known whether this has been achieved, the estimates of the costs of administering blood generated here could assist this aim. These cost estimates can be used by hospital managers and decision-makers to assess the budget impact of policies to use blood more efficiently, for example the single unit transfusion policy, which recommends that non-bleeding patients are given one unit at a time and reassessed to determine whether further transfusion is required. The transparency of the cost estimates generated here would allow the impact of such a policy, which may have different impacts on the transfusion laboratory and nursing inputs into transfusion, to be assessed. More generally these cost estimates can be used in any economic evaluation in which blood transfusions need to be costed, thus helping to produce more accurate cost and cost-effectiveness estimates to guide policy. Although the use of these cost estimates in sensitivity analyses of the two economic evaluations presented in this thesis did not alter conclusions, there was little difference in resource use between intervention groups in either study. It is possible that in other studies, with greater differences in resource use between groups, that their inclusion might influence cost-effectiveness decisions.

Clinical guidelines recommend a restrictive transfusion threshold for most patient groups,[83, 89, 125, 126, 190, 191] but acknowledge that this is based on limited and often poor quality evidence for patients with acute or chronic cardiovascular disease, or make no recommendation for these patients. Recent NICE guidelines recommend the use of POC tests after cardiac surgery.[155] The results presented in this thesis cast doubt on both these recommendations, and they may need to be reconsidered in the light of this new evidence. The lack of a difference between groups in both economic evaluations is an

important message for policy makers. Clinical papers supporting restrictive transfusion thresholds, often conclude that this strategy is likely to be cost saving.[121, 192] While a restrictive threshold does save blood, and reduce costs associated with transfusion, the evidence generated in this thesis does not suggest that a restrictive threshold saves the NHS money overall. It is misleading to assume that a restrictive threshold is cost saving. Similarly an argument in favour of the introduction of POC tests is that it will be cost saving,[157, 164] and yet no evidence was generated here to support this view.

Finally in this chapter areas for further research are described.

8.8 Future research

There are several areas where future research could build on the findings of this thesis. In terms of the costs of administering blood, additional primary data collection could be undertaken to reliably estimate the costs of staff inputs to transfusion in alternative settings, particularly in theatre, but also in the emergency department and the intensive care unit. It would also be useful to quantify the inputs and associated costs of porters conveying blood samples and blood products around the hospital. Methods similar to the micro-costing studies presented here could be used.

Further research and validation studies are needed to investigate whether resource use data can reliably be obtained from routine administrative datasets for the purposes of economic evaluation. It would be useful to identify the types of resource use data which can reliably be captured from routine sources, and the types of data for which routine sources are unlikely to be sufficient. If routine sources cannot provide all the information sought for a study, the value of additional information could be estimated and used to determine whether it is worthwhile to find other ways of collecting the unavailable data from an alternative source.

Further work is required to determine the most appropriate transfusion management strategies after cardiac surgery. In terms of transfusion thresholds, it would be worth investigating the hypothesis that a liberal threshold is superior to a restrictive threshold for cardiac patients, and to identify the specific threshold which optimises transfusion management. A large RCT comparing restrictive and liberal thresholds in patients having cardiac surgery is underway in Canada and the US (the TRICS-III trial) and will provide new evidence on this topic.[152] Given the uncertainty around the findings of the COPTIC analyses and the limitations of the study, there is a need for further work in this area, and particularly for a rigorously conducted RCT. This would enable the impact of the POC tests on patients' care pathways to be directly observed, and for individual patient data to be collected on clinical outcomes, resource use and health-related quality of life. More generally, given the lack of strong evidence in many areas of transfusion practice in cardiac surgery, it is vital that further studies are conducted to fill these information gaps, and ensure that clinically effective and cost-effective practices are identified.

8.9 Concluding remarks

A blood transfusion is one of the most common procedures in hospitals in the developed world, and yet there has been a lack of reliable information on the costs of administering transfusions and on the cost-effectiveness of alternative transfusion management strategies in cardiac surgery. Through detailed empirical work, this thesis provides health economists and decision-makers with accurate information on the costs of administering transfusions for use in future studies, and evidence of the cost-effectiveness of two transfusion management strategies. In any economic evaluation comparing interventions where transfusions are given, a failure to fully account for the costs of transfusion could bias results in favour of the intervention with the greater blood use, and might even lead to incorrect cost-effectiveness conclusions. Reliable information on the cost-effectiveness of

transfusion strategies in cardiac surgery is needed to inform clinical guidelines and policy. The evidence presented here will be disseminated to health economists, clinicians and decision-makers via future peer-reviewed journal articles, presentations and a summary report, with a view to being used to inform practice, and ultimately to lead to more efficient use of donated blood and other scarce NHS resources for the benefit of the NHS and patients.

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Appendix 1: Methods and results of the literature review of the costs of administering blood

Aims and methods

A literature review was undertaken to identify references which report the costs of administering blood to establish what is known in this field, and to identify costs which can act as comparators to the micro-costing work presented in Chapter 4. Search strategies were informed by previous related literature reviews (particularly those conducted as part of the NICE guidelines on blood transfusion),[83] the Centre for Reviews and Dissemination terms for searching for economic evaluations,[193] and the keywords and Medical Subject Headings (MeSH) of known papers in this field.[28, 97, 98, 194, 195] The search strategies were also designed with input from an information specialist at the University of Oxford.

The electronic databases Medline and Embase were searched through Ovid on 15 February 2016. The Cochrane Library was not searched as economic evaluation papers were not expected to meet the inclusion criteria. An electronic search strategy was developed for each database (see **Appendix 2**), combining terms for blood transfusion and cost using both MeSH and free text terms to identify potential studies for inclusion. Searches were limited to references published from 2003 onwards to ensure that results were applicable to current practice, in line with the criteria set in the evidence review for the NICE guidelines on blood transfusion.[83] Searches were also limited to the English language to ensure that papers could be reviewed in detail. Conference abstracts were excluded since these are not likely to contain sufficient detail on the methods or results for comparative purposes.

Papers were sought which used primary or secondary data to estimate the costs of administering blood in a developed country. Papers in which the cost of the blood products and the cost of administration were combined and could not be split were excluded as they would not provide useful (and comparable) information on the costs of blood administration. Papers which reported or used estimates from previous studies without adding any new evidence were excluded.

Titles and abstracts of all references returned were reviewed for relevance. Potentially eligible studies were identified and full text papers obtained. Full texts were also obtained for references where it was not possible to determine relevance from the title and abstract,

these papers were reviewed and a decision made on the inclusion or exclusion of each. The reference lists of papers included in the review were also reviewed to identify any further relevant literature.

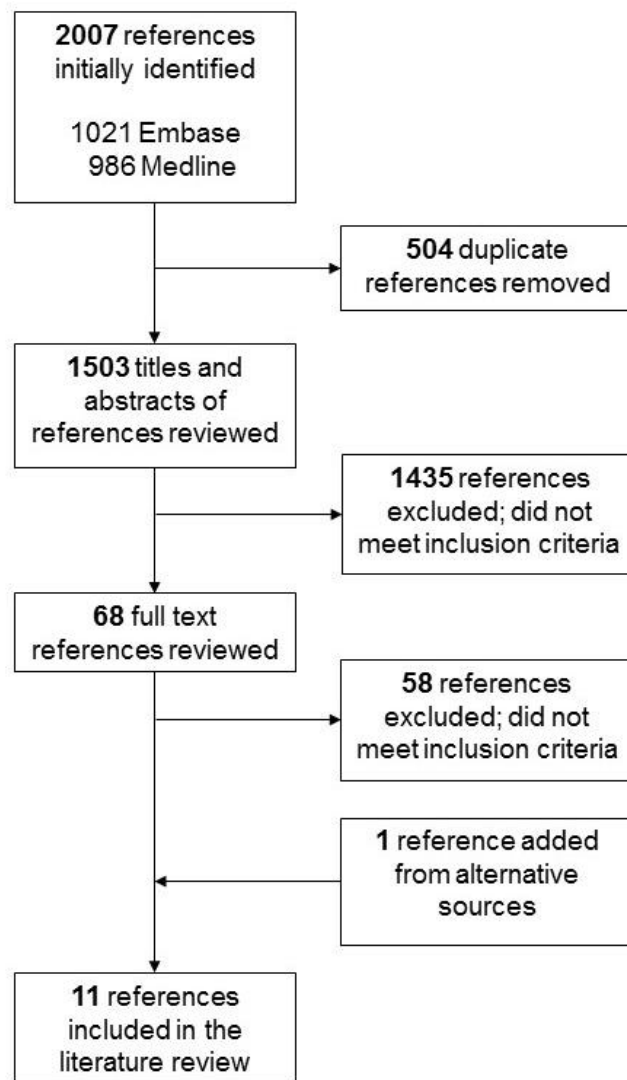
For papers meeting the inclusion criteria, information was extracted on the country of origin, the year of data collection, the study design and population, the cost perspective and the elements included and the costing approach. In terms of results, the cost per unit transfused excluding the cost of the blood product was extracted, together with the currency and price year. To facilitate meaningful comparisons, costs were inflated to 2015 prices using country specific inflation indices, then converted into UK pounds using gross domestic product purchasing power parities.[196-202]

The quality of included studies was assessed using a checklist (**Appendix 3, Table 1**). This checklist contained those items on the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist that are relevant to costing studies,[48] and was supplemented by items from other quality checklists for costing studies.[47, 65, 203] For each item on the checklist, a study scored one if it was fully addressed, zero if it was not fully addressed or no score if it was not applicable to that study. An overall summary score for each study was then generated by expressing the total score as a percentage of the maximum possible score.

Results

Figure 1 summarises the references identified in the literature review. 2,007 references were initially identified, which reduced to 1,503 once duplicates had been removed. Ten references met the inclusion criteria and one further reference was added from other sources,[83] so 11 papers in total were included in the review (**Appendix 4** provides a complete list). Two papers were by the same authors and reported identical transfusion costs, hence these papers are treated as one study. Most of the papers excluded at the title and abstract review stage did not consider the costs of transfusion; many of the papers excluded during the full-text review reported a unit cost of an activity (a group and screen or crossmatch for example), but with no details of the source data.

Figure 1: References identified in the literature review



The material extracted from the ten studies is reported in full in **Appendix 5**, and summarised in **Table 1**. Three (30%) studies were conducted in the UK, the rest are from around the world. Most studies (90%) reported the costs of transfusing RBCs, one study considered platelets only, and one study considered RBCs, platelets, FFP and cryoprecipitate. Half of the studies were multi-centre prospective studies, only one was a retrospective study. Nine studies (90%) used a bottom-up costing approach and in nine studies costing (excluding costing of blood products) was undertaken from the hospital or health system perspective. Four studies reported a societal perspective for some or all of their cost estimates; this was most frequently associated with capturing blood donors' lost productivity or leisure time, which has been excluded in this analysis.

Table 1: Summary of the characteristics of studies included in the literature review

Characteristic	Categories	Number (%) of studies
Study setting	United Kingdom	3 (30%)
	Canada	1 (10%)
	Greece	1 (10%)
	Korea	1 (10%)
	Spain	1 (10%)
	Sweden	1 (10%)
	United States	1 (10%)
	United States / Austria / Switzerland	1 (10%)
Blood products considered	Red blood cells	9 (90%)
	Platelets	2 (20%)
	Fresh frozen plasma	1 (10%)
	Cryoprecipitate	1 (10%)
Study design	Multi-centre prospective study	5 (50%)
	Single-centre prospective study	3 (30%)
	Retrospective study at the national level	1 (10%)
	Secondary sources and expert opinion	1 (10%)
Costing approach	Bottom-up	9 (90%)
	Top-down	1 (10%)
Costing perspective*	Hospital / health system	9 (90%)
	Societal	1 (10%)
Cost elements*	Laboratory testing	9 (90%)
	Administering blood to a patient	8 (80%)
	Transfusion reactions / infections	7 (70%)
	Conveying blood within hospital	5 (50%)
	Wastage	5 (50%)
	Increased length of stay	4 (40%)
	Storage of blood products	3 (30%)
	Transfusion committees	1 (10%)
	Loss of production for the patient	1 (10%)
Location of transfusion	Ward	5 (50%)
	Mixed	3 (30%)
	Outpatients	1 (10%)
	Not applicable (laboratory only)	1 (10%)

* For the cost elements of interest here, i.e. excluding the cost of blood products

The breadth of resources and costs included in the studies varied considerably. Nine studies (90%) included the costs of the blood products as well as additional costs associated with transfusion. Most studies included at least some of the costs incurred by the blood bank to identify blood groups and issue products (90%) and the costs incurred at the bedside in administering a transfusion (80%). Costs associated with transfusion reactions or transfusion transmitted infections were included in seven (70%) of the studies. Half of the studies captured the costs of conveying blood products around the hospital and half included costs associated with the wastage of blood products. Other costs less frequently captured included the additional length of stay associated with transfusions and the costs of maintaining a sufficient supply of blood products. Half of the studies considered

the costs of transfusion on a ward only, while three studies (30%) considered the costs of transfusion more generally. Six studies (60%) reported at least some resource use separately from costs (most commonly staff time), which is useful for comparative purposes.

The costs associated with transfusion that were identified in the literature review are summarised in **Table 2**. Cost estimates ranged from £5 for a group and screen only, and from £48 to £482 per unit of RBCs transfused. Where separate costs are provided for first and subsequent units (within the same transfusion episode), the costs of subsequent units are always lower than the first unit; a patient's blood group only needs to be identified once and the preparation and consumables associated with transfusion are already set up for subsequent units.

Although costs have been converted into a common currency and price year, it is difficult to compare the costs presented in **Table 2** since they each include different elements. Most studies (80%) included the laboratory and nursing costs associated with transfusion, which were in the order of £50 to £60 per unit in each of the studies. The exception was Shander *et al.* (2010),[28] where the costs were three to four times this amount (figures not reported, but estimated from pie charts). This was a very detailed study, and the list of inputs within each cost element was probably more comprehensive than other studies. This study also captured activity relating to transfusion but which might not have resulted in transfusion, which other studies may not have captured. For example, the total number of group and screens performed in a year were apportioned across the total number of RBC units transfused in the year, regardless of whether they resulted in a transfusion, thus ensuring that all costs incurred by the transfusion laboratory in relation to group and screens were incorporated into the costs per transfusion. The highest total cost estimate per unit transfused was also reported in Shander *et al.*,[28] the authors reported that indirect overhead costs (for elements such as administration, laundry, depreciation on buildings) were the largest contributor to costs; these may not have been included in other studies, or captured to the same level of detail.

Table 2: Costs per unit transfused from the literature review, excluding blood products

First author and publication year	Country	Price year and currency	Cost per unit transfused excluding blood products (for RBCs unless otherwise stated) in price year and currency of the paper	Cost per unit transfused excluding blood products (for RBCs unless otherwise stated) in 2015 UK pounds
Agrawal (2006)	UK	2004/05 UK pounds	291.93	385.64
Amin (2004)	Canada	2002 US dollars	43.86	48.05
Glenngård (2005)	Sweden	2003 Swedish kroner	1702.72 for first unit, 1155.86 for subsequent units	159.55 for first unit, 108.31 for subsequent units
Kavanos (2006)	Greece	2004 Euros	42.88	57.79
Muñoz (2014) / Muñoz (2013)	Spain	2012 Euros	52	58.75
NICE (2015)	UK	2012/13 UK pounds	70.32 for first unit, 45.46 for subsequent units	73.63 for first unit, 47.60 for subsequent units
Riley (2012)	US	Year N/R (2011 assumed), US dollars	81.54 for first unit of platelets, 15.28 for subsequent units of platelets	63.74 for first unit of platelets, 11.94 for subsequent units of platelets
Shander (2010)	US, Austria, Switzerland	2008 US dollars	561.05	482.14
Shin (2013)	Korea	Year N/R (2012 assumed), Korean won	5920*	4.77
Varney (2003)	UK	2000/01 UK pounds	RBCs 153, fresh frozen plasma 53, platelets 264, cryoprecipitate 45	RBCs 227.34, fresh frozen plasma 78.75, platelets 392.27, cryoprecipitate 66.86

N/R, Not reported; RBC, Red blood cell; US, United States; UK, United Kingdom

* Cost for an automated (rather than manual) group and screen extracted, as deemed more appropriate for comparative purposes

Only the study by Varney and Guest (2003) considered more than one type of blood product.[97] In this study the costs associated with administering a single unit of RBCs or platelets were much higher than the costs of administering FFP or cryoprecipitate. The top-down costing approach and the aggregated data used in this study precludes a greater understanding of why this might be the case. The costs associated with a platelet transfusion were much lower in Riley *et al.* (2012) compared to Varney and Guest (2003);[97, 195] however it is difficult to draw comparisons between these two studies as the cost elements included in each are completely different.

The assessment of study quality is reported in **Appendix 3 (Table 2)**. This assessment indicates that key information was under-reported; overall studies met 55% of the quality criteria. The implied time horizon for each study was short, but none of the studies explicitly stated what this was. Only 40% of studies were deemed to include all appropriate costs within cost estimates; the costs of capital equipment or overheads were most frequently omitted. While different cost elements were reported, there was often a lack of detail on the specific components included. Only two studies (20%) reported any variability around cost estimates, and only two studies conducted any sensitivity analyses to test assumptions made.

Appendix 2: Search strategies used to identify references which report the costs of administering blood

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present, Ovid MEDLINE(R) Daily Update February 14, 2016

1. exp blood transfusion/
2. ((blood or red cell or rbc or platelet* or plasma or ffp or cryoprecipitate or prothrombin) adj3 (transfus* or retransfus* or therap*)).ti,ab.
3. (hemotransfus* or haemotransfus*).ti,ab.
4. ((blood adj2 (management or administ*5 or component*1)) or blood support).ti,ab.
5. or/1-4
6. exp "costs and cost analysis"/
7. cost*.ti.
8. (price* or pricing*).ti,ab.
9. (cost* adj2 (unit* or estimat* or variable*)).ab.
10. or/6-9
11. 5 and 10
12. blood transfusion/ec
13. blood banks/ec
14. 12 or 13
15. 11 or 14
16. editorial.pt.
17. letter.pt.
18. 16 or 17
19. 15 not 18
20. animals/ not (animals/ and humans/)
21. 19 not 20
22. limit 21 to english language
23. limit 22 to yr="2003 -Current"

Embase 1974 to 2016 February 14

1. exp *blood transfusion/
2. ((blood or red cell or rbc or platelet* or plasma or ffp or cryoprecipitate or prothrombin) adj3 (transfus* or retransfus* or therap*)).ti,ab.
3. (hemotransfus* or haemotransfus*).ti,ab.
4. ((blood adj2 (management or administ*5 or component*1)) or blood support).ti,ab.
5. or/1-4
6. exp health care cost/
7. cost*.ti.
8. (price* or pricing*).ti,ab.
9. (cost* adj2 (unit* or estimat* or variable*)).ab.
10. or/6-9
11. 5 and 10
12. conference.pt.
13. editorial.pt.
14. letter.pt.
15. note.pt.
16. or/12-15
17. 11 not 16
18. exp animal/
19. exp human/
20. 18 not (18 and 19)
21. 17 not 20
22. limit 21 to english language
23. limit 22 to yr="2003 -Current"

Appendix 3: Assessing the quality of costing studies

Table 1: Checklist for the quality assessment of costing studies

Item	Criteria
1	Is the costing objective clearly stated?
2	Is the setting and location for the study clearly described?
3	Is the perspective of the study described and related to the costs being evaluated?
4	Is the time horizon over which costs are evaluated stated?
5	Is the choice of discount rate stated?
6	Are methods for estimating costs (or resource use and unit costs) clearly described?
7	Are all appropriate costs included in the cost estimates? (E.g. capital costs and overheads as well as staff time and consumables)
8	Are the dates of the estimated costs (or resource quantities and unit costs) reported?
9	Are methods for adjusting estimated (unit) costs to the year of reported costs, and any currency adjustments described?
10	Is resource use reported separately from (unit) costs?
11	Is variability around cost estimates presented?
12	Were sensitivity analyses undertaken to test the robustness of assumptions?
13	Is the funder stated and, if funded by a commercial company, were the analyses conducted independently of the funder?

Table 2: Quality assessment for each study included in the literature review

First author and publication year	Checklist item													Total score	Maximum possible score	Percentage*
	1	2	3	4	5	6	7	8	9	10	11	12	13			
Agrawal (2006)	1	1	1	0		1	0	1	1	1	0	0	0	7	12	58
Amin (2004)	1	1	1	0		1	1	1	1	0	1	1	1	10	12	83
Glenngård (2005)	1	1	1	0		0	0	0	1	1	0	0	0	5	12	42
Kavarnos (2006)	1	1	0	0		1	0	1		0	0	0	0	4	11	36
Muñoz (2014/2013)	1	1	1	0		1	1	0	1	0	0	0	0	6	12	50
NICE (2015)	1		1	0		1	0	1	1	1	0	0	1	7	11	64
Riley (2012)	1	1	0	0		1	0	0		1	0	0	1	5	11	45
Shander (2010)	1	1	1	0		1	1	1	1	1	1	0	0	9	12	75
Shin (2013)	1	0	0	0		0	0	0		1	0	0	1	3	11	27
Varney (2003)	1	1	1	0		1	1	1		0	0	1	0	7	11	64

* Total score as a percentage of the maximum possible score

Appendix 4: References included in the literature review of the costs of administering blood

1. Agrawal S, Davidson N, Walker M, Gibson S, Lim C, Morgan CL, et al. (2006) Assessing the total costs of blood delivery to hospital oncology and haematology patients. *Current Medical Research and Opinion* 22(10):1903-9.
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Appendix 5: Summary of the methods used in studies providing estimates of the costs of transfusion

First author and publication year	Country	Year of data	Study design and population	Cost perspective	Cost elements (for RBCs unless stated otherwise)	Costing approach	Resource use presented separately to unit costs	Location of transfusion
Agrawal (2006)	United Kingdom	2004	Multi-centre, prospective study at two hospitals	Hospital	Laboratory testing, administering blood to a patient, transport of blood within hospital, wastage, increased length of stay, transfusion transmitted infections	Bottom-up costing using a time and motion study, and secondary sources	Yes for staff time	Ward (oncology / haematology)
Amin (2004)	Canada	2001 - 2002	Multi-centre, prospective study at eight hospitals	Hospital	Laboratory testing, administering blood to a patient, transport of blood within hospital, wastage*, transfusion reactions	Bottom-up costing using structured questionnaires and interviews	No	Inpatients (general medicine ward, operating room, intensive care unit, emergency department)

First author and publication year	Country	Year of data	Study design and population	Cost perspective	Cost elements (for RBCs unless stated otherwise)	Costing approach	Resource use presented separately to unit costs	Location of transfusion
Glenngård (2005)	Sweden	N/R	Multi-centre, prospective study at six hospitals	Societal	Laboratory testing, administering blood to a patient, transport of blood within hospital, adverse reactions/ infections, longer hospital stay and associated loss of production	Bottom-up costing using interviews with hospital staff, published data and secondary sources	Yes for staff time and materials on the ward	Ward
Kavanos (2006)	Greece	2004	Multi-centre, prospective study at a public hospital	Hospital	Laboratory testing and storage, administering blood to a patient, extended length of stay (due to complications or blood shortages)	Bottom-up costing using data requests and interviews	No	Outpatients

First author and publication year	Country	Year of data	Study design and population	Cost perspective	Cost elements (for RBCs unless stated otherwise)	Costing approach	Resource use presented separately to unit costs	Location of transfusion
Muñoz (2014) / Muñoz (2013)	Spain	N/R	Single-centre prospective study	Hospital	Laboratory testing, administering blood to a patient, group and screen excluded	Bottom-up costing (time-driven activity-based costing approach)	No	Ward (orthopaedics)
NICE (2015)	United Kingdom	2004 for secondary sources, assume 2015 for expert opinion	Secondary sources and expert opinion	Hospital	Laboratory testing, administering blood to a patient, transport of blood within hospital, wastage	Update of bottom-up costing with expert opinion	Yes for staff time	Ward
Riley (2012)	USA	N/R	Single-centre prospective study	Hospital	Platelets only: Laboratory testing and storage of platelets, administering platelets to a patient, transfusion reactions	Bottom-up costing (process map of steps and time and motion study)	Yes for staff time	Ward (patient care unit for haematopoietic stem cell transplantation)

First author and publication year	Country	Year of data	Study design and population	Cost perspective	Cost elements (for RBCs unless stated otherwise)	Costing approach	Resource use presented separately to unit costs	Location of transfusion
Shander (2010)	USA, Switzerland, Austria	2007	Multi-centre, prospective study at four hospitals	Hospital	Laboratory testing and storage, administering blood to a patient, transport of blood within hospital, wastage*, acute transfusion reactions	Bottom-up costing (activity-based costing, time and motion study)	Yes for staff time	Inpatients excluding the emergency department (surgical population)
Shin (2013)	Korea	2012	Single-centre prospective study	Hospital	Group and screen	Bottom-up costing	Yes for staff time, reagents / consumables	N/A
Varney (2003)	United Kingdom	2000 - 2001	Retrospective study at the national level	Health system (National Health Service)	For RBCs, platelets, FFP, cryoprecipitate: transfusion committees, transfusion-related complications, additional hospital stay	Top-down costing using published data and interviews	No	All settings

FFP, Fresh frozen plasma; N/R, Not reported; RBC, Red blood cell

* Wastage costs were captured in the study as part of the cost of blood products, these were excluded from the figures reported in Chapter 3.

Appendix 6: Direct inputs into transfusion data collection forms

Data collection forms for Oxford and then Reading are provided here.

Laboratory Inputs into Transfusion Practice

Data Collection Forms

Please use the following data collection forms when undertaking activities related to transfusion.

Form 1: Booking in a Batch of Blood Samples

Form 2: Processing a Batch of Group and Screens

Form 3: Antibody Investigations

Form 4: Issue Products by Electronic Issue

Form 5: Cross-Match, Not by Electronic Issue

Form 6: Stock Control

Form 7: Audit Trail for Blood Products

Thank you for taking the time to help with data collection. Please place completed forms in the box provided.

If you have any queries, please contact Liz Stokes, Department of Public Health, University of Oxford on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 1: Booking in a Batch of Blood Samples

Please complete this form when you book in a batch of blood samples.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls, please record the approximate time that you spend on the call(s). If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of routine samples in batch	Number of antenatal samples in batch	Approx. time spent on phone calls (minutes)	Comments
Label the blood samples							
Check sufficient information has been provided on the Blood Grouping and Transfusion form, check form and sample details match, and enter details on to the computer							

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.4, 19th February 2013

Laboratory Inputs into Transfusion Practice

Form 2: Processing a Batch of Group and Screens

Please complete this form when you process a batch of group and screens.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of staff	Unique staff number(s)	Number of samples in batch	Number requiring check group	Comments
Centrifuge samples and create worksheet							
Check off and start batch							
Authorise grouping results on analyser							
Authorise antibody results on analyser							
Report results							
Sort request cards and file samples							

Did the batch fail and need to be re-run? Yes / No (delete as appropriate)

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.3, 18th February 2013

Laboratory Inputs into Transfusion Practice

Form 3: Antibody Investigations

Please complete this form when you conduct antibody investigations for a patient.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Comments
Set-up investigation				
Read results				
Additional work 1				
Additional work 2				
Additional work 3				
Additional work 4				
Additional work 5				
Checking and authorisation				

Question 2: Consumables used

Please list the consumables and the quantities of consumables used in this process. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Diamed PolySpecific ID Cards	
Antibody Identification Panel	
Other?	
Other?	
Other?	

Consumable	Quantity
Yellow Pipette tips	
Blue Pipette tips	
Other?	
Other?	
Other?	

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 4: Issue Products by Electronic Issue

Please complete this form when you issue a blood product for a patient by electronic issue.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Please circle where the blood product(s) is/are for: John Radcliffe / Churchill / NOC / Horton

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Type of product	Number of units issued	Comments
Select appropriate products						
Thaw frozen products if required						
Check and issue product and store ready for dispatch						
Boxing up for dispatch						

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 5: Cross-Match, Not by Electronic Issue

Please complete this form when you conduct a wet cross-match of red blood cells for a patient.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Please circle where the blood product(s) is/are for: John Radcliffe / Churchill / NOC / Horton

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of units cross-matched	Comments
Select appropriate products					
Set up serological crossmatch					
Complete serological crossmatch, read and input results					
Check and issue product and store ready for dispatch					
Boxing up for dispatch					

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 6: Stock Control

Please complete this form when you conduct the daily sort through each fridge at the JR, and when you process returns from other hospitals.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of staff	Unique staff number(s)	Comments
Sort through issue fridges at JR and return products past their reservation period					
Store products in appropriate place					
Process returns from the NOC					
Store returns from the NOC in the appropriate place					
Process returns from the Churchill					
Store returns from the Churchill in the appropriate place					

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.4, 19th February 2013

Laboratory Inputs into Transfusion Practice

Form 7: Audit Trail for Blood Products

Please fill in this form when you complete the audit trail for blood products.

Please record the date _____

Question 1: Time period and activity

Please record the time period covered by this audit of blood products.

Start date: _____ and end date: _____

Please record the number of units transfused in this period: _____

Please record the number of units issued in this period: _____

Question 2: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of patients in batch	Number of units in batch	Comments
Check unfated list for any units incorrectly returned to stock						
Check appropriate location of the patient at the time of transfusion						
Produce and dispatch 'unfated unit' letter						
Record fate of unit upon letters return						
Chase unreturned letters						

Thank you for taking the time to complete this form.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.4, 2nd April 2013

Laboratory Inputs into Transfusion Practice

Data Collection Forms

Please use the following data collection forms when undertaking activities related to transfusion.

Form 1: Booking in a batch of blood samples and processing the group and screens

Form 2: Antibody investigations

Form 3: Issue products by electronic issue

Form 4: Automated cross-match

Form 5: Manual cross-match

Form 6: Stock control

Form 7: Blood orders

Form 8: Audit trail for blood products

Thank you for taking the time to help with data collection. Please place completed forms in the box provided.

If you have any queries, please contact Liz Stokes, Department of Public Health, University of Oxford on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 1: Booking in a batch of blood samples and processing the group and screens

Please complete this form when you book in a batch of blood samples and process the group and screens.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of staff	Unique staff number(s)	Number of routine samples in batch	Number of antenatal samples in batch	Approx. time spent on phone calls etc (minutes)	Comments
Check sufficient information has been provided on the Blood Grouping and Transfusion Form. Check form and sample details match, label the blood samples and place the samples in the centrifuge								
Enter details on to the computer and check if products can be issued electronically								
Check on the computer that the bar code on the samples reads properly								
Check worklist								
Authorise anomalous grouping/antibody results on analyser								
File samples								

Did the batch fail and need to be re-run? Yes / No (delete as appropriate)

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.2, 24th April 2013

Laboratory Inputs into Transfusion Practice

Form 2: Antibody investigations

Please complete this form when you conduct antibody investigations for a patient.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Approx. time spent on phone calls etc (minutes)	Comments
Set-up investigation					
Read results					
Additional work 1					
Additional work 2					
Additional work 3					
Additional work 4					
Additional work 5					
Checking and authorisation					
Send aways					

Question 2: Consumables used

Please list the consumables and the quantities of consumables used in this process. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Diamed PolySpecific ID Cards	
Antibody Identification Panel	
Rh/K cards	
Other?	
Other?	

Consumable	Quantity
Yellow Pipette tips	
Blue Pipette tips	
Other?	
Other?	
Other?	

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.2, 24th April 2013

Laboratory Inputs into Transfusion Practice

Form 3: Issue products by electronic issue

Please complete this form when you issue a blood product for a patient by electronic issue.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Please circle where the blood product(s) is/are for: RBH / Satellite

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Type of product	Number of units issued	Approx. time spent on phone calls etc (minutes)	Comments
Select appropriate products, check and validate							
Set frozen products to thaw if required							
Check and issue product							
Second check							
Store ready for dispatch (through Blood Track)							
Boxing up for dispatch (for satellites/NW etc)							

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.2, 24th April 2013

Laboratory Inputs into Transfusion Practice

Form 4: Automated cross-match

Please complete this form when you conduct an automated cross-match of red blood cells for a patient.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Please circle where the blood product(s) is/are for: RBH / Satellite

Please circle whether the patient needed an antibody screen: Yes / No

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of units cross-matched	Approx. time spent on phone calls etc (minutes)	Comments
Set up automated cross-match						
Input results						
Check and issue product						
Second check						
Store ready for dispatch (through Blood Track)						
Boxing up for dispatch (for satellites/NW etc)						

Question 2: Consumables used

Please list the consumables and the quantities of consumables used in this process. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Diamed PolySpecific ID Cards	
Other?	
Other?	

Consumable	Quantity
ABO Cards	
Other?	
Other?	

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.2, 24th April 2013

Laboratory Inputs into Transfusion Practice

Form 5: Manual cross-match

Please complete this form when you conduct a manual cross-match of red blood cells for a patient.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Please circle where the blood product(s) is/are for: RBH / Satellite

Please circle whether the patient needed an antibody screen: Yes / No

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of units cross-matched	Approx. time spent on phone calls etc (minutes)	Comments
Select appropriate products						
Set up serological crossmatch						
Complete serological crossmatch, read and input results						
Check and issue product						
Second check						
Store ready for dispatch (through Blood Track)						
Boxing up for dispatch (for satellites/NW etc)						

Question 2: Consumables used

Please list the consumables and the quantities of consumables used in this process. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Diamed PolySpecific ID Cards	
Other?	
Other?	

Consumable	Quantity
ABO Cards	
Other?	
Other?	

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.2, 24th April 2013

Laboratory Inputs into Transfusion Practice

Form 6: Stock control

Please complete this form when you conduct the daily sort through each fridge, process returns from satellites and do a stock count.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of staff	Unique staff number(s)	Approx. time spent on phone calls etc (minutes)	Comments
Daily fridge audit						
Return blood to stock fridge						
Return blood from satellites						
Stock count						

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 7: Blood orders

Please complete this form when you order and book in blood product deliveries.

Please record the date _____

Question 1: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of staff	Unique staff number(s)	Approx. time spent on phone calls etc (minutes)	Comments
Order products: AM top up						
Wand AM order into computer and store in fridge						
Order products: PM main order						
Order products: PM top up						
Wand PM order into computer and store in fridge						
Order products: AM main order						

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Form 8: Audit trail for blood products

Please fill in this form when you complete the audit trail for blood products.

Please record the date _____

Question 1: Time period and activity

Please record the time period covered by this audit of blood products.

Start date: _____ and end date: _____

Please record the number of units transfused in this period: _____

Please record the number of units issued in this period: _____

Question 2: Time for tasks

Please record the following information for each task in the process, and use the blank lines for additional tasks. If you get interrupted with telephone calls or anything else, please record the approximate time that this takes up. If there is anything unusual about the time taken, please record details in the comments column.

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of patients in batch	Number of units in batch	Approx. time spent on phone calls etc (minutes)	Comments
Check for unfated units							
Follow up unfated units:							
Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Unique staff number(s)	Number of patients in batch	Blood product type & number of each	Approx. time spent on phone calls etc (minutes)	Comments
Patient 1							
Patient 2							
Patient 3							
Patient 4							
Patient 5							

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Version 0.3, 6th June 2013

Appendix 7: Senior staff (indirect) inputs into transfusion data collection forms

Data collection forms for senior BMS and then transfusion laboratory managers are provided here. Forms used in Oxford are provided, the forms used in Reading were very similar.

Laboratory Inputs into Transfusion Practice

Time spent by Senior BMS on bench and non-bench activities

Please record the date _____ and your unique number _____.

Morning part 1: 8.30am to morning break

Please record how this time was spent in the table below.

	Activities	Time (minutes)
	Bench work	
N	Training	
O	Telephone queries (excluding antenatal queries)	
N	Stock issues and cold chain	
	Antibody support	
B	Antenatal support (including telephone queries)	
E	Supply / reagent issues	
N	Trauma / HEMS	
C	SOPs	
H	Validation of new equipment	
W	Other _____	
O	Other _____	
R	Other _____	
K	Other _____	
	TOTAL TIME	

Morning part 2: Post break to lunch

Please record how this time was spent in the table below.

	Activities	Time (minutes)
	Bench work	
N	Training	
O	Telephone queries (excluding antenatal queries)	
N	Stock issues and cold chain	
	Antibody support	
B	Antenatal support (including telephone queries)	
E	Supply / reagent issues	
N	Trauma / HEMS	
C	SOPs	
H	Validation of new equipment	
W	Other _____	
O	Other _____	
R	Other _____	
K	Other _____	
	TOTAL TIME	

Please turn over and record how your time was spent in the afternoon.

Afternoon part 1: lunch to afternoon break

Please record how this time was spent in the table below.

	Activities	Time (minutes)
	Bench work	
N	Training	
O	Telephone queries (excluding antenatal queries)	
N	Stock issues and cold chain	
	Antibody support	
B	Antenatal support (including telephone queries)	
E	Supply / reagent issues	
N	Trauma / HEMS	
C	SOPs	
H	Validation of new equipment	
W	Other _____	
O	Other _____	
R	Other _____	
K	Other _____	
	TOTAL TIME	

Afternoon part 2: Post break to 5pm

Please record how this time was spent in the table below.

	Activities	Time (minutes)
	Bench work	
N	Training	
O	Telephone queries (excluding antenatal queries)	
N	Stock issues and cold chain	
	Antibody support	
B	Antenatal support (including telephone queries)	
E	Supply / reagent issues	
N	Trauma / HEMS	
C	SOPs	
H	Validation of new equipment	
W	Other _____	
O	Other _____	
R	Other _____	
K	Other _____	
	TOTAL TIME	

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Laboratory Inputs into Transfusion Practice

Time spent by Laboratory Manager on non-bench (and bench) activities

Please record the date _____ and your unique number _____.

Morning

Please record how your time was spent in the table below.

	Morning Part 1: 8.30am - 10.30am	Morning Part 2: 10.30am - 1pm
Activities	Time (minutes)	Time (minutes)
Telephone / email queries (excluding antenatal queries)		
IT		
Troubleshooting		
Meetings		
Training medics		
Unfated units		
Audit and statistics		
SOPs		
Generic staff issues		
Managing laboratory staff		
Report writing		
Investigating incidents		
Antenatal support (including telephone / email queries)		
Bench work		
Training		
Stock issues and cold chain		
Antibody support		
Supply / reagent issues		
Trauma / HEMS		
Validation of new equipment		
Other _____		
Other _____		
Other _____		
Other _____		
TOTAL TIME		

Please turn over and record how your time was spent in the afternoon.

Afternoon

Please record how your time was spent in the table below.

	Afternoon Part 1: 1pm – 3pm	Afternoon Part 2: 3pm - 5pm
Activities	Time (minutes)	Time (minutes)
Telephone / email queries (excluding antenatal queries)		
IT		
Troubleshooting		
Meetings		
Training medics		
Unfated units		
Audit and statistics		
SOPs		
Generic staff issues		
Managing laboratory staff		
Report writing		
Investigating incidents		
Antenatal support (including telephone / email queries)		
Bench work		
Training		
Stock issues and cold chain		
Antibody support		
Supply / reagent issues		
Trauma / HEMS		
Validation of new equipment		
Other _____		
Other _____		
Other _____		
Other _____		
TOTAL TIME		

Thank you for taking the time to complete this form. Please place in the box provided.

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Please provide a summary of the IT equipment used by the hospital transfusion laboratory.

Item	Number of items
Computers	
Printers	
Specialist printers	
Fridge tracking	

Maintenance of equipment items

Please record the annual maintenance costs for each item of hospital transfusion laboratory equipment below.

[illegible]

Equipment on a service contract

Please record the annual cost for each item of equipment on a service contract below.

Item	Annual Cost for 2011/12

Building

In order to apportion the costs of the building, the size of the hospital transfusion laboratory (m²) would be useful information. Is the size of the HTL known? This size should include office space and storage as well as the laboratory areas.

Size of HTL: _____ m²

Overheads

As well as the costs of the space in the building, the running costs of the building - power, heat, light, and cleaning need to be included, as well as other hospital overheads such as personnel and administration. Does the HTL get billed for these items by the Trust? If so, what did the HTL pay for these running costs and overheads for financial year 2011/2012?

Running costs and overheads: £ _____

Hospital Transfusion Laboratory activity per year

Outputs such as the number of samples processed and the number of units issued need to be obtained, in order to apportion overheads appropriately. Please record the HTL activity for financial year 2011/2012 below.

Activity	Total number in 2011/2012
Blood products received from stock holding unit	
RBCs	
Frozen products (FFP/ Cryoprecipitate)	
Platelets	
Other	
Blood products issued	
RBCs	
Frozen products (FFP/ Cryoprecipitate)	
Platelets	
Other	
Blood products Used	
RBCs	
Frozen products (FFP/ Cryoprecipitate)	
Platelets	
Other	
Group and save - transfusion	
Group and save - antenatal	
Cross-matches – electronic issue	
Cross-matches – not electronic issue	
Remote issue	

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Thank you for taking the time to complete this questionnaire.

Appendix 9: Nursing inputs into transfusion data collection forms

Data collection forms for Oxford and then London are provided here.

FORM 1 Nursing Inputs into Transfusion Practice**Blood Sample Collection for Blood Grouping and Transfusion**

Please complete this form when you take a blood sample and request blood for a patient.

Please record your unique number _____ and the date _____

Time

Please record the start and finish times for the following tasks:

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Comments
Prepare tray, gather equipment, approach the patient and explain the procedure, generate a wristband (if necessary), carry out identification checks with patient and wristband			
Take blood sample and label it			
Complete the request form, bag up and dispatch the sample			

Consumables

Please list the consumables and the quantities of consumables used to take the blood sample. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Wristband (include only if it was necessary to generate)	
Vacutainer	
Blood bottle with anticoagulant	
Butterfly	
Hyperdermic needle	
Gloves	
Tourniquet	

Consumable	Quantity
Syringe	
10ml Saline	
5ml Hepsal	
Dressing pack	
Medi-Swab	
Cotton wool and tape	

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Thank you for taking the time to complete this form. Please place in the box provided.

Please complete Form 2 when you administer a transfusion.

Version 2, 3rd October 2011

FORM 2 Nursing Inputs into Transfusion Practice



Blood Administration

Please circle the type of blood product prescribed: RBCs Platelets

Please circle the number of units prescribed: 1 2 3 Other: _____

Please circle the mode of administration: Cannula Central line

Please record the date _____

Time

Please record the start and finish times for the following tasks. If any additional tasks were completed in relation to administering blood product(s), please give details in the blank rows provided, and estimate the associated time involved. Please record your unique number and ask your colleague to record their unique number if more than one nurse was involved in the process. **After recording a time for a task, please record all associated consumables used on the back of this form.**

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of nurses involved	Nurse(s) unique number	Comments
Obtain a prescription					
Confirm blood product has arrived					
Preparation of trolley and equipment, approach the patient and explain the procedure					
Cannulation / flush out central line (delete as appropriate)					
Blood unit 1: Generate pick up slip and collect blood product					
Unit 1: Identification checks with patient, pre-transfusion observations, medications associated with transfusion and start transfusion					
Unit 1: Observations after transfusion begun					
Unit 1: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					
Blood unit 2: Generate pick up slip and collect blood product					
Unit 2: Identification checks with patient, pre-transfusion observations, medications associated with transfusion and start transfusion					

Please turn over and record consumables used on the back of this form, and continue recording times associated with the second and third units of blood (if appropriate) ...

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of nurses involved	Nurse(s) unique number	Comments
Unit 2: Observations after transfusion begun					
Unit 2: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					
Blood unit 3: Generate pick up slip and collect blood product					
Unit 3: Identification checks with patient, pre-transfusion observations, medications associated with transfusion and start transfusion					
Unit 3: Observations after transfusion begun					
Unit 3: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					

Consumables

Please list the consumables and the quantities of consumables used to administer blood product(s). Common items are listed, but lines are left blank for you to add additional items used. Since this section is completed over the course of a day, potentially by more than one person, please record items as a tally chart.

Consumable	Tally	Consumable	Tally
Red cell administration set		Medi-Swab	
Platelet administration set		Gloves	
Red cell pump administration set		Tourniquet	
Blood warming set		Cotton wool and tape	
IV dressing		Piriton	
Syringe		Paracetamol	
Cannula		Frusamide - IV / oral (delete as appropriate)	
5ml Hepsal			
10ml Saline			

If you have any queries, please contact Liz Stokes on 01865 289276 or elizabeth.stokes@dph.ox.ac.uk.

Thank you for taking the time to complete this form. Please place in the box provided.

Version 2, 3rd October 2011

FORM 1 Nursing Inputs into Transfusion Practice**Blood Sample Collection for Blood Grouping and Transfusion**

Please complete this form when you take a blood sample and request blood for a patient.

Please record your unique number _____ and the date _____

Time

Please record the start and finish times for the following tasks:

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Comments
Prepare tray, gather equipment, approach the patient and explain the procedure, generate a wristband (if necessary), carry out identification checks with patient and wristband			
Take blood sample and label it			
Complete the request form, bag up and dispatch the sample			

Consumables

Please list the consumables and the quantities of consumables used to take the blood sample. Common items are listed, but lines are left blank for you to add additional items used. If items are not used, please enter a zero.

Consumable	Quantity
Wristband (include only if it was necessary to generate)	
Vacutainer	
Blood bottle with anticoagulant	
Butterfly	
Hyperdermic needle	
Cannula	
Luer adapter	
IV dressing	
Tourniquet	

Consumable	Quantity
Syringe	
10ml Saline	
5ml Hepsal	
Dressing pack	
Medi-Swab	
Cotton wool and tape	
Gloves	
Apron	

If you have any queries, please contact Kelly Radford on 0207 188 5935 or kelly.radford@gstt.nhs.uk.

Thank you for taking the time to complete this form. Please place in the box provided.

Please complete Form 2 when you administer a transfusion.

FORM 2 Nursing Inputs into Transfusion Practice



Blood Administration

Please circle the type of blood product prescribed: RBCs Platelets

Please circle the number of units prescribed: 1 2 3 Other: _____

Please circle the mode of administration: Cannula Central line

Please record the date _____

Time

Please record the start and finish times for the following tasks. If any additional tasks were completed in relation to administering blood product(s), please give details in the blank rows provided, and estimate the associated time involved. Please record your unique number and ask your colleague to record their unique number if more than one nurse was involved in the process. **After recording a time for a task, please record all associated consumables used on the back of this form.**

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of nurses involved	Nurse(s) unique number	Comments
Obtain a prescription					
Confirm blood product has arrived					
Preparation of trolley and equipment, approach the patient and explain the procedure					
Cannulation / flush out central line (delete as appropriate)					
Blood unit 1: Pre-transfusion observations					
Unit 1: Generate pick up slip and collect blood product					
Unit 1: Identification checks with patient, medications associated with transfusion and start transfusion					
Unit 1: Observations after transfusion begun					
Unit 1: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					
Blood unit 2: Generate pick up slip and collect blood product					
Unit 2: Identification checks with patient, medications associated with transfusion and start transfusion					

Please turn over and record consumables used on the back of this form, and continue recording times associated with the second and third units of blood (if appropriate) ...

Task	Start Time (to the nearest minute)	Finish Time (to the nearest minute)	Number of nurses involved	Nurse(s) unique number	Comments
Unit 2: Observations after transfusion begun					
Unit 2: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					
Blood unit 3: Generate pick up slip and collect blood product					
Unit 3: Identification checks with patient, medications associated with transfusion and start transfusion					
Unit 3: Observations after transfusion begun					
Unit 3: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product					

Consumables

Please list the consumables and the quantities of consumables used to administer blood product(s). Common items are listed, but lines are left blank for you to add additional items used. Since this section is completed over the course of a day, potentially by more than one person, please record items as a tally chart. **Please write 'in place' next to cannula if this has already been inserted.**

Consumable	Tally	Consumable	Tally
Blood product administration set		Medi-Swab	
Blood warming set		Gloves	
IV dressing		Tourniquet	
Syringe		Cotton wool and tape	
Cannula		Piriton	
5ml Hepsal		Paracetamol	
10ml Saline		Frusamide - IV / oral (delete as appropriate)	

If you have any queries, please contact Kelly Radford on 0207 188 5935 or kelly.radford@gstt.nhs.uk.

Thank you for taking the time to complete this form. Please place in the box provided.

Version 1, 17th November 2011

Appendix 10: More detailed results of nursing inputs into transfusion

Table 1: Nursing time associated with taking a blood sample and requesting blood

Task	Mean (SD) time (minutes)	
	Oxford (n=28)	London (n=30)
Prepare tray, gather equipment, approach the patient and explain the procedure, generate a wristband (if necessary), carry out identification checks with patient and wristband	5.1 (2.9)	5.6 (3.8)
Take blood sample and label it	7.0 (4.8)	8.4 (10.7)
Complete the request form, bag up and dispatch the sample	4.9 (2.2)	4.6 (3.5)
Total time	17.0 (6.1)	18.6 (14.5)

SD, Standard deviation

Table 2: Nursing time associated with a single transfusion

Task	Mean (SD) time (minutes)	
	Oxford (n=85)	London (n=59)
Obtain a prescription	4.6 (3.3)	4.9 (4.4)
Confirm blood product has arrived	5.0 (4.2)	2.9 (3.5)
Preparation of trolley and equipment, approach the patient and explain the procedure	4.5 (2.7)	3.8 (3.0)
Cannulation / flush out central line	5.3 (5.0)	7.5 (11.8)
Blood unit 1: Pre-transfusion observations (London only)		3.0 (1.9)
Blood unit 1: Generate pick up slip and collect blood product	5.2 (5.2)	5.7 (3.3)
Unit 1: Identification checks with patient, pre-transfusion observations (Oxford only), medications associated with transfusion and start transfusion	5.3 (2.8)	4.2 (5.4)
Unit 1: Observations after transfusion begun	0	3.0 (1.5)
Final Unit: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product	7.3 (2.7)	6.2 (5.8)
Total time	37.2 (9.5)	41.1 (22.1)

SD, Standard deviation

Table 3: Inputs into blood administration by blood product and mode of administration

Mode	Blood product	Oxford				London			
		Time (n)	Mean time (mins)	Consumables (n)	Mean consumables cost (£)	Time (n)	Mean time (mins)	Consumables (n)	Mean consumables cost (£)
All	All	85	37.2	77	5.28	59	41.1	59	5.47
Cannula	RBCs	30	34.8	28	5.47	29	40.9	28	6.26
Cannula	Platelets	13	42.7	12	5.89	9	36.0	9	5.12
Central line	RBCs	14	37.7	12	4.61	10	48.2	10	7.72
Central line	Platelets	18	37.1	15	3.54	10	35.8	11	1.09

RBC, Red blood cell

n = Number of complete forms

Table 4: Nursing time associated with subsequent units transfused

Task	Mean (SD) time (minutes)	
	Oxford (n=79)	London (n=29)
Blood unit 2/3: Generate pick up slip and collect blood product	2.7 (1.5)	5.7 (2.4)
Unit 2/3: Identification checks with patient, pre-transfusion observations (Oxford only), medications associated with transfusion and start transfusion	5.5 (2.5)	4.0 (1.9)
Unit 2/3: Observations after transfusion begun	0	3.8 (2.8)
Non final unit 1/2: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product	3.1 (1.7)	4.7 (3.3)
Total time	11.2 (4.0)	18.1 (5.8)

SD, Standard deviation

Appendix 11: Interviews with nurses

Four semi-structured interviews with nurses working in theatre and ED were conducted to explore the generalisability of the cost estimates of transfusion on the haematology day units with alternative settings. This appendix describes the methods and results, and discusses the findings.

Methods

This work was conducted in the two hospitals in Oxford and London where the detailed costing study was undertaken. Two interviews were conducted at each of the two hospitals, one with a nurse working in theatre, and one with a nurse working in ED.

An interview schedule was drawn up based on the Forms 1 and 2 used to collect the data in the previous costing study. The interview schedule can be found in **Appendix 12**. For the two tasks of taking a blood sample and placing a request for blood, and for administering a transfusion, the schedule presented the list of steps in the process on the haematology day unit, and asked nurses whether these steps would be done in their setting, and if so, who would undertake them, and how long that step might take. A list of consumables was also presented for each task, and nurses asked to say what would be used. At the end of the interview, the staff time and consumable estimates based on the primary data collection on the haematology day unit were shared with nurses.

At each hospital, two nurses took part in the interviews, one experienced in working in theatre, the other experienced in working in ED. A local collaborator approached nurses to identify willing participants who had worked in theatre/ED for three years or more. This was a very low risk study, participants' agreement to be interviewed was taken as implicit consent. Interviews were not recorded, and the names of interviewees will be kept anonymous. Research governance approval for the study was obtained at each hospital. Four interviews were conducted in December 2015.

Findings from the four interviews were summarised qualitatively. This work was exploratory; with small numbers of interviews the aim was not to produce definitive quantitative estimates, but to provide some context to the previous work, and identify areas for further work.

Results

Results are summarised firstly for theatre, and then for ED.

Theatre: taking a blood sample

At both hospitals, the majority of patients have had a blood sample taken for a group and screen before they arrive in theatre. If this has not been done, once the cannula has been inserted for anaesthesia, then either the anaesthetist (at one hospital) or an anaesthetist or a nurse (at the other hospital) would take a blood sample and complete the request form. Given that the cannula has already been inserted, the additional time and costs of taking this sample are less than on the day unit. At both hospitals, this process was estimated to take approximately five minutes and the cost of consumables was negligible (7p).

Theatre: administering a transfusion

In theatre it is the anaesthetist who decides if a patient requires blood. Blood then needs to be requested (if there are no remote issue fridges), a pick-up slip generated, the blood prescribed and identification checks carried out between the staff, patient and the bag of blood, before it can be hung up and administered to the patient. Patients are continually monitored in theatre, so additional observations before and during transfusion are not required. At the end of transfusion, the bag would be taken down and its use recorded, to complete an audit trail for that unit of product. Although the order of steps varied a little between the two hospitals, the same key tasks were undertaken, and the estimated time to administer a single unit was similar (12-13 minutes). There was agreement about the additional consumables required, just a blood administration set and a blood warming set, costing approximately £21. If several units were ordered at the same time, then there is little additional staff time associated with the second unit (just a few minutes); if blood needs to be ordered again, then the times are similar to the first unit.

Emergency department: taking a blood sample

In ED, there are two types of patient who need blood – emergencies coming into resuscitation who need O negative blood, and patients who need blood urgently (within four hours) such as those with trauma, or vascular bleeding complications. There are relatively few of these patients, many more may need blood during their stay. A blood sample for a group and screen is taken soon after arrival in ED for patients who are thought likely to need a transfusion or surgery, these patients will have several samples taken for different tests, for example a full blood count. This would be taken by a nurse or healthcare assistant at one hospital and a nurse or doctor at the other. The process for taking a blood sample is the same for both types of patient, and similar to the process on the day unit, and

estimated to take slightly less time (11-16 minutes). A cannula would be inserted for taking the blood sample, and then be ready for transfusion or for another purpose. The consumables required were similar at both hospitals, with an estimated cost of £4.

Emergency department: administering a transfusion

The time taken to administer blood varies depending on whether it is an emergency, or an urgent need for blood. Oxford is a trauma centre, and therefore more likely to see emergency patients. In Oxford, if a patient is coming in with major bleeding, a phone call will be made before the patient arrives to activate the massive haemorrhage protocol, which notifies the transfusion laboratory that O negative RBCs and FFP are required, and notifies the porters that this needs collecting. It was estimated to take a doctor or nurse five minutes to activate the massive haemorrhage protocol, and a nurse five minutes to perform identification checks and start transfusion; subsequent units would take just a minute. Observations before and during transfusion would not be necessary as the patient would be being continually monitored by a doctor. If a rapid fluid warmer is used, which warms the blood and pumps it in quickly, consumable costs are of the order of £130. The London hospital involved in this study is not a trauma centre, and therefore is less likely to care for such patients. Warmers and rapid infusers are not available in ED at that hospital even in resuscitation as they would get very little use. O negative blood is available in ED, and if two units are needed in an emergency, it was estimated to take 22 minutes to administer them.

In Oxford and London, if a patient urgently requires a transfusion, a nurse or doctor needs to telephone the transfusion laboratory to request the blood; the steps thereafter would be undertaken by a nurse and are similar to the steps in the process on the day unit. Generally steps would be undertaken more quickly than on the day unit, it was estimated to take 20-25 minutes of staff time to administer a single unit of blood and 11-20 minutes for subsequent units. There was agreement about the consumables required, which have an estimated cost of £1. However it should be noted that at both hospitals while blood samples are frequently taken in ED for group and screens, and for cross-matching, often the patient has moved on from ED before the transfusion is given, or at least before it is finished. It is quite rare to perform tasks associated with ending a transfusion or subsequent units in ED.

Discussion

The second micro-costing study presented in Chapter 4 estimated the nursing staff inputs and associated costs of administering blood on a haematology day unit. The interviews described here have explored the same processes in alternative hospital settings.

Evidence from the interviews suggests that there are some similarities and some differences in the inputs required to administer a transfusion in theatre or ED compared to the haematology day unit. In terms of taking a blood sample and requesting a group and screen (and potentially blood products), this would more often be done before a patient arrived in theatre either at a pre-operative assessment or on the ward prior to surgery. In these settings, the costs are likely to be similar to those estimated on the haematology day unit. If the blood sample is taken in theatre, this is likely to take less time than on the day unit, but may be undertaken by a much higher grade of staff (an anaesthetist rather than a nurse). These two factors may balance each other out; it was estimated to take approximately a third of the time to take the blood sample and complete the request form, but an anaesthetist is likely to be paid three times a nurse's salary. Overall therefore, the staff costs associated with a blood sample for a group and screen for a surgical patient may be similar to those reported on the haematology day unit.

It was estimated to take less than half the staff time to administer a blood transfusion in theatre compared to the day unit (approximately 12-15 minutes, and just a few minutes for subsequent units if they had been ordered at the same time as the first unit). Consumable costs in theatre are likely to be higher as blood warming sets are routinely used.

In ED, the estimated time involved in taking a blood sample and requesting a group and screen was slightly less than the time reported on the day unit. The time associated with blood administration was much less in ED; just 10 minutes for the first unit and a minute for subsequent units for an emergency patient in Oxford, 22 minutes for two emergency units of O negative blood in London, and 20-25 minutes for the first unit and 11-20 minutes for subsequent units for a patient needing blood urgently. When the consumables for taking a blood sample and administering blood are considered together, the costs were similar to those reported on the day unit, unless a patient has major haemorrhage and a rapid infuser is used, the consumable costs for which are of the order of £130 (Oxford only).

Appendix 12: Interview schedule

The interview schedule for Oxford and then London is provided.

Comparing the costs of administering a blood transfusion to patients on the day unit with other hospital settings

Interview Schedule, Oxford, Draft 2

Circle as appropriate

ED / Theatre

Inputs into Transfusion Practice: Blood Sample Collection for Blood Grouping and Transfusion

Time

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Prepare tray, gather equipment, approach the patient and explain the procedure, generate a wristband (if necessary), carry out identification checks with patient and wristband				
Take blood sample and label it				
Complete the request form, bag up and dispatch the sample				

Inputs into Transfusion Practice: Blood Sample Collection for Blood Grouping and Transfusion

Consumables

Consumable	Would this be used, and if so, how many?	Comments
Vacutainer		
Blood bottle with anticoagulant		
Butterfly		
Tourniquet		
Medi-Swab		
Cotton wool and tape		
Gloves		
Hyperdermic needle		
Syringe		
10ml Saline		
5ml Hepsal		
Dressing pack		
Wristband (if need to generate)		
Anything else?		

Nursing Inputs into Transfusion Practice: Blood Administration

Data was collected on RBC and platelets transfusions, 1-3 units, via cannula or via a central line

Time

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Obtain a prescription				
Confirm blood product has arrived				
Preparation of trolley and equipment, approach the patient and explain the procedure				
Cannulation / flush out central line				Would either a cannula or a central line be used?
Blood unit 1: Generate pick up slip and collect blood product				
Unit 1: Identification checks with patient, pre-transfusion observations, medications associated with transfusion and start transfusion				
Unit 1: Observations after transfusion begun				
Final Unit: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product				

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Blood unit 2/3: Generate pick up slip and collect blood product				
Unit 2/3: Identification checks with patient, pre-transfusion observations, medications associated with transfusion and start transfusion				
Unit 2/3: Observations after transfusion begun				
Non final unit 1/2: End of transfusion – removal of cannula [N/A here], observations after transfusion, disposal of consumables and completion of audit trail for blood product				

Nursing Inputs into Transfusion Practice: Blood Administration

Consumables

Consumable	Would this be used, and if so, how many?	Comments
Red cell administration set		
IV dressing		
Syringe		
Cannula		
10ml Saline		
Medi-Swab		
Gloves		
Tourniquet		
Cotton wool and tape		
Red cell pump administration set		
Blood warming set		
5ml Hepsal		
Piriton		
Paracetamol		
Frusamide - IV / oral (delete as appropriate)		
Anything else?		

Comparing the costs of administering a blood transfusion to patients on the day unit with other hospital settings

Interview Schedule, GSTFT, Draft 2

Circle as appropriate

ED / Theatre

Inputs into Transfusion Practice: Blood Sample Collection for Blood Grouping and Transfusion

Time

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Prepare tray, gather equipment, approach the patient and explain the procedure, generate a wristband (if necessary), carry out identification checks with patient and wristband				
Take blood sample and label it				
Complete the request form, bag up and dispatch the sample				

Inputs into Transfusion Practice: Blood Sample Collection for Blood Grouping and Transfusion

Consumables

Consumable	Would this be used, and if so, how many?	Comments
Wristband (if need to generate)		
Vacutainer		
Blood bottle with anticoagulant		
Butterfly		
Cannula		
Luer adapter		
IV dressing		
Tourniquet		
10ml Saline		
Medi-Swab		
Cotton wool and tape		
Gloves		
Apron		
Hyperdermic needle		
Syringe		
5ml Hepsal		
Dressing pack		
Anything else?		

Nursing Inputs into Transfusion Practice: Blood Administration

Data was collected on RBC and platelets transfusions, 1-3 units, via cannula or via a central line

Time

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Obtain a prescription				
Confirm blood product has arrived				
Preparation of trolley and equipment, approach the patient and explain the procedure				
Cannulation / flush out central line				Would either a cannula or a central line be used?
Blood unit 1: Pre-transfusion observations				
Unit 1: Generate pick up slip and collect blood product				
Unit 1: Identification checks with patient, medications associated with transfusion and start transfusion				
Unit 1: Observations after transfusion begun				
Final Unit: End of transfusion – removal of cannula, observations after transfusion, disposal of consumables and completion of audit trail for blood product				

Task	Would this task be done?	Who would undertake this task?	How long would this take?	Comments
Blood unit 2/3: Generate pick up slip and collect blood product				
Unit 2/3: Identification checks with patient, medications associated with transfusion and start transfusion				
Unit 2/3: Observations after transfusion begun				
Non final unit 1/2: End of transfusion – removal of cannula [N/A here], observations after transfusion, disposal of consumables and completion of audit trail for blood product				

Nursing Inputs into Transfusion Practice: Blood Administration

Consumables

Consumable	Would this be used, and if so, how many?	Comments
Blood product administration set		
IV dressing		
Syringe		
Cannula		
10ml Saline		
Medi-Swab		
Gloves		
Tourniquet		
Cotton wool and tape		
Red cell pump administration set		
Blood warming set		
5ml Hepsal		
Piriton		
Paracetamol		
Frusamide - IV / oral (delete as appropriate)		
Anything else?		

Appendix 13: Applying the quality checklist to the cost of administering blood study

Quality assessment of the cost of administering blood study

Item	Criteria	Score
1	Is the costing objective clearly stated?	1
2	Is the setting and location for the study clearly described?	1
3	Is the perspective of the study described and related to the costs being evaluated?	0
4	Is the time horizon over which costs are evaluated stated?	0
5	Is the choice of discount rate stated?	N/A
6	Are methods for estimating costs (or resource use and unit costs) clearly described?	1
7	Are all appropriate costs included in the cost estimates? (E.g. capital costs and overheads as well as staff time and consumables)	1
8	Are the dates of the estimated costs (or resource quantities and unit costs) reported?	1
9	Are methods for adjusting estimated (unit) costs to the year of reported costs, and any currency adjustments described?	1
10	Is resource use reported separately from (unit) costs?	1
11	Is variability around cost estimates presented?	0
12	Were sensitivity analyses undertaken to test the robustness of assumptions?	0
13	Is the funder stated and, if funded by a commercial company, were the analyses conducted independently of the funder?	1
Total score		8
Maximum possible score		12
Percentage*		67%

* Total score as a percentage of the maximum possible score

Appendix 14: TITRe2 data collection forms

This appendix provides the TITRe2 case report forms relevant to the economic evaluation, the EQ-5D questionnaire used at six weeks post-randomisation (it was also used pre-operatively and at three months follow up), and the three month follow up questionnaire.

POST-OPERATIVE INFORMATION & DAILY CHECKS FOR ALL PATIENTS - (con)

Centre Code	Patient Name	Patient Study ID

OPERATION TYPE:

CABG only ☐ Valve only ☐ CABG + valve ☐ Other ☐ If other, specify:

SUMMARY OF Hb, Hct AND RBC TRANSFUSION DATA FOR DURATION OF HOSPITAL STAY

Complete this table **daily** for **ALL CONSENTED PATIENTS** for **each day** the patient was in hospital after their operation up to and including day 10. NB: Day 0 is the day of the patient's operation.

		Please complete both Hb and Hct if recorded (indicate with NR if not recorded on any day)		RBC transfusion received?	
Day	Date (dd/mm/yyyy)	Lowest Hb (g/dL)	Lowest Hct (%)	Yes	No
0 *	___ / ___ / ____			☐	☐
1	___ / ___ / ____			☐	☐
2	___ / ___ / ____			☐	☐
3	___ / ___ / ____			☐	☐
4	___ / ___ / ____			☐	☐
5	___ / ___ / ____			☐	☐
6	___ / ___ / ____			☐	☐
7	___ / ___ / ____			☐	☐
8	___ / ___ / ____			☐	☐
9	___ / ___ / ____			☐	☐
10	___ / ___ / ____			☐	☐

* Note: for day 0 (i.e. day of surgery), complete post-op details only

For **randomised** participants **use this form and B2 to monitor breaches of protocol** allocation (giving or withholding RBC in contravention of allocated group).
If there are any instances of this, complete relevant form (in Section E)

Please complete the following for **ALL** patients at discharge:

Status at end of operation (complete post-operatively) Alive ☐ Dead ☐
Patient status at discharge from cardiac surgery unit Alive ☐ Dead ☐

TOTAL BLOOD PRODUCTS USED DURING HOSPITAL STAY

Total blood products given intra-operatively and post-operatively (units) (if none, enter 0)

RBC FFP Platelets Cryoprecipitate Activated Factor VII Yes ☐ No ☐
Beriplex Yes ☐ No ☐

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

_____/_____/_____
Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

_____/_____/_____
_____/_____/_____
* Names must appear on the site signature & delegation log

Version 5.0, 01/09/2011

RBC TRANSFUSION FORM - randomised patients only (rand)

Centre Code	Patient Name	Patient Study ID

PLEASE COMPLETE THIS SECTION DAILY FOR EACH RBC UNIT TRANSFUSED (Post-op—only one RBC unit should be transfused then recheck the Hb/Hct before transfusing another unit unless there are clear clinical reasons to do otherwise.)

Did the patient receive any RBC transfusions during their stay? Yes ☐ No ☐

If **Yes**, complete one row per unit in table below for each unit transfused (include all RBC given intra-operatively, post-operatively and for any re-operations).

If more than 10 RBC units are transfused, use extension form H2 for additional units.			Only complete cells below if 'Reason for transfusion given' is "Per protocol" (code F)						
			Date and time of transfusion	Reason (use code from table below)	Date and time of breach that triggered prescription	Hb/Hct at "trigger" breach		RBC prescribed <24 hours since "trigger" breach	
Unit	Unit Batch No	dd/mm/yyyy 24 hour clock		dd/mm/yyyy 24 hour clock	Hb	Hct	Yes	No	
1		/ /		/ /					
		:		:					
2		/ /		/ /					
		:		:					
3		/ /		/ /					
		:		:					
4		/ /		/ /					
		:		:					
5		/ /		/ /					
		:		:					
6		/ /		/ /					
		:		:					
7		/ /		/ /					
		:		:					
8		/ /		/ /					
		:		:					
9		/ /		/ /					
		:		:					
10		/ /		/ /					
		:		:					

Code	Reason for transfusion given:	Code	Reason for transfusion given:
A	Intra-operatively (no E1 or E2 needed)	D	Pre-randomisation (post-op) (complete Note To File)
B	Re-operation (no E1 or E2 needed)	E	In breach of protocol (complete form E1 for each unit)
C	Treatment according to protocol discontinued (check G1 completed, no E1 or E2 needed)	F	Per protocol (*complete E2 for each breach recorded in the final column)

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

----- / /

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

----- / /

Version 6.0, 31/01/2011

* Names must appear on the site signature & delegation log

DETAILS OF PERI-OPERATIVE PERIOD - (rand)

Centre Code	Patient Name	Patient Study ID
OPERATION DETAILS		
Responsible consultant surgeon (initials)		Start of operation (time entered theatre) (24 hour clock) :
First Operator (initials)		End of operation (time) (24 hour clock) :
Date of operation (dd/mm/yyyy)		
Lowest Hct during surgery . % Unrecorded ☐		
CPB used? Yes ☐ No ☐ If CPB used: Total bypass min		
Cumulative cross-clamp time min		
Myocardial protection used: Blood ☐ Crystalloid ☐ Other ☐ N/A ☐		
No of distal coronary anastomoses:		Harvest site(s):
Valve(s) replaced / repaired:		Right arm Yes ☐ No ☐
Aortic Yes ☐ No ☐		Left arm Yes ☐ No ☐
Mitral Yes ☐ No ☐		Right leg Yes ☐ No ☐
Tricuspid Yes ☐ No ☐		Left leg Yes ☐ No ☐
Pulmonary Yes ☐ No ☐		LIMA Yes ☐ No ☐
		RIMA Yes ☐ No ☐
		Other Yes ☐ No ☐
Blood saving techniques: Tranexamic acid Yes ☐ No ☐ Cell Saver Yes ☐ No ☐		
Trasylol Yes ☐ No ☐		
POST-OPERATIVE DETAILS		
Total chest tube drainage at 4 h ml		Was post-op cell salvage used? Yes ☐ No ☐
Total chest tube drainage at 12 h ml		
RE-OPERATION DETAILS (Enter details of 1st re-operation below, for more than 1 re-operation, complete H5)		
How many times was chest re-opened (at any time) during hospital stay? (if none, enter 0) if >0, complete below $\pm$ H5		
Reason why chest was re-opened (tick all that apply): Bleeding ☐ Cardiovascular instability ☐ Infection ☐ Other ☐		
Date of re-operation (dd/mm/yyyy)	Re-op start time (24 hour clock) :	Re-op end time (24 hour clock) :
HIGHEST CREATININE ON EACH POST-OPERATIVE DAY OF HOSPITAL STAY (Day 1 is the 1st day after operation)		
Please collect for 10 days post-op.		
Day 1: Creatinine: μ mol / L	Day 6: Creatinine: μ mol / L	N/A ☐
Day 2: Creatinine: μ mol / L	Day 7: Creatinine: μ mol / L	N/A ☐
Day 3: Creatinine: μ mol / L	Day 8: Creatinine: μ mol / L	N/A ☐
Day 4: Creatinine: μ mol / L	Day 9: Creatinine: μ mol / L	N/A ☐
Day 5: Creatinine: μ mol / L	Day 10: Creatinine: μ mol / L	N/A ☐
Name of person completing form* (capitals)		Date completed (dd/mm/yyyy)
Signature of person completing form		
Name of person entering data* (capitals)		Date data entered (dd/mm/yyyy)
Signature of person entering data		

* Names must appear on the site signature & delegation log

Version 7.0, 01/09/2011

ASEPSIS ASSESSMENT DAY 3 - (rand)

Centre Code	Patient Name	Patient Study ID

ASEPSIS WOUND ASSESSMENT - Day 3

'Day 3' inspection (If unable to complete on day 3, please complete as close to day 3 as possible)

Date performed ___/___/___ N/A - patient discharged/died by day 3 ☐
N/A - patient not randomised by day 3 ☐
dd/mm/yyyy

	Chest		Right Arm			Left Arm			Right Leg			Left Leg			Other		
	Yes	No	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA
Is the dressing or wound wet?*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Does the wound feel hot?*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*Ask patient, or if unconscious, check with nursing staff

If any of the above answers are YES, please complete wound scoring (below) for each affected wound.
 (If there are more than 2 affected wounds, please print out continuation sheet Form H3 for additional space)

1st Wound being scored: Chest ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg ☐ Other ☐

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	___/___/___
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	___/___/___
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	___/___/___
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia [†]	☐	☐	___/___/___

2nd Wound being scored: Chest ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg ☐ Other ☐

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	___/___/___
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	___/___/___
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	___/___/___
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia [†]	☐	☐	___/___/___

* including vac therapy

[†] Including debridement in theatre

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

Version 5.0, 31/01/2011

* Names must appear on the site signature & delegation log

ASEPSIS ASSESSMENT DAY 5 - (rand)

Centre Code	Patient Name	Patient Study ID

ASEPSIS WOUND ASSESSMENT - Day 5

'Day 5' inspection (If unable to complete on day 5, please complete as close to day 5 as

Date performed

____ / ____ / ____

dd/mm/yyyy

N/A - patient discharged/died by day 5 ☐N/A - patient not randomised by day 5 ☐

	Chest		Right Arm			Left Arm			Right Leg			Left Leg			Other		
	Yes	No	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA
Is the dressing or wound wet?*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Does the wound feel hot?*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*Ask patient, or if unconscious, check with nursing staff

If any of the above **answers** are YES, please complete wound scoring (below) for each affected wound.
 (If there are more than 2 affected wounds, please print out continuation sheet Form H3 for additional space)

1st Wound being scored: Chest ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg ☐ Other ☐

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	____/____/____
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	____/____/____
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	____/____/____
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia†	☐	☐	____/____/____

2nd Wound being scored: Chest ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg ☐ Other ☐

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	____/____/____
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	____/____/____
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	____/____/____
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia†	☐	☐	____/____/____

* including vac therapy

† Including debridement in theatre

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

_____/_____/____

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

_____/_____/____

Version 5.0, 31/01/2011

* Names must appear on the site signature & delegation log

Centre Code	Patient Name	Patient Study ID

'Day 8' inspection (If unable to complete on day 8, please complete as close to day

N/A - patient not randomised by day 8

Chest		Right Arm			Left Arm			Right Leg			Left Leg			Other		
Yes	No	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA	Yes	No	NA

[illegible][illegible]

*If any of the above answers are YES, please complete wound scoring (below) for each affected wound.
(If there are more than 2 affected wounds, please print out continuation sheet Form H3 for additional space)*

1st Wound being scored: Chest ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg ☐ Other ☐

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	__/__/__
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	__/__/__
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	__/__/__
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia [†]	☐	☐	__/__/__

2nd Wound being scored: Chest Right Arm Left Arm Right Leg Left Leg Other

Proportion of wound affected	0%	<20%	20-39%	40-59%	60-79%	>80%		Yes	No	If Yes, please give date (dd/mm/yyyy)
Serous exudates	☐	☐	☐	☐	☐	☐	Antibiotics given for wound infection	☐	☐	___/___/___
Erythema	☐	☐	☐	☐	☐	☐	Isolation of bacteria	☐	☐	___/___/___
Purulent exudates	☐	☐	☐	☐	☐	☐	Drainage of pus under local anaesthesia*	☐	☐	___/___/___
Separation of deep tissue	☐	☐	☐	☐	☐	☐	Drainage of pus under general anaesthesia†	☐	☐	___/___/___

* including vac therapy

[†] Including debridement in theatre

Name of person completing form* (capitals)

Signature of person completing form

Date completed (dd/mm/yyyy)

Name of person entering data* (capitals)

Date data entered (dd/mm/yyyy)

Version 5.0, 31/01/2011

* Names must appear on the site signature & delegation log

SUMMARY OF INFECTIOUS POST-OPERATIVE COMPLICATIONS - (rand)

Centre Code	Patient Name	Patient Study ID
« » « » « »	«name»	« » «S » « » « » « »

INFECTIOUS EVENTS SUMMARY

Please add details for **all courses of antibiotics (excluding post-op prophylaxis)** prescribed to the patient during their post-op hospital stay. Data collection is recommended on day 3, 5, 8 (if not previously discharged) and on discharge. For all courses **provide anonymised copies of the drug chart**, with patient study ID and initials, to the TITRe 2 co-ordinating centre.

Was the patient given antibiotics at any time during their post-operative stay (excluding prophylaxis)? Yes ☐ No ☐ If Yes, how many courses? ☐

For each course of antibiotics given to the patient, please complete a section below:

1	Name of antibiotic: _____	Date and time started antibiotic: ____/____/____	____:____	
		dd/mm/yyyy	(24 hour clock)	
	Were the antibiotics: Oral? ☐ IV? ☐	Duration of course: ____ days		
	Site of suspected infection (tick all that apply): Respiratory ☐ Wound ☐ Blood ☐ Other ☐			
	In the 24h preceding the start of antibiotics did the patient have any of the following symptoms?			
	Temperature > 38°C or < 36°C?	Yes ☐ No ☐ Unrecorded ☐		Was infection subsequently confirmed by positive culture? Yes ☐ No ☐
	Heart rate > 90 beats per minute?	Yes ☐ No ☐ Unrecorded ☐		
	Respiratory rate > 20 breaths per minute?	Yes ☐ No ☐ Unrecorded ☐		
	PaCO ₂ < 32 mmHg or < 4.3 kPa?	Yes ☐ No ☐ Unrecorded ☐		
	WBC count > 12,000 / mm ³ or < 4,000 / mm ³ ?	Yes ☐ No ☐ Unrecorded ☐		
2	Name of antibiotic: _____	Date and time started antibiotic: ____/____/____	____:____	
		dd/mm/yyyy	(24 hour clock)	
	Were the antibiotics: Oral? ☐ IV? ☐	Duration of course: ____ days		
	Site of suspected infection (tick all that apply): Respiratory ☐ Wound ☐ Blood ☐ Other ☐			
	In the 24h preceding the start of antibiotics did the patient have any of the following symptoms?			
	Temperature > 38°C or < 36°C?	Yes ☐ No ☐ Unrecorded ☐		Was infection subsequently confirmed by positive culture? Yes ☐ No ☐
	Heart rate > 90 beats per minute?	Yes ☐ No ☐ Unrecorded ☐		
	Respiratory rate > 20 breaths per minute?	Yes ☐ No ☐ Unrecorded ☐		
	PaCO ₂ < 32 mmHg or < 4.3 kPa?	Yes ☐ No ☐ Unrecorded ☐		
	WBC count > 12,000 / mm ³ or < 4,000 / mm ³ ?	Yes ☐ No ☐ Unrecorded ☐		
3	Name of antibiotic: _____	Date and time started antibiotic: ____/____/____	____:____	
		dd/mm/yyyy	(24 hour clock)	
	Were the antibiotics: Oral? ☐ IV? ☐	Duration of course: ____ days		
	Site of suspected infection (tick all that apply): Respiratory ☐ Wound ☐ Blood ☐ Other ☐			
	In the 24h preceding the start of antibiotics did the patient have any of the following symptoms?			
	Temperature > 38°C or < 36°C?	Yes ☐ No ☐ Unrecorded ☐		Was infection subsequently confirmed by positive culture? Yes ☐ No ☐
	Heart rate > 90 beats per minute?	Yes ☐ No ☐ Unrecorded ☐		
	Respiratory rate > 20 breaths per minute?	Yes ☐ No ☐ Unrecorded ☐		
	PaCO ₂ < 32 mmHg or < 4.3 kPa?	Yes ☐ No ☐ Unrecorded ☐		
	WBC count > 12,000 / mm ³ or < 4,000 / mm ³ ?	Yes ☐ No ☐ Unrecorded ☐		

Name of person completing form* (capitals) _____ Signature of person completing form _____ Date completed (dd/mm/yyyy) ____/____/____

Name of person entering data* (capitals) _____ Date data entered (dd/mm/yyyy) ____/____/____

Version 4.0, 27/07/2010

* Names must appear on the site signature & delegation log

SUMMARY OF ISCHAEMIC POST-OPERATIVE COMPLICATIONS - (rand)

Centre Code	Patient Name	Patient Study ID

ISCHAEMIC EVENTS SUMMARY		
Please add details of all ischaemic events as they occur. Data collection is recommended on day 3, 5, 8 (if not previously discharged) and on discharge. Please also provide documentary evidence of verification as appropriate *.		
COMPLICATION	If yes, please complete date and time when first documented in the notes:	VERIFICATION*
Permanent stroke Yes ☐ No ☐	dd/mm/yyyy : (24 hour clock) If time is not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐ Not known ☐	Yes ☐ No ☐ CT ☐ MRI ☐
Suspected myocardial infarction Yes ☐ No ☐	dd/mm/yyyy : (24 hour clock) If time is not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐ Not recorded ☐	Which Troponin was measured? I ☐ T ☐ Please give highest level ng/L* μg/L* ng/ml* *delete as applicable
Gut infarction Yes ☐ No ☐	dd/mm/yyyy : (24 hour clock) If time is not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐ Not known ☐	Yes ☐ No ☐ Laparotomy ☐ Post mortem ☐
Acute kidney injury Yes ☐ No ☐	dd/mm/yyyy : (24 hour clock) If time is not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐ Not known ☐	Yes ☐ No ☐ AKIN criteria Stage 1, 2 or 3 (see box below for definitions)

If Yes to Acute kidney injury, please specify most severe stage experienced (complete on discharge):

Stage 1: Serum creatinine increase $\geq 0.3\text{mg/dl}$ ($\geq 26.4\mu\text{mol/l}$) or increase to 1.5-fold to 2-fold from baseline[†] OR urine output $< 0.5\text{ml/kg/h}$ for $> 6\text{h}$.

Stage 2: Serum creatinine increase $> 2\text{-fold}$ to 3-fold from baseline[†] OR urine output $< 0.5\text{ml/kg/h}$ for $> 12\text{h}$.

Stage 3: Serum creatinine increase $> 3\text{-fold}$ from baseline[†] or serum creatinine $\geq 4.0\text{mg/dl}$ ($\geq 354\mu\text{mol/l}$) with an acute increase of at least 0.5mg/dl ($44\mu\text{mol/l}$) OR need for renal replacement therapy (RRT) irrespective of stage at time of RRT OR urine output $< 0.3\text{ml/kg/h}$ for 24h or anuria for 12h .

[†] baseline refers to pre-operative serum creatinine measurement

*NB. Documentary evidence should take the form of copies of the relevant report (i.e. CT / MRI / PM / biochemistry / operation) / obs chart / copy of page in notes signed off by doctor / copy of discharge letter containing the relevant information.
Please anonymise copies of documentation and add the patient's study ID & initials before sending to the co-ordinating centre

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

----- / ----- / -----

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

----- / ----- / -----

Version 4.0, 25/07/2011

* Names must appear on the site signature & delegation log

SUMMARY OF OTHER POST-OPERATIVE COMPLICATIONS - (rand)

Centre Code	Patient Name	Patient Study ID

SUMMARY OF OTHER COMPLICATIONS (For all re-occurrences of complications, complete H5) <i>Please add details of all other events listed below if / when they occur. Data collection is recommended on day 3, 5, 8 (if not previously discharged) and on discharge.</i>												
Complication* (see TITRe 2 trial manual, section 10, for full definitions)	Yes No		Date and time first documented in notes		If time is unknown please indicate time of day				SAE*		Number of events (enter 0 if none)	
			Date (dd/mm/yyyy)	Time (24 hour clock)	AM	PM	Overnight	Unknown	Yes	No		
Transient ischaemic attack												
Pancreatitis												
Intestinal obstruction/perforation												
Post-operative haemorrhage (400ml/h for 1h or 200ml/h for 4h)												
ARDS												
Re-intubation/ventilation (if >1, use H5 to record multiple instances)												
Tracheostomy												
Initiation of mask CPAP												
Pneumothorax requiring chest drainage												
Pleural effusion requiring drainage												
Pacing												
SVT/AF requiring treatment												
VF/VT requiring intervention												
Deep vein thrombosis												
Pulmonary embolus												
Low cardiac output requiring management (including IABP)												
Wound dehiscence requiring rewiring/treatment												
Other GI (specify)												
Other pulmonary (specify)												
Other arrhythmia (specify)												
Other thromboembolic (specify)												

Tick SAE as Yes for any complications listed that met the definition of serious, i.e. are/were life-threatening, resulted in persistent or significant disability/incapacity, prolonged hospitalisation or resulted in death.

If any complications listed above resulted in **death**, or another event not listed was serious (see box above), you **MUST** report it to the CTEU as an SAE using the forms in **Section F** within 24h of discovering the event.

Please use this box for any additional information/comments on Forms C5-C7:

Name of person completing form* (capitals)	Signature of person completing form	Date completed (dd/mm/yyyy)
_____	_____	____/____/____
Name of person entering data* (capitals)	Date data entered (dd/mm/yyyy)	
_____	____/____/____	

* Names must appear on the site signature & delegation log

Centre Code	Patient Name	Patient Study ID

Date and time first admitted to CICU/HDU post-operatively	__ / __ / ____	__: : __	N/A ☐	(Tick N/A if not applicable)
	dd/mm/yyyy	(24 hour clock)		
Date and time of extubation <i>(Use H5 if patient was re-extubated)</i>	__ / __ / ____	__: : __	N/A* ☐	(*).e. N/A if patient dies whilst intubated)
	dd/mm/yyyy	(24 hour clock)		
Patient discharged from CICU/HDU to:	General ICU ☐ Ward ☐ Patient died ☐ Home ☐ Other ☐			
Date and time first admitted to general ICU (if applicable)	__ / __ / ____	__: : __	N/A ☐	
	dd/mm/yyyy	(24 hour clock)		
Date and time first admitted to ward (if applicable)	__ / __ / ____	__: : __	N/A ☐	
	dd/mm/yyyy	(24 hour clock)		
If time admitted to ward not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐				

How many times was the patient readmitted? (if none, enter 0)				If >0, please complete section below $\pm$ H5, if 0, go to status at discharge	
Date and time patient 1st readmitted to:	CICU/HDU ☐	General ICU ☐	Ward ☐		
Date and time patient 2nd readmitted to:	CICU/HDU ☐	General ICU ☐	Ward ☐		
				dd/mm/yyyy	(24 hour clock)

Date of discharge from cardiac surgery unit or date of death (if patient died before discharge)*:

	dd/mm/yyyy

Where was the patient discharged from cardiac surgery unit to?

Other unit in this hospital	☐	→ Give date of final discharge from hospital / death*		OR Ongoing	☐
Home	☐		dd/mm/yyyy		
Other hospital	☐	→ Give name			
Other	☐	→ Specify (e.g. died)			

*Note: please ensure that deaths are reported on the study SAE form (Section F)

Is the patient available to answer questions? Yes ☐ No ☐ *If Yes, enter date answered & details below:*
dd/mm/yyyy

Ask: "Did you think being in one group would be better for your health than the other, if so, which?" No ☐ Group 1 (<9g/ ☐ Group 2 (<7.5g/ ☐

Ask: "Do you know, or think that you know, which group you were put into?" Yes ☐ No ☐

If 'Yes', ask: "Which group do you think you were put into?" Group 1 (<9g/ ☐ Group 2 (<7.5g/ ☐

Have you reminded the patient about the postal questionnaires at 6 and 12 weeks? Yes ☐ No ☐

Version 10.0. 22/03/2012

* Names must appear on the site signature & delegation log

INFORMATION ABOUT MEDICATIONS- (rand)

Centre Code	Patient Name	Patient Study ID

Please complete on discharge: details of medication patients were on at baseline, in theatre /CICU/CHDU and at discharge. Do NOT include any analgesics or laxatives.

REGULAR MEDICATIONS AT BASELINE (i.e. on admission to the cardiac surgery unit, include

	Yes	No		Yes	No
Digoxin	☐	☐	Statins	☐	☐
Diuretics	☐	☐	Anti-arrhythmic	☐	☐
Beta blockers	☐	☐	Heparin/clexane	☐	☐
Calcium antagonists	☐	☐	IV GTN/nitrates	☐	☐
Aspirin	☐	☐	FeSO ₄	☐	☐
Oral Nitrates	☐	☐	Other please specify	☐	☐
Angiotensin 2 blockers	☐	☐			
ACE inhibitors	☐	☐			
Warfarin	☐	☐			
Clonidogrel	☐	☐			

MEDICATIONS IN THEATRE / CICU / CHDU

	Yes	No		Yes	No
Hydroxyethyl starch (HES/HAES)	☐	☐	Gelofusin	☐	☐
Human albumin solution (HAS)	☐	☐	Inotropes	☐	☐

MEDICATIONS ON DISCHARGE (i.e. at time of discharge from cardiac surgery unit)

	Yes	No		Yes	No
Digoxin	☐	☐	Statins	☐	☐
Diuretics	☐	☐	Insulin	☐	☐
Beta blockers	☐	☐	Oral anti-diabetics	☐	☐
Calcium antagonists	☐	☐	Anti-arrhythmic	☐	☐
Aspirin	☐	☐	Heparin/clexane	☐	☐
Oral Nitrates	☐	☐	IV GTN/nitrates	☐	☐
Angiotensin 2 blockers	☐	☐	FeSO ₄	☐	☐
ACE inhibitors	☐	☐	Other please specify	☐	☐
Warfarin	☐	☐			
Clonidogrel	☐	☐			

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

_____ / _____ / _____

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

_____ / _____ / _____

Version 7.0, 31/01/2011

* Names must appear on the site signature & delegation log

SAE INITIAL REPORT FORM—Complete ONE form per SAE (rand)

Centre Code

« « «

Patient Study ID

« «S « « « «

1. PARTICIPANT DETAILS

Patient initials: Sex: Male ☐ Female ☐ Date of Birth: / / (dd/mm/yyyy)

2. BRIEF DESCRIPTION OF EVENT (max 70 characters)

3. REASON FOR REPORTING EVENT AS SAE (please tick as many as apply)

	Yes	No		Yes	No
Resulted in death * <i>*Please provide copy of PM report or death certificate</i>	☐	☐	Required hospitalisation	☐	☐
Is / was life-threatening	☐	☐	Prolonged an ongoing hospitalisation	☐	☐
Resulted in persistent or significant disability / incapacity	☐	☐	Other (if Yes, please specify below)	☐	☐

4. DETAILS OF ONSET AND DURATION

Date and time of onset: / / : : (dd/mm/yyyy) 24 hour clock

End date and time (if resolved): / / : : (dd/mm/yyyy) (24 hour clock)

5. OUTCOME OF EVENT

Resolved, no sequelae ☐ Resolved, with sequelae * ☐ Ongoing * (please complete and return follow-up report form within 5 days) ☐ Died * (give cause and PM details or Death Certificate) ☐

*Give details:

6. FURTHER DETAILS OF EVENT

Maximum intensity of event (up until time of initial report):
Mild: an event easily tolerated by patient, causing minimal discomfort, not interfering with everyday activities.* ☐
Moderate: an event interfering with normal everyday activities.* ☐
Severe: an event that prevents normal everyday activities.* ☐
(* 'interfering with everyday activities' refers to activities that the patient was previously capable of doing at that stage in their recovery)

Full description of event, including body site, reported signs and symptoms and diagnosis where possible:

7. DETAILS OF RESEARCH INTERVENTION

Protocol allocated group: **Group 1: 'Liberal'** (Hb < 9.0 g / dL OR HCT < 27) ☐ OR **Group 2: 'Restrictive'** (Hb < 7.5 g / dL OR HCT < 22) ☐

Last Hb / HCT recorded prior to onset of event: . g / dL OR . %

Has the patient received a RBC transfusion since randomisation and prior to onset of event? Yes ☐ No ☐

If Yes: Date and time of last RBC transfusion given before onset of event: / / : : (dd/mm/yyyy) (24 hour clock) Number of units given at that transfusion:

First Hb / HCT recorded after transfusion: . g / dL OR . % Tick if not available ☐

Was treatment of patient according to allocated protocol group permanently discontinued? Yes ☐ No ☐

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

* Names must appear on the site signature & delegation log

Version 5.0, 04/03/2010

SAE INITIAL REPORT FORM—Complete ONE form per SAE (rand)

Centre Code

Patient Study ID

«S

8. ACTION TAKEN AND FURTHER INFORMATION (further space available in box 11)

Please describe action taken below:

Please record any other information relevant to assessment of case (e.g. medical history, test results) below.

--	--

9. RELATEDNESS (see trial manual for definitions)

In the opinion of the PI or delegated doctor, was the event related either to having given or having withheld a RBC transfusion?

Not related ☐ Unlikely to be related ☐ Possibly related * ☐ Probably related * ☐ Definitely related * ☐

* If one of these is selected, please indicate whether the doctor considered the event to be related to:

RBC transfusion being given ☐ OR RBC transfusion being withheld ☐

10. DETAILS OF PRINCIPAL INVESTIGATOR, OR DELEGATED DOCTOR, AT THIS SITE

The completed SAE form must be signed off by the PI or other delegated doctor at the site, prior to faxing to the TITRe 2 study office.

I confirm that the contents of this form (pages F1 and F2) are accurate and complete

Name:

Job title / role in study:

Signature

Date: (dd/mm/yyyy)

11. ADDITIONAL INFORMATION (refer to box number of this SAE form that additional information applies to)

Box number	Further information

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

_____/_____/_____

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

_____/_____/_____

* Names must appear on the site signature & delegation log

Version 5.0, 31/01/2011

SAE FOLLOW-UP FORM—Complete ONE form per SAE (rand)

Centre Code

« « «

Patient Study ID

« «S « « « «

The follow-up SAE form should be completed for:

1. All 'ongoing' SAEs (NB: follow-up reports should be provided every 5 days until SAE is resolved)
2. Any SAE for which additional relevant information has become available since the initial report (e.g. lab results, post mortem, pathology report, etc)
3. Any SAE for which the TITRe 2 study office has requested further information

1. PARTICIPANT DETAILS

Patient initials Sex: Male ☐ Female ☐ Date of Birth (dd/mm/yyyy) / /

2. SAE DETAILS

Date of onset of SAE: / / dd/mm/yyyy Date Initial SAE report sent to TITRe 2 Co-ordinating Centre: / / dd/mm/yyyy

3. FURTHER DETAILS OF EVENT

Maximum intensity of event (up until time of follow-up report): Mild: an event easily tolerated by patient, causing minimal discomfort, not interfering with everyday activities.* ☐ Moderate: an event interfering with normal everyday activities.* ☐ Severe: an event that prevents normal everyday activities.* ☐

(* 'interfering with everyday activities' refers to activities that the patient was previously capable of doing at that stage in their recovery)

Full description of event, including body site, reported signs and symptoms and diagnosis where possible:

4. OUTCOME OF EVENT

Resolution date and time (once resolved) / / : : dd/mm/yyyy (24 hour clock)
Resolved, no sequelae ☐ Resolved, with sequelae* ☐ Ongoing * (please complete and return follow-up report form within 5 days) ☐ Died * (give cause and PM details if available) ☐
Was treatment of patient according to allocated protocol group permanently discontinued? Yes ☐ No ☐

*Give details:

5. ADDITIONAL ACTION TAKEN AND FURTHER INFORMATION SINCE INITIAL REPORT

Describe further action taken & record any other information relevant to assessment of case (e.g. medical history, test results):

6. DETAILS OF PRINCIPAL INVESTIGATOR, OR DELEGATED DOCTOR, AT THIS SITE

The completed SAE follow-up form must be signed off by the PI or delegated doctor at the site, prior to faxing to the TITRe 2 co-ordinating centre.

Name: Job title / role in study:

I confirm that the contents of this form are accurate and complete.

Signature: Date: / / (dd/mm/yyyy)

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

----- / -----

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

----- / -----

Version 4.0, 04/03/2010

* Names must appear on the site signature & delegation log

POST-OPERATIVE EXTENSION FORM - (rand)

Centre Code	Patient Name	Patient Study ID
«	_____	«S « « «

Complete Section(s) 1, 2 3, and/or 4 as necessary.
Multiple copies of this CRF can be completed if required
(e.g. for multiple re-occurrences of complications, re-intubations and/or re-admissions).

SECTION 1: RE-OPERATION DETAILS (for >1 re-operation)

Reason why chest was re-opened (tick all that apply): Bleeding ☐ Cardiovascular instability ☐ Infection ☐ Other ☐

Date of re-operation (dd/mm/yyyy) Re-op start time (24 hour clock) Re-op end time (24 hour clock)

SECTION 2: RE-INTUBATION & RE-EXTUBATION

	Date/time of re-extubation dd/mm/yyyy (24 hour clock)	Re-extubation N/A* ☐ *Patient died
Date/time of re-intubation dd/mm/yyyy	Date/time of re-extubation dd/mm/yyyy (24 hour clock)	Re-extubation N/A* ☐ *Patient died

SECTION 3: READMISSIONS TO ANY WARDS (before hospital discharge)

Date/time of re-admission to CICU/HDU dd/mm/yyyy	Date/time of re-admission to ward dd/mm/yyyy
Date/time of re-admission to CICU/HDU dd/mm/yyyy	Date/time of re-admission to ward dd/mm/yyyy

SECTION 4: OTHER COMPLICATIONS RE-OCCURRENCE

Complete this section for re-occurrence of any post-operative complications, using the relevant code from the list given.

		SAE*		COMPLICATION CODES:
Code	Date started (dd/mm/yyyy):	Yes	No	
☐		☐	☐	COMPLICATION CODES: M=VF/VT requiring intervention, N=pacing, O=other arrhythmia, P=DVT, Q=pulmonary embolus, R=Other thromboembolic complication S=low cardiac output requiring management, T=wound dehiscence
☐		☐	☐	
☐		☐	☐	
☐		☐	☐	
☐		☐	☐	

A=TIA,
 B=pancreatitis,
 C=intestinal obstruction/perforation,
 D=other GI complication,
 E=post-op haemorrhage,
 F=ARDS,
 G=tracheostomy,
 H=initiation of CPAP,
 I=pneumothorax requiring chest drainage,
 J=pleural effusion requiring drainage,
 K=other pulmonary complication,
 L=SVT/AF requiring treatment,

*Tick SAE as Yes for any complications listed that met the definition of serious, i.e. are/were life-threatening, resulted in persistent or significant disability/incapacity, prolonged hospitalisation or resulted in death.

Name of person completing form* (capitals) _____ Signature of person completing form _____ Date completed (dd/mm/yyyy) _____

Name of person entering data* (capitals) _____ Date data entered (dd/mm/yyyy) _____

Version 2.0, 31/01/2011

* Names must appear on the site signature & delegation log

READMISSIONS IN FOLLOW-UP PERIOD

Centre Code	Patient Name	Patient Study ID

Complete 1 form per hospital admission for 'expected' complications. Complete SAE form for any fatalities OR 'unexpected' complications resulting in readmission.

Date of admission
dd/mm/yyyy

Complete this form for any of the 'expected' complications occurring post-discharge but before the end of study follow-up, which fit into the following criteria:

i) Increased length of hospital admission, ii) causes hospitalisation iii) life threatening, iv) persistent or significant disability, v) caused death. The events are all 'expected' and therefore do not require an SAE form to be completed unless the event caused death.

INFECTIVE COMPLICATIONS (causing readmission)

Yes ☐ No ☐ If Yes: Site of suspected infection (tick all that apply):

Respiratory ☐ Surgical Wound ☐ Blood ☐ Other (specify):

ISCHAEMIC COMPLICATIONS (causing readmission)

SUSPECTED MYOCARDIAL INFARCTION Yes ☐ No ☐ If Yes Troponin I or T measured ☐ Highest level µg/L

Date of sample
dd/mm/yyyy

PERMANENT STROKE Yes ☐ No ☐ If Yes Stroke confirmed by: CT ☐ MRI ☐ Other ☐

GUT INFARCTION Yes ☐ No ☐ If Yes Gut infarction confirmed by: Laparotomy ☐ Post mortem ☐

ACUTE KIDNEY INJURY Yes ☐ No ☐ If Yes AKI criteria (see box below for definitions) Stage 1, 2 or 3 ☐

Stage 1: Serum creatinine increase ≥ 0.3 mg/dl (≥ 26.4 µmol/l) or increase to 1.5-fold to 2-fold from baseline[†] OR urine output < 0.5 ml/kg/h for > 6 h.

Stage 2: Serum creatinine increase > 2 -fold to 3-fold from baseline[†] OR urine output < 0.5 ml/kg/h for > 12 h.

Stage 3: Serum creatinine increase > 3 -fold from baseline[†] or serum creatinine ≥ 4.0 mg/dl (≥ 354 µmol/l) with an acute increase of at least 0.5 mg/dl (44 µmol/l) OR need for renal replacement therapy (RRT) irrespective of stage at time of RRT OR urine output < 0.3 ml/kg/h for 24 h or anuria for 12 h

[†] baseline refers to pre-operative serum creatinine measurement

OTHER "EXPECTED" COMPLICATIONS (causing readmission)

Yes ☐ No ☐ Code (from list) Specify below for codes: S, T, U & V:

Yes ☐ No ☐ Code (from list) Specify below for codes: S, T, U & V:

Yes ☐ No ☐ Code (from list) Specify below for codes: S, T, U & V:

COMPLICATION CODES:

A= TIA,
B= Pancreatitis,
C= Intestinal obstruction/perforation,
D= Post-op haemorrhage,
E= ARDS,
F= Tracheostomy,
G= Initiation of CPAP,
H= Pneumothorax requiring chest drainage,
I= Pleural effusion requiring drainage,
J= SVT/AF requiring treatment,
K= VF/VT requiring intervention,
L= Pacing,
M= DVT,

N= Pulmonary embolus,
O= Low cardiac output requiring management,
P= Wound dehiscence,
Q= Re-operation,
R= Cardiac tamponade,
W= Re-intubation.

For the following codes please specify in the box provided

S= Other GI complication,
T= Other pulmonary complication,
U= Other arrhythmia,
V= Other thromboembolic Complication,

Name of person completing form* (capitals) Signature of person completing form Date completed (dd/mm/yyyy)

Name of person entering data* (capitals) Date data entered (dd/mm/yyyy)

Version 5.0, 17/04/2012

* Names must appear on the site signature & delegation log

To be completed by co-ordinating centre before sending to patient:

Patient's name: < to be customised for patient >

Patient study ID: _____ < to be customised for patient >

Date sent: (dd/mm/yyyy) ____ / ____ / ____

TITRe² Study

(Reducing Blood Transfusion following Cardiac Surgery)

6-week Follow-up EQ5D Questionnaire

Dear < patient title & surname to be inserted >,

Thank you for taking part in the TITRe 2 research study. As part of this study we would like to know about your general health and how you are feeling at the moment. We would be very grateful if you could complete the questions on the following pages about this.

When you have completed the questionnaire, please sign and date in the box below:

Signed:

Date Completed (Day, Month, Year):

 / /

In about 6 weeks time, the research team will contact you by telephone to ask you some questions about how you have been since your operation. Please let us know the best phone number to contact you on, and your preferred time of day to be contacted, in the box below. We will try our best to call you around this time.

Telephone number:
(please include dialling code):

What is the best time of
day for us to call you?

Please return the completed booklet in the enclosed pre-paid envelope to: < freepost address to be inserted >

Permission to reproduce the EQ-5D has been granted by the EuroQol Research Foundation.

Euroqol Quality of Life Scale

We are wanting to know about your general well being.

Below are five sections about general well being. Please tick one box for each section to indicate which statement best describes your health state today.

Section A: Mobility

- | | |
|---------------------------------------|--------------------------|
| 1. I have no problems walking about | ☐ |
| 2. I have some problems walking about | ☐ |
| 3. I am confined to bed | ☐ |

Section B: Self-care

- | | |
|--|--------------------------|
| 1. I have no problems with self-care | ☐ |
| 2. I have some problems with self-care | ☐ |
| 3. I am unable to wash or dress myself | ☐ |

Section C: Usual activities

(e.g. work/study/housework/family/leisure activities)

- | | |
|--|--------------------------|
| 1. I have no problems with doing my usual activities | ☐ |
| 2. I have some problems with doing my usual activities | ☐ |
| 3. I am unable to perform my usual activities | ☐ |

Section D: Pain/Discomfort

- | | |
|---------------------------------------|--------------------------|
| 1. I have no pain or discomfort | ☐ |
| 2. I have moderate pain or discomfort | ☐ |
| 3. I have extreme pain or discomfort | ☐ |

Section E: Anxiety/Depression

- | | |
|---|--------------------------|
| 1. I am not anxious or depressed | ☐ |
| 2. I am moderately anxious or depressed | ☐ |
| 3. I am extremely anxious or depressed | ☐ |

EQ - 5D

Health Questionnaire

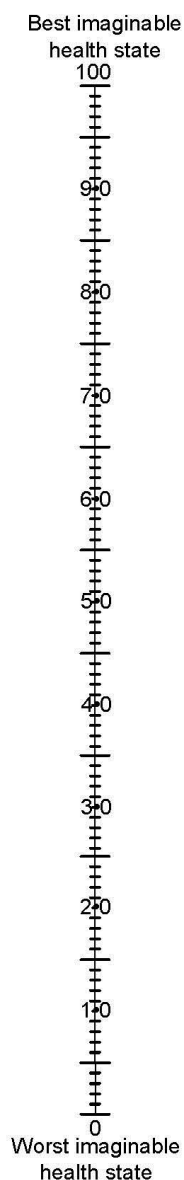
English version for the UK
(validated for use in Eire)

Please go on to the next page →

To help people say how good or bad their health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own
health state
today**



Thank you very much for completing these questions and for your support of the TITRe 2 Study.

Please remember to sign and date the box on the front page before returning the questionnaire in the pre-paid envelope provided.

To be completed by co-ordinating centre before sending to patient:

Patient Name:

Study ID:

Date sent: (dd/mm/yyyy)

TITRe2

3 Month Follow-up Questionnaire

Dear

Thank you for taking part in the TITRe 2 research study. We would like to know some more details about how you have been and what has happened to you since you left hospital after your heart surgery. This questionnaire is divided into 4 sections. Section 1 is about how your wounds have healed after your operation. Section 2 is about any visits to hospital you may have made. Section 3 is about other medical care that you may have had. Finally, Section 4 is for any other information that may be relevant.

We would be very grateful if you could complete all the sections. If you have any queries, please call 0117 342 3564.

When you have completed the questionnaire, please sign and date in the box below:

Signed:	
Date completed (Day, Month, Year):	/ /

Please return the completed questionnaire in the enclosed pre-paid envelope to: *Clinical Trials Evaluation Unit, Bristol Heart Institute, FREEPOST SWB2225, BRISTOL, BS2 8ZZ*

SECTION 1: WOUND HEALING

Section 1 - the following questions ask about how your wounds have healed after your heart surgery. Please tick the boxes as appropriate and write your answers where requested.

1 Where did you go after you were discharged from
on

(a) Home or to a relative / friend ☐

(b) To another hospital or care home ☐

If (b) please specify the name of the hospital or care home:

How long did you stay in this other hospital or care home for? days

2 The hospital where you had your operation has told us that you had main surgical wounds (not including drains).

Have all of these wounds healed without any problem at all?

Yes ☐

No ☐

If 'No' for any wound, please answer questions 3 to 10 below for each wound .

If 'Yes', please go straight to Section 2 on the next page

	Yes	No	Yes	No	Yes	No	Yes	No
3 Has the wound been red?	☐	☐	☐	☐	☐	☐	☐	☐
4 Has the wound discharged clear yellow fluid?	☐	☐	☐	☐	☐	☐	☐	☐
5 Has the wound discharged pus?	☐	☐	☐	☐	☐	☐	☐	☐
6 Has the wound broken open?	☐	☐	☐	☐	☐	☐	☐	☐
7 Have you been given antibiotics for wound infection?	☐	☐	☐	☐	☐	☐	☐	☐
8 Has a district nurse had to dress the wound?	☐	☐	☐	☐	☐	☐	☐	☐
9 Has a doctor opened/drained an abscess?	☐	☐	☐	☐	☐	☐	☐	☐
10 Has the wound been opened and cleaned under general anaesthetic in hospital?	☐	☐	☐	☐	☐	☐	☐	☐

END OF SECTION 1

SECTION 2: HOSPITAL VISITS

Section 2: The following questions ask about all visits you have made to any hospital since you were discharged after your heart surgery.

Section 2(a) - Admissions to Hospital

Since leaving hospital after your heart surgery (either the hospital where you had your operation or the hospital that you were discharged to straight afterwards), have you been admitted to any hospital for an overnight stay or longer for any reason?

Yes ☐

No ☐

If 'No', please go to straight to Section 2(b). If 'Yes', please answer all questions below.

If 'Yes', how many times? ☐

Please complete all the details below for each hospital stay

(If you have been admitted more than 3 times please use an extra sheet to write down the details.)

	Admission 1	Admission 2	Admission 3
Date (dd/mm/yyyy)			
Which hospital?			
Reason for admission?			
How many days were you admitted for?	days	days	days
Did you spend any time in an intensive care unit?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
If 'Yes', how many days?	days	days	days
How did you travel to hospital?			
Friend/relative in private car	☐	☐	☐
Self driven in own car	☐	☐	☐
Taxi (self paid)	☐	☐	☐
Taxi (hospital paid)	☐	☐	☐
Public transport	☐	☐	☐
Hospital transport	☐	☐	☐
Ambulance	☐	☐	☐
Other (specify)			
What was your route of admission?			
Via A&E	☐	☐	☐
GP referral	☐	☐	☐
Self-referral to cardiology	☐	☐	☐
From outpatient appointment	☐	☐	☐
Other (specify)			

Section 2(b) - Visits to Accident and Emergency (A&E)

Since leaving hospital after your heart surgery (either the hospital where you had your operation or the hospital that you were discharged to straight afterwards), have you visited any hospital A&E department for something relating to your heart surgery but did not have to stay overnight.

Yes ☐

No ☐

→ If 'No', please go to straight to Section 2(c).

If 'Yes', how many times? ☐

Please complete all the details below for each A&E visit

(If you have been to A&E without staying overnight more than 3 times please use an extra sheet to write down the details.)

	A&E Visit 1	A&E Visit 2	A&E Visit 3
Date (dd/mm/yyyy)			
Which hospital?	 	 	
Reason for visit?	 	 	
How did you travel to hospital?			
Friend/relative in private car	☐	☐	☐
Self driven in own car	☐	☐	☐
Taxi (self paid)	☐	☐	☐
Taxi (hospital paid)	☐	☐	☐
Public transport	☐	☐	☐
Hospital transport	☐	☐	☐
Ambulance	☐	☐	☐
Other (specify)			

** Please ensure that the reason for visit was related to your heart surgery and did not result in an overnight stay.*

Section 2(c) – Outpatient Appointments

Since leaving hospital after your heart surgery (either the hospital where you had your operation or the hospital that you were discharged to straight afterwards), have you had any appointments to visit an outpatient department or clinic (excluding warfarin/INR clinics or cardiac rehabilitation) at a hospital?

Yes ☐

No ☐

→ If 'No', please go to straight to Section 3.

If 'Yes', how many times? ☐

Please complete all the details below for each outpatient appointment

(If you have attended more than 3 outpatient appointments please use an extra sheet to write down the details.)

	Outpatient Visit 1	Outpatient Visit 2	Outpatient Visit 3
Date (dd/mm/yyyy)			
Which hospital?			
Which department/clinic?			
Cardiac surgery	☐	☐	☐
Cardiology (non-surgical)	☐	☐	☐
Renal/dialysis unit	☐	☐	☐
Stroke clinic	☐	☐	☐
Other (specify)			
How did you travel to hospital?			
Friend/relative in private car	☐	☐	☐
Self driven in own car	☐	☐	☐
Taxi (self paid)	☐	☐	☐
Taxi (hospital paid)	☐	☐	☐
Public transport	☐	☐	☐
Hospital transport	☐	☐	☐
Ambulance	☐	☐	☐
Other (specify)			

SECTION 3: OTHER MEDICAL CARE

The following questions ask about any other medical care you may have received, since you were discharged from hospital after your heart surgery. For example, this may include visits to your GP surgery, NHS walk-in centre, warfarin/INR clinics, cardiac rehabilitation or visits at home from a GP or nurse. You do not need to tell us about anything you have already told us about in section 2.

Since leaving hospital after your heart surgery, have you visited or seen any of the following?

	Yes	If 'Yes', how many times?	No
GP (at surgery)?	☐	→	☐
GP (at home)?	☐	→	☐
Out of hours GP centre?	☐	→	☐
NHS Walk-in Centre?	☐	→	☐
General Practice Nurse (at surgery)?	☐	→	☐
District/community nurse (at home)?	☐	→	☐

	Yes (specify)	How many times?	No
Other NHS or social services person (at home)?		→	☐
		→	
		→	
Other NHS or social services person (elsewhere)? E.g. cardiac rehabilitation, warfarin/INR clinics, occupational health.		→	☐
		→	
		→	

SECTION 4: ADDITIONAL INFORMATION

Please tell us about anything else which you think might be relevant. This may include more details about hospital visits, or other medical care, that you have not already mentioned in Sections 2 or 3.

(continue on a separate sheet if necessary)

Finally, we would like to check whether you know which of the two groups you were put into for the trial. The two groups are:

Group 1: patients receive a blood transfusion at the first signs that their haemoglobin level is moderately low

Group 2: patients do not receive a blood transfusion unless their haemoglobin reaches a lower level

- 1) Did you think being in one group would be better for your health than the other? Yes ☐ No ☐
- 2) If Yes, which group did you think would be better for your health? ☐ Group 1 (9g/dL)
☐ Group 2 (7.5g/dL)
- 3) Do you know, or think that you know, which group you were put into? Yes ☐ No ☐
- 4) If Yes, which group do you think you were put into? ☐ Group 1 (9g/dL)
☐ Group 2 (7.5g/dL)
- 5) After the study has ended, would you like us to write to you to tell you which group you were put into and what were the results were? Yes ☐ No ☐

END OF QUESTIONNAIRE

Thank you very much for your time and for answering these questions.

We would be very grateful if you could return this questionnaire in the pre-paid envelope provided.

Appendix 15: Unit costs for TITRe2

Table 1: Unit costs for surgery, inpatient stays and blood products

Resource	Unit cost (£)	Reference
Cardiac surgery and reoperations		
CABG	6714	NHS Reference Costs 2012/13.[138] Elective inpatients. HRG code EA14 for service codes 170 (Cardiothoracic surgery) and 172 (Cardiac surgery). For each code, the costs associated with the average LOS reported were subtracted at a cost of £392 per day (see 'Cardiac ward stay'), and £227 was subtracted for blood products based on data from an audit of blood transfusion in cardiac surgery.[93] An average cost for the codes was then generated, weighted by activity.
Valve	7336	NHS Reference Costs 2012/13.[138] Elective inpatients. HRG codes EA17 (single valve) and EA52 (more than 1 valve) for service codes 170 and 172. For each code, the costs associated with the average LOS reported were subtracted at a cost of £392 per day, and £659 was subtracted for blood products.[93] An average cost for the codes was then generated for single and more than 1 valve procedures, weighted by activity. Finally these 2 figures were weighted to produce an average that reflects the proportion of single valve procedures in TITRe2 participants (90% single, 10% more than 1 valve).
CABG and valve	8054	NHS Reference Costs 2012/13.[138] Elective inpatients. HRG code EA51 for service codes 170 and 172. For each code, the costs associated with the average LOS reported were subtracted at a cost of £392 per day, and £1421 was subtracted for blood products.[93] An average cost for the codes was then generated, weighted by activity.
Other	8298	NHS Reference Costs 2012/13.[138] Elective inpatients. HRG code EA20 for service codes 170 and 172. For each code, the costs associated with the average LOS reported were subtracted at a cost of £392 per day, and £1421 was subtracted for blood products.[93] An average cost for the codes was then generated, weighted by activity.
Reoperations <3 hours, excluding blood and LOS	6608	As 'Other' cardiac procedure above, but the lower quartile unit cost was used rather than the mean cost.
Reoperations <3 hours, including blood, excluding LOS	8029	As 'Reoperations <3 hours, excluding blood and LOS', with £1421 for blood products added back in.
Reoperations ≥3 hours, excluding blood and LOS	8298	As 'Other' cardiac procedure above.

Resource	Unit cost (£)	Reference
Reoperations ≥3 hours, including blood, excluding LOS	9719	As 'Other' cardiac procedure above, with £1421 for blood products added back in.
Inpatient stay		
Cardiac ward day	392	NHS Reference Costs 2012/13.[138] Weighted average of elective inpatient excess bed day costs for relevant HRGs (EA14, EA16, EA17, EA19, EA20, EA22, EA51, EA52, excluding any service codes for paediatrics).
HDU day	619	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (XC07Z, 0 organs supported).
CICU day	1190	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (weighted average of XC01Z - XC06Z, 1-6 organs supported).
General ICU day	1608	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (weighted average of XC01Z - XC03Z, 4-6 organs supported).
Ward day for another unit in the hospital, or at another hospital	265	NHS Reference Costs 2012/13.[138] Non-elective inpatient excess bed day cost across all activities.
Blood products		
Red blood cells	123.31	NHSBT Price List 2012/13[139]
RBC administration cost, first unit	56.06	Cost estimate generated in Chapter 4 (Table 4.13), and deflated to 2012/13 prices.* The number of group and screens required for each patient based on the days transfusions were received was calculated, and any excess nursing costs associated with group and screens was subtracted (at a cost of £7.85).
RBC administration cost, subsequent units	35.42	Cost estimate generated in Chapter 4 (Table 4.13), and deflated to 2012/13 prices.*
Fresh frozen plasma	27.46	NHSBT Price List 2012/13[139]
Fresh frozen plasma administration cost	37.24	Cost estimate generated in Chapter 4 (Table 4.14), and deflated to 2012/13 prices.* Excess nursing costs associated with a group and screen of £7.85 per transfusion episode were subtracted if a patient had RBCs, and the cost was already captured there. Excess nursing costs associated with a group and screen were also excluded if patients had more units than the assumed number in a transfusion episode (4.4 units).
Platelets	209.30	NHSBT Price List 2012/13[139]

Resource	Unit cost (£)	Reference
Platelets administration cost	56.72	Cost estimate generated in Chapter 4 (Table 4.14), and deflated to 2012/13 prices.* Excess nursing costs associated with a group and screen of £7.85 per transfusion episode were subtracted if a patient had RBCs, and the cost was already captured there. Excess nursing costs associated with a group and screen were also excluded if patients had more units than the assumed number in a transfusion episode (1.2 units).
Cryoprecipitate	189.19	NHSBT Price List 2012/13[139]
Cryoprecipitate administration cost	48.28	Cost estimate generated in Chapter 4 (Table 4.14), and deflated to 2012/13 prices.* Excess nursing costs associated with a group and screen of £7.85 per transfusion episode were subtracted if a patient had RBCs, and the cost was already captured there. Excess nursing costs associated with a group and screen were also excluded if patients had more units than the assumed number in a transfusion episode (2 units).

CABG, Coronary artery bypass grafting; CICU, Cardiac intensive care unit; HDU, High dependency unit; HRG, Healthcare resource group; ICU, Intensive care unit; LOS, Length of stay; NHSBT, NHS Blood and Transplant; RBC, Red blood cell

*Unit costs in 2014/2015 prices were deflated to 2012/2013 prices using the hospital and community health services inflation index.[142]

Table 2: Unit costs for blood saving techniques, fluids and medications in theatre/CICU/HDU

Resource	Assumed quantity	Unit cost* (£)	Reference
Tranexamic acid	5g intravenously	15.50	BNF 66[141]
Aprotinin	6 million KIU intravenously	316.83	Davies, Brown, Haynes et al.[148] using data from BNF 47.[204]
Intra- / post-operative cell salvage		176	Davies, Brown, Haynes et al.[148]
Activated Factor VII	5mg intravenously	2486.60	Oxford University Hospitals NHS Foundation Trust, 2013
Beriplex® (CSL Behring UK Ltd)	1500 IU intravenously	420	District General Hospital, South Central, 2014
Hydroxyethyl starch (HES)	1500ml intravenously	40.60	BNF 58[149]
Human albumin solution	500ml intravenously	36	District General Hospital, South Central, 2014
Gelatin (Gelofusine, B. Braun Medical Ltd)	1500ml intravenously	7.92	Teaching Hospital, South Central, 2013
Inotropes	Noradrenaline 1mg/hour for 5 days	57.30	eMIT, 2014[140]
Hartmann's solution	1500ml intravenously	2.67	Teaching Hospital, South Central, 2013
Gelatin (Isoplex, Beacon Pharmaceuticals)	1500ml intravenously	22.07	BNF 66[141]

BNF, British National Formulary; eMIT, electronic Marketing Information Tool; KIU, Kallikrein Inhibitor Units

*Unit costs which were not in 2012/2013 prices were inflated to 2012/2013 prices using the hospital and community health services inflation index.[142]

Table 3: Unit costs for antibiotics

Drug name	Route	Assumed dose/frequency per day	Daily cost (£)	Source
Amikacin	IV	500mg 3xday	18.42	eMIT[140]
Amoxicillin	Oral	500mg 4xday	0.10	eMIT[140]
Amoxicillin	IV	500mg 4xday	1.46	eMIT[140]
Aztreonam	IV	1g 3xday	28.20	BNF[141]
Benzyl-penicillin	IV	1.2g 4xday	7.56	BNF[141]
Caspofungin	IV	70mg first day, 50mg 1xday subsequent days	416.78 day 1, 327.67 thereafter	BNF[141]
Cefalexin	Oral	250mg 4xday	0.11	eMIT[140]
Cefotaxime	IV	1g 2xday	1.22	eMIT[140]
Ceftazidime	IV	1g 3xday	2.56	eMIT[140]
Ceftriaxone	IV	1g 1xday	0.53	eMIT[140]
Cefuroxime	IV	750mg 3xday	1.37	eMIT[140]
Cefuroxime 1.5g	IV	1.5g 3xday	2.13	eMIT[140]
Cefuroxime 750mg	IV	750mg 3xday	1.37	eMIT[140]
Chloramphenicol	IV	1g 4xday	5.56	BNF[141]
Ciprofloxacin	Oral	500mg 2xday	0.05	eMIT[140]
Ciprofloxacin	IV	400mg 2xday	2.02	eMIT[140]
Clarithromycin	Oral	250mg 2xday	0.13	eMIT[140]
Clarithromycin	IV	500mg 2xday	5.24	eMIT[140]
Clindamycin	Oral	150mg 4xday	0.24	eMIT[140]
Clindamycin	IV	600mg 3xday	7.27	eMIT[140]
Co-amoxiclav	Oral	375mg 3xday	0.21	eMIT[140]
Co-amoxiclav 625mg	Oral	625mg 3xday	0.22	eMIT[140]
Co-amoxiclav	IV	600mg 3xday	1.64	eMIT[140]
Co-amoxiclav 1.2g	IV	1.2g 3xday	1.91	eMIT[140]
Colistimethate sodium	Oral	1 million units 2xday	3.36	BNF[141]
Colistimethate sodium	IV	1 million units 2xday	3.36	BNF[141]
Co-trimoxazole	Oral	960mg 2xday	0.49	eMIT[140]

Drug name	Route	Assumed dose/frequency per day	Daily cost (£)	Source
Co-trimoxazole	IV	960mg 2xday	7.12	BNF[141]
Daptomycin	IV	350mg 1xday	62.00	BNF[141]
Demeclocycline	Oral	150mg 4xday	11.64	BNF[141]
Doxycycline	Oral	200mg first day, 100mg 1xday subsequent days	0.07 day 1, 0.03 thereafter	eMIT[140]
Ertapenem	IV	1g 1xday	31.65	BNF[141]
Erythromycin	Oral	250mg 4xday	0.11	eMIT[140]
Erythromycin	IV	Erythromycin lactobionate 1g 4xday	43.92	BNF[141]
Flucloxacillin	Oral	250mg 4xday	0.11	eMIT[140]
Flucloxacillin	IV	0.25g 4xday	1.68	eMIT[140]
Fluconazole	Oral	400mg first day, 200mg 1xday subsequently	0.19 day 1, 0.09 thereafter	eMIT[140]
Fluconazole	IV	400mg first day, 200mg 1xday subsequently	1.80 day 1, 0.94 thereafter	eMIT[140]
Fusidic acid	Oral	500mg 3xday	1.81	BNF[141]
Gentamicin	IV	80mg 3xday	1.57	eMIT[140]
Imipenem	IV	500mg 4xday	17.67	eMIT[140]
Levofloxacin	Oral	500mg 1xday	0.23	eMIT[140]
Levofloxacin	IV	500mg 1xday	1.87	eMIT[140]
Linezolid	Oral	600mg 2xday	89.00	BNF[141]
Linezolid	IV	600mg 2xday	89.00	BNF[141]
Meropenem	IV	0.5g 3xday	7.86	eMIT[140]
Metronidazole	Oral	400mg 3xday	0.05	eMIT[140]
Metronidazole	IV	500mg 3xday	1.20	eMIT[140]
Nitrofurantoin	Oral	50mg 4xday	5.23	BNF[141]
Oseltamivir	Oral	75mg 2xday	3.08	BNF[141]
Piperacillin/tazobactam	IV	4.5g 3xday	5.68	eMIT[140]
Rifampicin	Oral	300mg 3xday	0.42	eMIT[140]
Rifampicin	IV	600mg 3xday	7.66	eMIT[140]

Drug name	Route	Assumed dose/frequency per day	Daily cost (£)	Source
Teicoplanin	IV	400mg 2xday for 3 doses, subsequently 400mg 1xday	12.24 day 1, 6.12 thereafter	eMIT[140]
Temocillin	IV	1g 2xday	50.90	BNF[141]
Timentin	IV	3.2g 3xday	15.99	BNF[141]
Trimethoprim	Oral	200mg 2xday	0.03	eMIT[140]
Vancomycin	IV	0.5g 2xday	2.32	eMIT[140]

BNF, British National Formulary; eMIT, electronic Marketing Information Tool; IV, Intravenous

Table 4: Unit costs for regular medications

Recorded on CRF	Assumed drug	Assumed route	Assumed dose/frequency per day	Daily cost (£) from BNF ^[141]
Digoxin	Digoxin	Oral	125mcg daily	0.04
Diuretics	Furosemide	Oral	40mg daily	0.03
Beta blockers	Atenolol	Oral	25mg daily	0.03
Calcium antagonists	Amlodipine	Oral	5mg daily	0.03
Aspirin	Aspirin	Oral	75mg daily	0.03
Oral nitrates	Isosorbide dinitrate	Oral	80mg daily	0.98
Angiotensin 2 blockers	Losartan	Oral	25mg daily	0.04
ACE inhibitors	Ramipril	Oral	5mg daily	0.04
Warfarin	Warfarin sodium	Oral	3mg daily	0.03
Clopidogrel	Clopidogrel	Oral	75mg daily	0.06
Statins	Simvastatin	Oral	40mg daily	0.04
Anti-arrhythmic	Amiodarone	Oral	200mg daily	0.06
Heparin/clexane	Enoxaparin sodium	S/C	20mg daily	2.27
IV GTN/nitrates	Glyceryl trinitrate	IV	25mg daily	6.49
FeSO ₄	Ferrous sulphate	Oral	200mg (65mg iron) 3xday	0.11

ACE, Angiotensin converting enzyme; BNF, British National Formulary; CRF, Case report form; FeSO₄, Ferrous sulphate; GTN, Glyceryl trinitrate; IV, Intravenous; S/C, Subcutaneous

Table 5: Resource use assumed for complications and total costs

Resource use assumed for complications and total costs are shown here, unit costs and sources are shown in the next table.

Complication	Treatment/Action	Cost (£)	Assumptions
Sepsis	No additional treatment	0	Antibiotics recorded separately and costed
Wound infection	No additional treatment	0	Antibiotics recorded separately and costed
Permanent stroke	Rehabilitation (plus scan)	139	
	CT scan	62	
	MRI scan	248	
Suspected MI	Emergency angiography, transthoracic echo, ECG	1868	
Gut infarction	CT scan	62	
	If confirmed by laparotomy	2693	
AKI - stage 3 only	Haemofiltration	1438	Assume treatment for 2 days
TIA	CT scan	62	
Pancreatitis	CT scan, parenteral nutrition, IV fluids	275.49	Reoperations already captured
Intestinal obstruction/perforation	Laparotomy, parental nutrition	2893	Reoperations already captured
Post-operative haemorrhage	Chest x-ray	41	Reoperations already captured. Assume no additional costs for participants who have a re-operation on the same day/following day as post-operative haemorrhage.
ARDS	Transoesophageal echo, 3 chest x-rays	395	Re-intubation and intensive care already captured
Re-intubation/ventilation	Transoesophageal echo, 3 chest x-rays	395	
Initiation of mask CPAP	CPAP, chest x-ray	539	
Tracheostomy	Tracheostomy, chest x-ray	5354	
Pneumothorax requiring chest drainage	Chest x-ray, chest drain	4218	
Pleural effusion requiring drainage	Chest x-ray, chest drain	4218	
Pacing	Temporary pacemaker	3073	
SVT/AF requiring treatment	Amiodarone	4.79	

Complication	Treatment/Action	Cost (£)	Assumptions
Deep vein thrombosis	Duplex scan of leg veins, intravenous heparin	202.43	Warfarin already captured
VF/VT requiring intervention	Transoesophageal echo, emergency coronary angiography, chest x-ray	2007	Emergency re-operations and re-intubation captured elsewhere
Low cardiac output requiring management (including IABP)	Transoesophageal echo, chest x-ray	313	
Wound dehiscence requiring rewiring/treatment	Minor treatment (£161), or Negative Pressure Wound Therapy (NPWT) therapy if stated (£3501)	161 or 3501	Assume reoperation covers this complication if reoperation the same day or next day
Cardiac tamponade	Transoesophageal echo, chest x-ray	313	Reoperations and RBCs already captured
Other GI complications			
Abominal distention/small bowel dilation/abdominal pain	CT scan	62	
Coffee ground vomitus	Omeprazole	12.68	
Colonic pseudo-obstruction	CT scan	62	
Constipation	Laxatives, enemas	2.25	
Diabetes inference/exacerbation	Insulin	138.60	
Diagnostic laparotomy	Laparotomy	2693	
Diarrhoea/diarrhoea and vomiting	Isolation room, stool culture and IV for dehydration	3592	
Duodenal ulcer	Endoscopy	676	
Dysphagia/poor swallow/difficult chewing with hoarse voice	Speech and language therapy review, nasendoscopy, oropharyngeal fluoroscopy and maybe CT head	370	
Gastric bubble	Nasogastric tube insertion	252	
Gastritis, Gastro oesophageal reflux	Omeprazole	12.68	
GI bleed	Endoscopy	676	
GI bleed - duodenal ulcer	Endoscopy and in severe cases laparotomy	2022	

Complication	Treatment/Action	Cost (£)	Assumptions
Haematemesis	Omeprazole	12.68	
Hepatic impairment	CT scan	62	
Ileus/gallstone ileus/paralytic ileus	CT scan	62	
Intestinal ischaemia	Laparotomy, CT scan	2755	
Ischaemic bowel and GI bleed	Laparotomy, CT scan	2755	
Laproscopy	Laproscopy	2693	
Melaena	Endoscopy, omeprazole	688.68	
Melaena and bleeding duodenal ulcers	Endoscopy, omeprazole	688.68	
Nausea and/or vomiting	Anti-nausea medication	0.63	
Nasogastric tube inserted	Nasogastric tube inserted	252	
Not absorbing due to abdominal aortic aneurysm repair	CT scan	62	
Rectal bleed	Endoscopy	676	
Upper GI bleed, due to transoesophageal echo	Endoscopy	676	
Other pulmonary complications – all assumed to have 2 chest x-rays, add £82 to all			
Suspected chest infection	No additional treatment	0	Antibiotics and re-intubation already captured
Aspiration pneumonia/pneumonia	No additional treatment	0	Antibiotics and re-intubation already captured
Bilevel positive airway pressure (BIPAP) commenced	BIPAP	498	
Basal atelectasis	Chest x-ray, physiotherapy	180	CPAP already captured
Basal respiratory wheeze	Nubulised 0.9% saline (10ml) or salbutamol (2.5 mg) 4 times daily	1035	
Bronchopneumonia	No additional treatment	0	Antibiotics and re-intubation already captured

Complication	Treatment/Action	Cost (£)	Assumptions
Fluid overload	No additional treatment	0	Antibiotics and re-intubation already captured
Left and right haemothorax/haemothorax requiring chest drainage	Chest drain	4177	
Heart failure	Diuretics	0.15	Re-intubation already captured
Increasing oxygen requirements, chest examination	Physiotherapy	139	CPAP and re-intubation already captured
Infection	No additional treatment	0	Antibiotics and re-intubation already captured
Left pneumothorax	Chest x-ray	41	
Lower respiratory tract infection	No additional treatment	0	Antibiotics and re-intubation already captured
Overloaded	Diuretics	0.15	Re-intubation already captured
Pericardial effusion/pericardial effusions with atelectasis	No treatment in mild cases	0	Reoperation and re-intubation already captured
Pleuritic pain	Analgesia	6	
Pneumonia and respiratory failure	No additional treatment	0	Antibiotics and re-intubation already captured
Pulmonary oedema	Diuretics	0.15	Re-intubation already captured
Right lower lobe collapse and atelectasis changes on chest x-ray	Chest x-ray, physiotherapy	180	CPAP and re-intubation already captured
Reduced air entry to bases/respiratory distress/respiratory failure	Physiotherapy	139	CPAP and re-intubation already captured
Respiratory arrest	No additional treatment	0	Re-intubation already captured
Slight decrease in entry in both bases	Physiotherapy	139	CPAP and re-intubation already captured
(Small) pleural effusion left side/right side/bilateral	No treatment	0	
Surgical emphysema	Chest drain, chest x-ray	4218	

Complication	Treatment/Action	Cost (£)	Assumptions
Aspirated on nasogastric tube insertion	Nasogastric tube insertion (if not already included)	252	
Disconnected chest drain	Chest drain	4177	
Increased pulmonary artery pressure	No treatment	0	
Left basal effusion and right basal collapse	Physiotherapy	139	CPAP and re-intubation already captured
<i>Other arrhythmia complications – all assumed to have 2 ECGs, add £106 to all</i>			
AV block/1st degree heart block/third degree AV block/complete heart block	No additional treatment	0	Pacing already captured
First degree heart block with atrial ectopics	No treatment	0	
Complete heart block, permanent pacemaker	Permanent pacemaker	14564	
Heart block-paced	No additional treatment	0	Pacing already captured
Arrhythmia	Amiodarone	4.79	
Asystole/P wave asystole/cardiac arrest/Pulseless electrical activity arrest	CPR	1491	Re-intubation already captured
Asystole with permanent pacemaker insertion	Permanent pacemaker	14564	
Atrial Flutter	Amiodarone	4.79	
Bradycardia/intermittant bradycardia/nodal bradycardia/sinus bradycardia	No additional treatment	0	Pacing already captured
Bradycardic episode with left bundle branch block, 24 hour tape performed	24 hour holter monitor	204	
Cardioversion	Cardioversion	808	
Heart rate irregular, commenced on amiodarone	Amiodarone	4.79	

Complication	Treatment/Action	Cost (£)	Assumptions
Ectopics/multiple ectopics/ventricular ectopics	No treatment	0	
Fast AF requiring amiodarone and pacing switched off	Amiodarone	4.79	
Junctional rhythm	No additional treatment	0	Pacing already captured
Left bundle branch block/new onset of left branch block/right bundle branch block	No treatment	0	
Loss of cardiac output	CPR	1491	Re-intubation already captured
New AF	No additional treatment	0	Pacing already captured
Permanent pacemaker implanted	Permanent pacemaker	14564	
SVT/Flutter	Amiodarone	4.79	
Sinus tachycardia	No treatment	0	
Type B Wolf Parkinson White pattern	No treatment	0	
Sinus pauses	No additional treatment	0	Pacing already captured
Vasovagal episode	No treatment	0	
Other thromboembolic complications			
CT head confirmed occipital infarction	CT scan	62	
Cerebral infarct	CT scan	62	
Saphenous vein graft thrombosed to right coronary artery	Coronary angiography	1694	
Thrombophlebitis	Analgesia	6	

AKI, Acute kidney injury; ARDS, Acute respiratory distress syndrome; AF, Atrial fibrillation; AV, Atrioventricular; BIPAP, Bilevel positive airway pressure; CPAP, Continuous positive airway pressure; CPR, Cardiopulmonary resuscitation; CT, Computed tomography; ECG, Electrocardiography; GI, Gastrointestinal; IABP, Intra-aortic balloon pump; IV, Intravenous; MI, Myocardial infarction; MRI, Magnetic resonance imaging; NPWT, Negative pressure wound therapy; PEA, Pulseless electrical activity; RBC, Red blood cell; SVT, Supraventricular tachycardia; TIA, Transient ischemic attack; VF/VT, Ventricular fibrillation/ Ventricular tachycardia

Table 6: Unit costs for complications

Treatment/Action	Unit cost* (£)	Reference
24 hour holter monitor	204	NHS Reference Costs 2012/13.[138] Day Cases. EA47Z Electrocardiogram Monitoring and stress testing. 320 Cardiology. Lower quartile cost.
Antibiotics (piperacillin/tazobactam, 4.5g IV 3xday for 5 days)	28.40	eMIT[140]
Amiodarone (1.2g IV, then oral 200mg 3xday for 1 week, 2xday for 1 week)	4.79	eMIT[140]
Analgesia (morphine sulphate, 10mg IV every 4 hours for 5 days)	6	eMIT[140]
Anti-nausea medication (ondanestron, 4mg IV for 5 days)	0.63	eMIT[140]
BIPAP	498	As CPAP
Cardioversion	808	Lord, Willis, Eatock et al.[205]
Chest drain	4177	NHS Reference Costs 2012/13.[138]
Chest x-ray	41	Teaching Hospital, South Central, 2012.
Coronary angiography	1694	NHS Reference Costs 2012/13.[138]
CPAP	498	Gray, Goodacre, Newby et al.[206]
CPR	1491	NHS Reference Costs 2012/13.[138]
CT scan	62	NHS Reference Costs 2012/13.[138] Diagnostic Imaging - Direct Access. RA08A Computerised Tomography Scan, one area, no contrast, 19 years and over. 100 General surgery.
Diuretics (furosemide 40mg orally for 5 days)	0.15	BNF[141]
Drainage of pus under local anaesthesia	426	NHS Reference Costs 2012/13.[138] Elective inpatients. JC43A Minor Skin Procedures, 13 years and over. 320 Cardiology
Drainage of pus under general anaesthesia	1919	NHS Reference Costs 2012/13.[138] Elective inpatients. JC43A Minor Skin Procedures, 13 years and over. 172 Cardiac Surgery

Treatment/Action	Unit cost* (£)	Reference
Duplex scan of leg veins	155	NHS Reference Costs 2012/13.[138] Diagnostic Imaging – Outpatients. RA10Z Computerised Tomography Scan, one area, pre and post contrast. 172 Cardiac Surgery
ECG	53	NHS Reference Costs 2012/13.[138] Directly Accessed Diagnostic Services. EA47Z Electrocardiogram Monitoring and stress testing.
Echo - transthoracic	121	NHS Reference Costs 2012/13.[138] Diagnostic Imaging – Outpatients. RA60A Simple Echocardiogram, 19 years and over. 172 Cardiac Surgery
Echo - transoesophageal	272	NHS Reference Costs 2012/13.[138] Day Cases. EA45Z Complex Echocardiogram, including Transoesophageal and Fetal Echocardiography. 320 Cardiology. Lower quartile cost.
Endoscopy	676	NHS Reference Costs 2012/13.[138]
Fluoroscopy	115	NHS Reference Costs 2012/13.[138] Diagnostic Imaging – Outpatients. RA16Z Contrast Fluoroscopy Procedures, less than 20 minutes. 172 Cardiac Surgery
Haemofiltration (assume for 2 days)	1438	NHS Reference Costs 2012/13.[138] Renal Dialysis at Base. LE01A. Haemodialysis for Acute Kidney Injury, 19 years and over.
Intra-aortic balloon pump – used in sensitivity analysis	2776	NICE Medical technology guidance 8.[207]
Intravenous fluids (Gelatin, 1500ml)	13.49	BNF[141]
Insulin (1000 units for 5 days)	138.60	BNF[141]
Intravenous heparin (initial 5,000 units, then 15,000 units every 12 hours for 5 days)	47.43	BNF[141]
Isolation room, stool culture and IV for dehydration	3592	NHS Reference Costs 2012/13[138]
Omeprazole (IV omeprazole 40mg for 3 days, then 40mg oral daily for 5 days)	12.68	BNF,[141] eMIT[140]
Laparoscopy	2693	As laparotomy
Laparotomy	2693	NHS Reference Costs 2012/13[138]
Laxatives, enemas (Bisacodyl, 5mg; Sodium citrate, assume for 5 days)	2.25	BNF,[141] eMIT[140]

Treatment/Action	Unit cost* (£)	Reference
Minor treatment for wound dehiscence	161	NHS Reference Costs 2012/13.[138] Elective inpatients. JC43A Minor Skin Procedures, 13 years and over. 320 Cardiology, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.
MRI scan	248	NHS Reference Costs 2012/13.[138] Diagnostic Imaging - Direct Access. RA07Z Magnetic Resonance Imaging Scan, requiring extensive patient repositioning and/or more than one contrast agent. 320 Cardiology
Nasendoscopy	115	As fluoroscopy
Nasogastric tube insertion	252	NHS Reference Costs 2012/13[138]
Negative pressure wound therapy	3501	NHS Reference Costs 2012/13.[138] Elective inpatients. JC42A Intermediate Skin Procedures, 13 years and over. 172 Cardiac Surgery, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.
Nebulised 0.9% saline (10ml) or salbutamol (2.5 mg) 4 times daily	1035	NHS Reference Costs 2012/13.[138]
Parenteral nutrition (assume 5 days)	200	NICE, Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition costing report.[208]
Permanent pacemaker	14564	NHS Reference Costs 2012/13[138]
Physiotherapy/rehabilitation	139	NHS Reference Costs 2012/13.[138] Elective inpatients. DZ30Z Chest Physiotherapy. 340 Respiratory Medicine.
Speech and language therapy review	109	NHS Reference Costs 2012/13.[138] Non Consultant Led Outpatient Attendances. WF01B Non-Admitted Face to Face Attendance, First. 652 Speech and Language Therapy.
Stroke (alternative cost used in sensitivity analysis)	705	NHS Reference Costs 2012/13.[138] Non elective inpatients. AA35E Stroke with CC Score 4-6, 300 General Medicine, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.
Temporary pacemaker	3073	NHS Reference Costs 2012/13.[138] Elective inpatients. EA39B Pacemaker Procedure without Generator Implant, including Re-siting and Removal of Cardiac Pacemaker System, with CC Score 2-4, 320 Cardiology, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.

Treatment/Action	Unit cost* (£)	Reference
Tracheostomy	5313	NHS Reference Costs 2012/13.[138]
Ultrasound	67	NHS Reference Costs 2012/13.[138] Diagnostic Imaging – Outpatients. Weighted average of RA25Z Ultrasound Mobile Scan or Intraoperative Procedures, less than 20 minutes; RA26Z Ultrasound Mobile Scan or Intraoperative Procedures, 20 to 40 minutes, RA27Z Ultrasound Mobile Scan or Intraoperative Procedures, more than 40 minutes. 100 General Surgery.

BIPAP, Bilevel positive airway pressure; BNF, British National Formulary; CPAP, Continuous positive airway pressure; CPR, Cardiopulmonary resuscitation; CT, Computed tomography; ECG, Electrocardiography; eMIT, electronic Marketing Information Tool; IV, Intravenous; LOS, Length of stay; MRI, Magnetic resonance imaging; NICE, National Institute for Health and Care Excellence

*Unit costs which were not in 2012/2013 prices were inflated to 2012/2013 prices using the hospital and community health services inflation index.[142]

Table 7: Unit costs for reattending hospital

Resource	Unit cost (£)	Reference
Ward day for readmissions	265	NHS Reference Costs 2012/13.[138] Non-elective inpatient excess bed day cost across all activities.
ICU day for readmissions	1168	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (weighted average of XC01Z - XC07Z, 0-6 organs supported).
A&E attendance, leading to admission	154	NHS Reference Costs 2012/13.[138] Accident and Emergency Services, excluding dental care. Weighted average of all admitted codes.
A&E attendance, not leading to admission	101	NHS Reference Costs 2012/13.[138] Accident and Emergency Services, excluding dental care. Weighted average of all non-admitted codes.
Ambulance to hospital	230	NHS Reference Costs 2012/13.[138] Ambulance services, ASS02, See and treat and convey.

A&E, Accident and Emergency; ICU, Intensive care unit

Table 8: Resource use assumed for readmission complications and total costs

Resource use assumed for readmission complications and total costs are shown here, unit costs and sources are shown in the next table. Resource use and costs for readmission complications as inpatient complications if not reported here.

Complication	Treatment/Action	Cost (£)	Assumption
Antibiotics			
- Site=respiratory	Antibiotics, chest x-ray	69.40	
- Site=surgical wound	Antibiotics, chest x-ray, CT scan	131.40	
- Site=blood	Antibiotics	28.40	
- Site=other - endocarditis	Antibiotics, chest x-ray, CT scan	131.40	
- Site=other - infective endocarditis	Antibiotics, chest x-ray, CT scan, transthoracic echo	252.40	
- Site=other - respiratory tract infection	Antibiotics, chest x-ray	69.40	
- Site=other - wound	Antibiotics, chest x-ray, CT scan	131.40	
- Site=other - all others including UTI	Antibiotics	28.40	
Deep vein thrombosis	Duplex scan of leg veins, intravenous heparin, warfarin	203.78	
Cardiac tamponade	Transoesophageal echo, chest x-ray, 2 RBCs	559.62	Reoperations captured elsewhere
Other GI complications			
Barrett's oesophagus	Endoscopy	676	
Dehydration, hypovolaemia secondary to 3 days of diarrhoea	Intravenous fluids	13.49	
Gastroenteritis	Intravenous fluids	13.49	
Oesophageal ulcer	Endoscopy	676	
Peritonitis	Laparotomy, CT scan	2755	
Vomiting related to amiodarone. Medication changed.	Intravenous fluids	13.49	
Other pulmonary complications – all assumed to have 2 chest x-rays and an ECG – add £135 to all			
Acute shortness of breath - treated with diuretics	Diuretics, transthoracic echo	121.15	

Complication	Treatment/Action	Cost (£)	Assumption
Breathing difficulties at routine outpatients. Kept in overnight for breathing assessment	Transthoracic echo	121	
Breathlessness and cough	Transthoracic echo	121	
Chest pain and shortness of breath	Transthoracic echo	121	
Chest pain on inspiration/coughing	CT scan	62	
Cough	No treatment	0	
Dyspnoea	Transthoracic echo	121	
End stage heart failure	Diuretics, transthoracic echo	121.15	
Failed extubation	No additional treatment	0	Covered in ICU cost
Left hydropneumothorax	Chest ultrasound, chest drain	4244	
Musculoskeletal chest pain	Analgesia	6	
Pleural effusion and bilateral pedal oedema	Chest ultrasound, diuretic therapy	67.15	
Pleural effusion not requiring drainage	Chest ultrasound	67	
Pleural effusion treated with increased dose of furosemide	Furosemide (80mg)	0.30	
Pleuritic left lung (not requiring drainage)	Analgesia	6	
Pulmonary fibrosis	No treatment	0	
Right sided pleural effusion and empyema, ultrasound guided drainage, 2 units blood transfused, treated with IV antibiotics	Chest drain, 2 units RBCs, IV antibiotics	4452.02	
Severe chest pain, possible PE but ruled out following investigations	Transthoracic echo, CT pulmonary angiogram (CT chest)	183	
Shortness of breath	Transthoracic echo	121	
Shortness of breath due to fluid overload, diuretics increased	Transthoracic echo, furosemide (80mg)	121.30	
Sudden onset of shortness of breath, small right pleural effusion	Transthoracic echo	121	

Complication	Treatment/Action	Cost (£)	Assumption
Suspected PE - diagnosed with pleuritic chest pain	CT scan, transthoracic echo	183	
<i>Other arrhythmia complications – all assumed to have 2 ECGs, add £106 to all</i>			
Accelerated junctional rhythm	No additional treatment	0	Pacing already captured
Atrial fibrillation	Amiodarone	4.79	
Chest discomfort, palpitations	No treatment	0	
Fast atrial flutter	Amiodarone	4.79	
Paroxysmal AF	Amiodarone	4.79	
Re-entry tachycardia	No additional treatment	0	Only cost permanent pacemaker if clear indication participant had this treatment
<i>Other thromboembolic complications</i>			
Pulmonary embolus	Transthoracic echo, CT pulmonary angiogram (CT chest), intravenous heparin for 5 days, warfarin	231.78	
Apical thrombus	Transthoracic echo, intravenous heparin for 5 days, warfarin	169.78	
Possible bilateral renal infarcts	CT scan, intravenous heparin, warfarin	110.78	
Small leg thrombus	Ultrasound of leg, intravenous heparin, warfarin	115.78	

AF, Atrial fibrillation; CT, Computed tomography; ECG, Electrocardiography; GI, Gastrointestinal; ICU, Intensive care unit; IV, Intravenous; PE, Pulmonary embolism; RBC, Red blood cell; UTI, Urinary tract infection

Table 9: Unit costs for readmission complications (not previously presented)

Treatment/Action	Unit cost (£)	Reference
Diuretics (furosemide 80mg orally for 5 days)	0.30	BNF[141]
Warfarin (3mg daily, assumed given for half of follow up time, 45 days)	1.35	BNF[141]

BNF, British National Formulary

Table 10: Unit costs for outpatient appointments

Speciality	Unit cost (£)	Service code	Reference
Anticoagulation service	25	324	These are all sourced from NHS Reference Costs 2012-13.[138] They are all average costs for each speciality (from the Total - Outpatient Attendances page, Total activity).
Cardiac rehabilitation	42	327	
Cardiac surgery	299	172	
Cardiology	131	320	
Cardiothoracic surgery	275	170	
Clinical haematology	151	303	
Colorectal surgery	113	104	
Dermatology	98	330	
Diabetic medicine	136	307	
Endocrinology	152	302	
Gastroenterology	137	301	
General medicine	153	300	
General surgery	128	100	
Geriatric medicine	204	430	
Hepatology	213	306	
Infectious diseases	142	350	
Medical oncology	138	370	
Nephrology	158	361	

Speciality	Unit cost (£)	Service code	Reference
Neurology	176	400	
Occupational therapy	63	651	
Ophthalmology	86	130	
Physiotherapy	42	650	
Plastic surgery	88	160	
Rehabilitation	90	314	
Respiratory medicine	150	340	
Stroke clinic	200	328	
Thoracic surgery	253	173	
Upper gastrointestinal surgery	120	106	
Urology	101	101	
Vascular surgery	142	107	

Table 11: Unit costs for other outpatient attendances

Resource	Unit cost (£)	Reference
Renal/ dialysis	157	NHS Reference Costs 2012/13.[138] Renal Dialysis at Base. LD02A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over.
Outpatient endoscopy	676	As endoscopy, previously given
ECG	53	As previously given
Electrocardiogram monitoring and stress testing	204	As previously given
CT scan	62	As previously given
Echo scan - transthoracic	121	As previously given
MRI scan	248	As previously given
Chest x-ray	41	As previously given
Chest x-ray and ultrasound	108	As previously given
Sigmoidoscopy	164	NHS Reference Costs 2012/13.[138] Procedures in Outpatients. FZ57Z Diagnostic or Therapeutic, Rigid Sigmoidoscopy, 19 years and over. 104 Colorectal Surgery.

CT, Computed tomography; ECG, Electrocardiography; MRI, Magnetic resonance imaging

Table 12: Costs for resource use associated with serious adverse events (not previously presented)

Treatment/Action	Unit cost* (£)	Reference
Bladder cystoscopy	129	NHS Reference Costs 2012/13.[138] Procedures in Outpatients. LB15E Minor Bladder Procedures, 19 years and over. 101 Urology.
Colonoscopy	257	NHS Reference Costs 2012/13.[138] Procedures in Outpatients. FZ51Z Diagnostic Colonoscopy, 19 years and over. 100 General Surgery
Diverticulitis	686	NHS Reference Costs 2012/13.[138] Elective inpatients. FZ83H Major Oesophageal, Stomach or Duodenum Procedures, 19 years and over with CC Score 4-6. 301 Gastroenterology, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.
ECG	477	NHS Reference Costs 2012/13.[138] Day Cases. EA47Z Electrocardiogram Monitoring and stress testing. 320 Cardiology.
Fasciotomy	6182	NHS Reference Costs 2012/13.[138] Non-elective inpatients. QZ02D Lower Limb Arterial Surgery with CC Score 6-10. 107 Vascular Surgery, with the costs associated with the average LOS reported subtracted at a cost of £265 per day.
Gastroscopy	676	As endoscopy
Groin scan/procedure of lymphatic system	3191	NHS Reference Costs 2012/13.[138]
Oesophagogastroduodenoscopy	676	As endoscopy
Leg amputation	13353	NHS Reference Costs 2012/13.[138] Non-elective inpatients. QZ11D Amputations with CC Score 8-13. 107 Vascular Surgery.
Re-catheterisation	1534	NHS Reference Costs 2012/13[138]
Stoma bag system	63.38	NHS Electronic Drug Tariff.[209] Part IXC - Stoma Appliances (Colostomy Sets). Weighted average of all sets.
Tesio-catheter insertion under fluoroscopy	325	NHS Reference Costs 2012/13[138]
Uroscopy	129	NHS Reference Costs 2012/13.[138] Procedures in Outpatients. LB15E Minor Bladder Procedures, 19 years and over. 101 Urology.

ECG, Electrocardiography

*Unit costs which were not in 2012/2013 prices were inflated to 2012/2013 prices using the hospital and community health services inflation index.[142]

Table 13: Unit costs for post-discharge community health and social care contacts

Resource	Unit cost* (£)	Reference
GP at surgery	34	Unit Costs of Health and Social Care 2013.[142] 10.8b, GP - unit costs. Per patient contact lasting 11.7 minutes. Excluding qualification costs and direct care staff costs.
GP at home	85	Unit Costs of Health and Social Care 2013.[142] 10.8b, GP - unit costs. Per out of surgery visit lasting 23.4 minutes. Excluding qualification costs and direct care staff costs.
Out-of-hours GP	34	As GP at surgery
Walk-in centre	34	As GP at surgery
GP nurse	11.37	Unit Costs of Health and Social Care 2013.[142] 10.6, Nurse (GP practice). £44 per hour of face-to-face contact, excluding qualification costs. Average contact 15.5 minutes.
District nurse	39	Unit Costs of Health and Social Care 2013.[142] 10.1, Community Nurse. Using data from NHS Reference Costs 2011/12,[138] the mean average cost for a face-to-face contact in district nursing services for 2012/2013 was £39, with an interquartile range of £33 to £46. Costs have been uprated using the HCHS pay & prices inflator.
Other NHS or social services		
Cardiac rehabilitation / exercise class	42	NHS Reference Costs 2012/13.[138] Total - Outpatient Attendances. 327 - Cardiac Rehabilitation.
Cardiac nurse	70	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing, N11AF, Specialist Nursing - Cardiac Nursing/Liaison, Adult, Face to face.
Diabetic nurse	70	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing, N15AF, Specialist Nursing - Diabetic Nursing/Liaison, Adult, Face to face.
Anticoagulation service	10	NHS Reference Costs 2012/13.[138] Non Consultant Led Outpatient Attendances; Non-Admitted Non-Face to Face Attendance, Follow-up, 324 - Anticoagulation Service.
Community pharmacist	69.64	Unit Costs of Health and Social Care 2013.[142] 9.6, Community pharmacist. £127 per hour of direct clinical activities. Contact assumed to be for 32.9 minutes ^a .
Cardiac rehabilitation by phone	50	NHS Reference Costs 2012/13.[138] Non Consultant Led Outpatient Attendances; Non-Admitted Non-Face to Face Attendance, Follow-up, 327 - Cardiac Rehabilitation.
Dietician	71	NHS Reference Costs 2012/13.[138] Community Health Services - Allied Health Professionals. A03 – Dietician.
Healthcare support worker	16	Unit Costs of Health and Social Care 2013.[142] 10.5, Clinical support worker nursing (community). £30 per hour of home visiting. Contact assumed to be for 32.9 minutes ^a .

Resource	Unit cost* (£)	Reference
Occupational therapist	53	Unit Costs of Health and Social Care 2013.[142] 13.2, Hospital occupational therapist. Using data from NHS Reference Costs 2011/12, the mean average cost for a non-consultant led (non-admitted) follow-up occupational therapy attendance was £53, with an interquartile range of £30 to £64. Costs have been uprated using the HCHS pay & prices inflator.
Physiotherapist	34	Unit Costs of Health and Social Care 2013.[142] 13.1, Hospital physiotherapist. Using data from NHS Reference Costs 2011/12, the mean average cost for a non-consultant-led (non-admitted) follow-up physiotherapy attendance was £34, with an interquartile range of £28 to £38. Costs have been uprated using the HCHS pay & prices inflator.
Social worker	87.19	Unit Costs of Health and Social Care 2013.[142] 11.2, Social worker (adult services). £159 per hour of face-to-face contact, excluding qualification costs. Contact assumed to be for 32.9 minutes ^a .
Other NHS or social services at home		
Cardiac rehabilitation / nurse	70	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing. N11AF Specialist Nursing - Cardiac Nursing/Liaison, Adult, Face to face.
Phone call to cardiology	49	NHS Reference Costs 2012/13.[138] Outpatients. WF01C, Non-Admitted Non-Face to Face Attendance, Follow-up. 320 – Cardiology.
Carer	8.50	Unit Costs of Health and Social Care 2013.[142] 11.6, Home care worker. The mean hourly cost of all home care including LA-funded and independent provision was £17. Just over half of local authority funded visits lasted 30 minutes. Sixteen per cent of visits were 15 minutes and 19 per cent of a home care workers' time was spent travelling. Assume 30 minute visit.
Community matron	68	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing. N06AF - Specialist Nursing - Active Case Management (Community Matrons), Adult, Face to face.
Community mental health team carer	36	Unit Costs of Health and Social Care 2013.[142] 10.2 Nurse (mental health), £65 per hour of face-to-face contact, excluding qualifications. Contact assumed to be for 32.9 minutes ^a .
Dietician	71	NHS Reference Costs 2012/13.[138] Community Health Services - Allied Health Professionals. A03 – Dietician.
Occupational therapist	73	Unit Costs of Health and Social Care 2013.[142] 9.2, NHS community occupational therapist. Using data from NHS Reference Costs 2011/12, the mean average cost for a one-to-one contact of occupational therapy services was £73, with an interquartile range of £50 to £86. Costs have been updated using the HCHS pay & prices inflator.
Paramedic	174	NHS Reference Costs 2012/13.[138] Ambulance Services. ASS01-See and treat or refer.

Resource	Unit cost* (£)	Reference
Physiotherapist	47	Unit Costs of Health and Social Care 2013.[142] 9.1, Community physiotherapist. Using data from NHS Reference Costs 2011/12, the mean average cost for a one-to-one contact in physiotherapy services was £47, with an interquartile range of £37 to £52. Costs have been uprated using the HCHS pay & prices inflator.
Social worker	87.19	Unit Costs of Health and Social Care 2013.[142] 11.2, Social worker (adult services). £159 per hour of face-to-face contact, excluding qualification costs. Contact assumed to be for 32.9 minutes ^a .
Nurse specialist	60	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing, N29AF, Other Specialist Nursing, Adult, Face to face.
Respiratory nurse	75	NHS Reference Costs 2012/13.[138] Community Health Services – Nursing, N08AF, Specialist Nursing - Asthma and Respiratory Nursing/Liaison, Adult, Face to face.
NHS direct call	13	NHS Direct annual report 2012/13.[210]
Indoor and outdoor grab rails	91	Unit Costs of Health and Social Care 2013.[142] 7.3.1, social services access improvements.
Mobile shower chair	55	Unit Costs of Health and Social Care 2013.[142] 7.3.1, social services shower.

GP, General practitioner; HCHS, Hospital and community health services

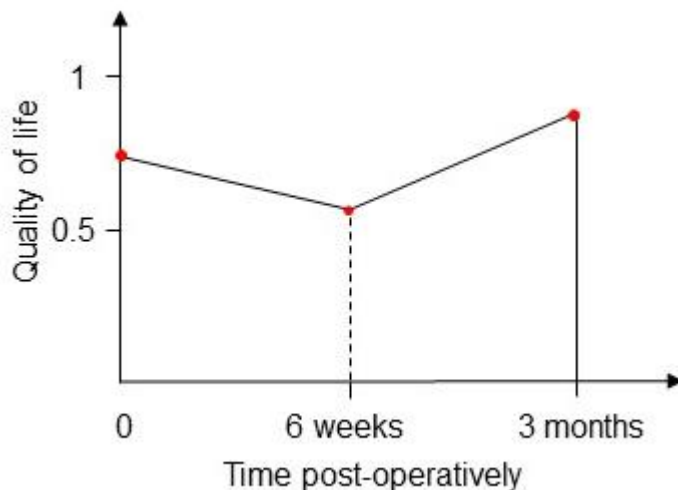
*Unit costs which were not in 2012/2013 prices were inflated to 2012/2013 prices using the hospital and community health services inflation index.[142]

^a Where no information was available on the duration of appointments, an average duration of 32.9 minutes has been assumed. This is the average length of a hospital physiotherapy session (Unit Costs of Health and Social Care 2013;[142] section 13.1).

Appendix 16: Calculation of QALYs

Total QALYs over the three month time horizon were calculated for each patient based on their EQ-5D scores pre-operatively, at six weeks and at three months post-operatively. An example of a QALY profile is shown in **Figure 1**, the red dots are the quality of life (utility) scores at each of the time points. QALYs were calculated assuming that each patient's utility changed linearly between the time points, hence the quality of life scores in **Figure 1** are joined by straight lines. For patients who died during the trial, their utility was assumed to change linearly between the preceding time point and the time of death, and a value of zero was given to patients from death onwards.

Figure 1: A QALY profile



The number of QALYs accrued by each patient was calculated using the area under the curve, (the enclosed area in **Figure 1** between the utility measurements and the x axis over the three month time horizon). Total QALYs gained were calculated for each patient by adding together QALYs gained from baseline to six weeks and from six weeks to three months. QALYs gained from baseline to six weeks were calculated by averaging a patient's EQ-5D scores at baseline and six weeks and multiplying by 42 days (or the number of days until death if this was within 42 days), and then dividing by 365.25 to convert to years. QALYs gained from six weeks to three months were calculated in a similar way. Once total QALYs gained were calculated for all patients, the average QALY gain for patients in each group was calculated. Alternative assumptions regarding the analysis of QALYs were investigated in sensitivity analyses, such as using the actual date of completion of the six week EQ-5D rather than assuming this was at exactly 42 days.

Appendix 17: Imputation methods for missing data

Multiple imputation was used to impute missing resource use and EQ-5D data. Multiple imputation uses regression to predict m values for each missing data cell, and enables all variables used in the economic evaluation and demographic data (both complete and incomplete) to be used to predict the values of missing data cells. Following recent guidelines,[77, 102] multiple imputation using chained equations was conducted using the *mi* command in Stata 14.[110] Following the rule of thumb in White *et al.*, that the number of imputations should be at least equal to the percentage of incomplete cases, 60 imputations were performed.[77]

Missing inpatient and post discharge resource use and EQ-5D data were imputed altogether, based on the available data and independent variables: centre, sex, age at operation and cardiac procedure (as four categories) in the regression equations. Multiple imputation was performed separately for each treatment group.

Multiple imputation is a flexible method for handling missing data. In two part questions (for example, did you visit your GP, and if yes, please record the number of visits) responses could be missing for one or both parts of the question. By imputing the number of GP visits, conditional on an indicator variable for GP visits (yes/no), multiple imputation can handle partial or completely missing data. All readmission variables, including ICU days, complications and SAEs, were imputed conditional on readmission LOS being greater than zero, i.e. only patients who had a readmission could then have complications in the follow up period. Indicator variables for SAEs included in the imputation only counted patients for whom a cost was attached to their SAE.

There were over 100 variables included in this analysis, approximately two thirds of which had some missing data. Individual regressions were specified for each of these variables, and tailored to the type of data being predicted. Logistic regression was used for some binary variables, and linear regression with prediction mean matching was used for continuous variables and others, since it is particularly flexible. Prediction mean matching uses an observed value from a patient (donor) with a similar predictive mean; when used here, a value was sampled from a pool of ten donors as advocated in recent guidance.[211]

While every effort was made to maintain the desired imputation structure, given the large number of variables, (including many binary and categorical variables) a couple of simplifications did need to be made to overcome problems associated with perfect prediction, collinearity and lack of convergence. It was not possible to include all the complete variables in the model, but key complete variables such as blood products, LOS by ward type, reoperations and reintubations were included. There were a couple of variables it was not possible to include in the multiple imputations. For readmissions, patients were asked to record whether they spent any time in an intensive care unit (ICU), and the number of days spent in ICU. This was poorly recorded (available for only nine of the 28 patients known to be readmitted to ICU). An indicator variable for readmitted to ICU (yes/no) was included in the imputation, if yes, then the average proportion of the readmission stay that was spent in ICU by the nine patients was applied to the total readmission days that had been imputed (40%). It was also not possible to impute the number of visits to NHS walk-in centres or GP out of hours centres, instead indicator variables for these resources were multiply imputed, and a mean number of visits from available data applied when costing this activity (these were relatively rare events, all affected less than 5% of patients). For hospital attendances post-discharge where it was not known whether patients were readmitted via A&E and/or arrived by ambulance, mean imputation was used to complete this information.

Once multiple imputation had been conducted, tabulations and summaries of the observed and imputed data were compared to check the validity of the imputations. To combine results across the imputations, Rubin's Rule was used to summarise data across the 60 datasets.[78] This approach accounts for the variability both within and between imputed datasets and takes uncertainty in the estimated mean into account.

Appendix 18: Bootstrapping of costs and QALYs

Bootstrapping was performed as follows: 100 bootstrap samples were drawn for each of the 60 imputed datasets, which created 6000 bootstrap replicates. For each bootstrap sample for each imputation, total costs were regressed on treatment group, and total QALYs were regressed on treatment group and baseline EQ-5D (the reason for including baseline EQ-5D is described in **Appendix 19**). The mean cost difference between the groups (restrictive minus liberal) was calculated, as well as the mean QALY difference between the groups adjusted for baseline EQ-5D.

The 6000 bootstrap replicates of the mean difference in costs and QALYs between the groups were used to represent graphically the uncertainty around the ICER on the cost-effectiveness plane (described in Chapter 2). In order that the points could be seen on the plane, only a random sample of 1000 replicates were plotted.

For each of the 60 imputations, the mean and SD of the 100 cost and QALY differences were estimated. These SDs are SDs of a column of means, so are actually SEs. Rubin's Rule was then used to combine the SEs across the 60 imputed datasets. 95% confidence intervals (CIs) around the cost and QALY differences were then generated based on these SEs, using a t distribution with degrees of freedom $v = (M-1)(1+r^{-1})^2$, where r is the ratio of the between-imputation component of the variance and the within-imputation component of the variance, and M is the number of imputed datasets.[76]

The combined cost and effectiveness results are expressed in terms of a cost-effectiveness acceptability curve (CEAC), which indicates the likelihood that the restrictive threshold is cost-effective for different levels that healthcare decision-makers are willing to pay for health gain. All 6000 bootstrap replicates were used to generate the CEAC. The ICERs and CEACs presented allow the reader and decision-makers to assess cost-effectiveness at a willingness-to-pay threshold of their choice.

Appendix 19: Adjustment for baseline utility

QALYs were adjusted for baseline EQ-5D to control for any potential imbalances in baseline utility in the estimation of the mean difference in QALYs between treatment groups, to avoid introducing bias.[147] Regression adjustment also allows for regression to the mean and increases precision. For each of the 60 imputed datasets, linear regression of total QALYs on treatment group and baseline EQ-5D was performed; the Stata command, *mi estimate* was used to combine the 60 imputed datasets, and Rubin's Rule was used to combine the standard errors across the 60 imputations. This provided an estimate of the QALY difference and its standard error between the trial groups, adjusted for baseline EQ-5D. The Stata command *nlcom* was then used to combine regression coefficients to obtain the mean QALYs in each trial group, adjusted for baseline EQ-5D.

Appendix 20: Sensitivity analysis methods

This appendix describes each of the sensitivity analyses conducted around costs and outcomes.

Sensitivity analyses around costs

Sensitivity analyses were conducted to investigate:

- Varying the unit costs of treatment of complications, ward stays, re-operations, drugs, and the costs of blood administration (further details below);
- Conducting the costing from the point of randomisation rather than the point of surgery, as undertaken in the base case analysis (further details below);
- Exploring the impact of any high cost patients (outliers) if the cost data are skewed;
- Considering non-NHS costs (further details below).

Sensitivity analyses around unit costs

The sensitivity analyses conducted around the unit costs of bed days, antibiotics, complications and outpatient visits are shown in **Table 1**.

Table 1: Sensitivity analyses performed around unit costs

SA	Resource / complication	Unit costs used in base case analysis	Alternative strategies for sensitivity analysis
1	Ward stay in cardiac unit (first admission)	£392	£265 (Cost used for ward stay beyond index cardiac admission)
2	Ward stay beyond index cardiac admission. (Further stay in another unit/hospital or readmission)	£265	£392 (Cost used for ward stay in cardiac unit, first admission)
3	Bed days in first admission	£1,608 General ICU £1,190 CICU £619 HDU £392 cardiac ward £265 another unit/hospital ward (£1,168 if known to be ICU)	Alter bed day costs in first admission by +/- 50%
4	Bed days in readmissions	£1,168 ICU £265 ward	Alter readmission ICU / ward costs by +/- 50%

SA	Resource / complication	Unit costs used in base case analysis	Alternative strategies for sensitivity analysis
5	Stroke	£139 for physiotherapy, and diagnostics as recorded (CT scan £62; MRI scan £248)	£705 (taken from NHS Reference Costs,[138] see Appendix 15, Table 6)
6	Wound dehiscence	Covered by reoperation if the 2 dates are the same; otherwise £161 unless negative pressure wound therapy is stated then £3501	Assume negative pressure wound therapy for those without reoperations (£3501)
7	Low cardiac output	£313; IABP not included	Add cost of IABP £2776
8	Chest drain	£4177	-50%: £2088.50
9	Pacing	£3073	+/- 50%
10	Tracheostomy	£5354 (includes 1 x-ray)	+/- 50%
11	Reoperations	£6608 if operation takes less than 3 hours, and £8298 if 3 hours or more. Reoperations in readmissions costed at £6608 + £1421 for blood products.	Cost all reoperations at the lower (£6608) and higher figures (£8298). Include £1421 for blood products for reoperations in readmissions.
12	Antibiotics	eMIT[140] where available, otherwise BNF[141] see Appendix 15, Table 3	Increase costs by 100%
13	Outpatient visits	See Appendix 15, Table 10 and Table 11	+/- 50%
14	Blood product administration	Costs from Chapter 4, see Appendix 15, Table 1	£0

BNF, British National Formulary; CICU, Cardiac intensive care unit; CT, Computed tomography; eMIT, electronic Marketing Information Tool; FFP, Fresh frozen plasma; HDU, High dependency unit; IABP, Intra-aortic balloon pump; ICU, Intensive care unit; LOS, Length of stay; MRI, Magnetic resonance imaging; SA, Sensitivity analysis

Costing from randomisation

Costs for three months from randomisation rather than from surgery were calculated for each patient. Events that occurred before randomisation were excluded: the cardiac procedure and blood saving techniques in theatre (tranexamic acid, aprotinin, and cell salvage). Costs associated with post-operative cell saver were included only if patients were randomised within four hours of surgery. The costs of RBCs given pre-randomisation and complications occurring pre-randomisation were excluded. For events which may have started before randomisation but extended beyond randomisation, such as length of stay and intubations, durations were calculated from the time of randomisation.

Resource use for other blood products (FFP, platelets, cryoprecipitate) and Activated Factor VII and Beriplex was captured for the hospital stay: it was not possible to determine if these resources were used pre- or post-randomisation. The costs of these products have

been included in this analysis. It was not possible to determine if fluids given in theatre, CICU or HDU were given pre- or post-randomisation; the costs of these products were excluded.

Any events occurring within three months of randomisation rather than of surgery were included in the analysis. Given that randomisation occurs after surgery, slightly more post-discharge resource use was included in this analysis compared to the costs to three months from surgery.

Considering non-NHS costs

Non-NHS costs were also considered as part of the sensitivity analyses. The base case analysis took an NHS and personal social services perspective in line with NICE guidance,[46] since this will be of most value to decision-makers in the UK. However, to consider any wider implications of the alternative transfusion thresholds beyond this perspective, analyses were conducted to determine whether non-NHS costs differed between the trial groups and, hence, whether there was a need to conduct a sensitivity analysis from a wider societal perspective.

Sensitivity analyses around outcomes

The assumptions for calculating QALYs that were explored in the sensitivity analyses are described in **Table 2**. A further sensitivity analysis was conducted examining life-years gained as a secondary outcome measure in the economic evaluation.

Table 2: Sensitivity analyses performed around QALY calculations

SA	Aspect of methodology	Strategy used in base case analysis	Alternative strategy for sensitivity analysis
1	Adjusting for baseline utility	Regression used to adjust for differences in baseline utility	No adjustment for baseline utility
2	QALY calculations for participants who die	Utility was assumed to change linearly between the preceding time point and the time of death	Use last observation carried forward until death
3	Timing of 6 week EQ-5D	EQ-5D at 6 weeks assumed to be completed at exactly 6 weeks	Use the date of completion of the 6 week EQ-5D
4	Timing	Calculate QALYs gained from time of surgery to 3 months	Calculate QALYs gained from randomisation to 3 months

Appendix 21: Detailed breakdown of total average costs per patient for both trial groups

Resource use	Restrictive threshold (n=1000) Mean cost (£) (SE)	Liberal threshold (n=1003) Mean cost (£) (SE)	Restrictive versus liberal threshold Mean cost (£) difference (95% CI)
Red blood cells			
Red blood cells	257 (12)	379 (13)	-122 (-157, 88)
Red blood cell administration	95 (4)	143 (5)	-48 (-60, 36)
Total red blood cells	352 (16)	522 (18)	-170 (-217, -124)
Cardiac procedure			
Initial cardiac surgery	7309 (18)	7313 (18)	-4 (-55, 47)
Blood products			
Fresh frozen plasma	27 (2)	26 (2)	1 (-3, 6)
Platelets	135 (7)	134 (7)	1 (-18, 20)
Cryoprecipitate	43 (5)	39 (4)	4 (-9, 18)
Blood product administration	78 (4)	74 (4)	4 (-7, 15)
Total blood products	283 (15)	273 (14)	11 (-30, 52)
Inpatient complications			
Primary outcome			
Antibiotics for infectious complication	21 (5)	14 (2)	7 (-4, 17)
Stroke	3 (1)	3 (1)	0 (-2, 2)
Suspected myocardial infarction	6 (3)	13 (5)	-7 (-19, 4)
Gut infarction	11 (6)	3 (3)	8 (-4, 20)
Acute kidney injury - stage 3	86 (11)	73 (10)	13 (-16, 42)
Other complications			
Reoperation	636 (70)	704 (75)	-67 (-268, 133)
Reintubation	28 (4)	29 (4)	-1 (-12, 9)
Tracheostomy	184 (32)	176 (31)	7 (-80, 95)
Mask CPAP	68 (6)	65 (7)	3 (-15, 22)
Pneumothorax requiring chest drainage	59 (16)	55 (15)	4 (-38, 47)
Pleural effusion requiring drainage	246 (33)	248 (36)	-2 (-96, 93)
Pacing	946 (48)	956 (47)	-9 (-141, 122)
SVT/AF requiring treatment	2 (0)	2 (0)	0 (0, 0)
VF/VT requiring intervention	44 (11)	16 (6)	28 (3, 53)
Low cardiac output	33 (3)	35 (4)	-1 (-11, 8)
Serious adverse events	17 (7)	12 (5)	5 (-13, 22)
Other inpatient complications	296 (54)	311 (54)	-15 (-164, 135)
Total complications & SAEs	2687 (137)	2714 (146)	-27 (-420, 367)
Inpatient length of stay			
Cardiac intensive care unit	1359 (138)	1330 (158)	29 (-383, 442)
High dependency unit	1916 (72)	1890 (74)	25 (-178, 229)
Ward	2221 (59)	2287 (68)	-66 (-242, 111)
Intensive care unit	8 (8)	17 (12)	-9 (-37, 19)
Another unit / hospital	339 (53)	396 (65)	-58 (-222, 106)

Resource use	Restrictive threshold (n=1000) Mean cost (£) (SE)	Liberal threshold (n=1003) Mean cost (£) (SE)	Restrictive versus liberal threshold Mean cost (£) difference (95% CI)
Total length of stay	5842 (199)	5920 (225)	-78 (-667, 511)
Blood saving techniques			
Tranexamic acid	13 (0)	13 (0)	0 (-1, 1)
Trasylol	13 (2)	11 (2)	2 (-3, 8)
Intra-operative cell salvage	85 (3)	88 (3)	-4 (-11, 4)
Post-operative cell salvage	10 (1)	8 (1)	2 (-2, 5)
Beriplex	22 (3)	20 (3)	-2 (-6, 10)
Factor VIIa	17 (7)	12 (6)	5 (-12, 22)
Total blood saving techniques	159 (9)	152 (8)	7 (-16, 30)
Fluids in theatre/CICU/HDU			
Inotropes	36 (1)	35 (1)	1 (-2, 3)
Gelofusin	7 (0)	7 (0)	0 (0, 0)
Hydroxyethyl starch (HES)	9 (1)	9 (1)	0 (-2, 1)
Other fluids	3 (0)	3 (0)	0 (-1, 0)
Total fluids	55 (1)	54 (1)	0 (-3, 3)
Readmissions to hospital			
Length of stay (ward and ICU)	462 (67)	498 (63)	-36 (-218, 145)
Complications and SAEs	273 (39)	261 (40)	11 (-98, 121)
Readmission via A&E &/or ambulance	52 (4)	48 (4)	5 (-7, 16)
Total readmissions	787 (93)	807 (89)	-20 (-274, 233)
A&E attendances			
Total A&E visits	9 (1)	8 (1)	1 (-2, 4)
Ambulance to A&E	7 (1)	4 (1)	3 (0, 6)
Total A&E	16 (2)	12 (2)	4 (-1, 9)
Outpatient appointments			
Cardiac surgery outpatient visits	131 (5)	152 (6)	-21 (-37, 5)
Cardiology outpatient visits	37 (2)	33 (2)	4 (-3, 11)
Other outpatient visits	30 (3)	31 (4)	-1 (-11, 8)
Ambulance to appointment	1 (0)	2 (1)	0 (-2, 1)
Total outpatients	201 (6)	217 (7)	-16 (-34, 3)
Other health and social care contacts			
General practitioner at surgery	67 (2)	71 (3)	-4 (-11, 3)
General practitioner at home	37 (3)	35 (3)	2 (-7, 11)
Practice nurse	18 (1)	18 (2)	0 (-4, 4)
District nurse	95 (9)	92 (10)	3 (-22, 29)
Other contacts	158 (10)	163 (12)	-5 (-35, 25)
Total other contacts	375 (14)	378 (16)	-3 (-48, 42)
Total costs	18092 (338)	18390 (367)	-298 (-1276, 680)

A&E, Accident and Emergency; CI, Confidence interval; CICU, Cardiac intensive care unit; CPAP, Continuous positive airway pressure; HDU, High dependency unit; ICU, Intensive care unit; SAE, Serious adverse event; SE, Standard error; SVT/AF, Supraventricular tachycardia/ Atrial fibrillation; VF/VT, Ventricular fibrillation/ Ventricular tachycardia

Costs do not always sum to totals due to rounding.

Appendix 22: Why does the difference in deaths not translate into a difference in QALYs?

Given the significant difference in deaths between the groups (more deaths in the restrictive group), potential reasons for why the difference in deaths did not appear to translate into a difference in QALYs were explored. It was thought that patients who died would have been sicker, which theoretically could have resulted in them reporting lower EQ-5D scores prior to death. QALY data for the following groups were plotted: all patients, for patients excluding deaths and only for deaths. This investigation revealed that it was not merely the patients who died who had low QALYs, but also many other patients. These low EQ-5D scores for surviving patients had the effect of 'diluting' the impact on the means of imputed zero EQ-5D scores for patients who died. Most of the patients who died had total QALYs of 0-0.05. When these patients were excluded, there were a few more patients in the liberal group with QALYs <0.05 than in the restrictive group and, overall, these low scores in the liberal group appear to have partly balanced out the greater number of deaths in the restrictive group. In addition, there were more patients in the restrictive group in the highest band for QALYs, which could also be balancing out the greater number of deaths in the restrictive group. It was concluded that there could genuinely be no real difference in QALYs between the restrictive and liberal groups, despite the difference in deaths.

Appendix 23: Sensitivity analysis results

Results of each of the sensitivity analyses around costs and outcomes are considered in turn.

Sensitivity analyses around unit costs

The results of the sensitivity analyses around the costs of bed days, antibiotics, complications, outpatient visits and blood administration are shown in **Table 1**. Compared to the sensitivity analysis which excluded all blood administration costs, costs in the base case were £173 higher in the restrictive group and £216 higher in the liberal group. Varying the cost of bed days during the index admission by +/- 50% had the greatest impact on total costs in each group (increasing and decreasing total costs to approximately £21,000 and £15,000 respectively). However, none of the sensitivity analyses had a great impact on the cost difference between the groups. The cost differences across the sensitivity analyses ranged from -£337 to -£254, so were all very similar to the base case cost difference of -£298 and to each other. These findings reinforce how similar resource use was between the groups.

Table 1: Results of sensitivity analyses around unit costs

Sensitivity Analysis	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold
	Mean cost (£) (SE)	Mean cost (£) (SE)	Mean cost (£) difference (95% CI)
Base case	18092 (338)	18390 (367)	-298 (-1276, 680)
SA1 (Ward stay, cardiac unit)	17373 (333)	17649 (362)	-277 (-1240, 686)
SA2 (Ward stay, beyond index cardiac admission)	18247 (348)	18572 (378)	-325 (-1331, 680)
SA3 (Bed days, first admission)			
+50%	21013 (428)	21350 (472)	-337 (-1585, 910)
-50%	15171 (255)	15430 (270)	-259 (-987, 469)
SA4 (Bed days, readmissions)			
+50%	18323 (349)	18639 (376)	-317 (-1321, 688)
-50%	17861 (330)	18141 (361)	-280 (-1239, 679)
SA5 (Stroke)	18101 (338)	18340 (368)	-299 (-1278, 681)
SA6 (Wound dehiscence)	18169 (343)	18464 (371)	-295 (-1284, 695)
SA7 (Low cardiac output)	18395 (346)	18703 (379)	-308 (-1314, 698)
SA8 (Chest drain)	17858 (329)	18167 (358)	-309 (-1265, 643)
SA9 (Pacing)			
+50%	18565 (345)	18868 (374)	-303 (-1301, 694)

Sensitivity Analysis	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold
	Mean cost (£) (SE)	Mean cost (£) (SE)	Mean cost (£) difference (95% CI)
-50%	17619 (332)	17912 (362)	-294 (-1256, 669)
SA10 (Tracheostomy)			
+50%	18184 (348)	18478 (377)	-295 (-1300, 711)
-50%	18000 (328)	18032 (358)	-302 (-1253, 649)
SA11 (Reoperations)			
£6608	18077 (337)	18378 (366)	-302 (-1276, 673)
£8298	18239 (345)	18559 (376)	-320 (-1319, 680)
SA12 (Antibiotics)	18114 (340)	18406 (368)	-292 (-1274, 690)
SA13 (Outpatient visits)			
+50%	18192 (337)	18498 (367)	-306 (-1283, 671)
-50%	17992 (338)	18283 (368)	-291 (-1269, 688)
SA14 (No blood administration)			
	17919 (334)	18174 (363)	-254 (-1220, 711)

BNF, British National Formulary; CI, Confidence interval; IV, Intravenous; SA, Sensitivity analysis; SE, Standard error

Costing from the point of randomisation

Patients were, on average, randomised 0.8 days after surgery. **Tables 2** and **3** present the mean resource use and mean costs to three months from randomisation. Patients in the restrictive group received on average one less unit of RBCs than patients in the liberal group, other resource use was similar between the groups. There was little difference in total costs of care from randomisation to three months between the two treatment groups. The total costs from randomisation are £8,968 (SE 315) in the restrictive group, and £9,190 (SE 348) in the liberal group, with a mean difference between the groups of -£222 (95% CI -1145, 700). The costs associated with RBCs are lower in the restrictive group compared to the liberal group, as expected. The costs of other inpatient and post-discharge resource use are very similar.

Total costs from randomisation are considerably less than total costs from surgery. Costs are lower because the costs of surgery and complications occurring before randomisation have been excluded and LOS costs are reduced. The LOS occurring pre-randomisation is at least in part time spent in CICU/HDU, since all patients go to CICU/HDU after surgery. RBC costs are also reduced, since some RBCs are transfused during surgery.

Table 2: Resource use per patient to three months from randomisation

Resource use component	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold % or Mean Difference (95% CI)
	Frequency (%) or Mean (SE)	Frequency (%) or Mean (SE)	
Red blood cells – number of units/patient	1.49 (0.08)	2.49 (0.09)	-1.00 (-1.23, 0.75)
Blood products – number of units/ patient			
Fresh frozen plasma	1.00 (0.06)	0.95 (0.06)	0.05 (-0.11, 0.21)
Platelets	0.65 (0.03)	0.64 (0.03)	0.01 (-0.09, 0.10)
Cryoprecipitate	0.23 (0.03)	0.21 (0.02)	0.02 (-0.05, 0.09)
Inpatient complications			
Primary outcome - number (%) of patient			
Antibiotics for infectious complication	319 (32%)	322 (32%)	0%
Stroke	11 (1%)	14 (1%)	0%
Suspected myocardial infarction	2 (0%)	4 (0%)	0%
Gut infarction	5 (1%)	1 (0%)	0%
Acute kidney injury - stage 3	47 (5%)	45 (4%)	0%
Other complications – number of events/ patient			
Reoperation	0.07 (0.01)	0.08 (0.01)	-0.01 (-0.04, 0.12)
Reintubation	0.05 (0.01)	0.06 (0.01)	-0.01 (-0.03, 0.02)
Trachestomy	0.03 (0.01)	0.03 (0.01)	0.00 (-0.02, 0.01)
Mask CPAP	0.10 (0.01)	0.09 (0.01)	0.01 (-0.02, 0.04)
Pneumothorax requiring chest drainage	0.01 (0.00)	0.01 (0.00)	0.00 (-0.01, 0.01)
Pleural effusion requiring drainage	0.06 (0.01)	0.06 (0.01)	0.00 (-0.02, 0.02)
Pacing	0.09 (0.01)	0.06 (0.01)	0.03 (-0.05, 0.00)
SVT/AF requiring treatment	0.35 (0.02)	0.33 (0.02)	0.02 (-0.03, 0.07)
VF/VT requiring intervention	0.02 (0.01)	0.01 (0.00)	0.01 (0.00, 0.02)
Low cardiac output	0.03 (0.01)	0.03 (0.01)	0.01 (-0.01, 0.02)
Inpatient length of stay - days/ patient			
Cardiac intensive care unit	0.89 (0.11)	0.86 (0.13)	0.03 (-0.31, 0.37)
High dependency unit	2.75 (0.12)	2.71 (0.12)	0.04 (-0.28, 0.37)
Ward	5.49 (0.15)	5.68 (0.17)	-0.19 (-0.63, 0.25)
Another unit / hospital	1.23 (0.19)	1.43 (0.22)	-0.20 (-0.77, 0.38)
Blood saving techniques – number (%) of patient			
Post-operative cell salvage*	24 (2%)	20 (2%)	0%
Readmissions to hospital			
Length of stay – days/patient	1.39 (0.16)	1.56 (0.18)	-0.17 (-0.64, 0.30)
A&E attendances			
Total A&E visits - number/patient	0.09 (0.01)	0.08 (0.01)	0.01 (-0.02, 0.04)
Outpatient appointments - number/patient			
Cardiac surgery outpatient visits	0.44 (0.02)	0.51 (0.02)	-0.07 (-0.13, -0.02)
Cardiology outpatient visits	0.28 (0.02)	0.26 (0.02)	0.02 (-0.03, 0.08)
Other outpatient visits	0.17 (0.02)	0.17 (0.02)	-0.01 (-0.06, 0.05)

Resource use component	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold % or Mean Difference (95% CI)
	Frequency (%) or Mean (SE)	Frequency (%) or Mean (SE)	
Other healthcare contacts - number/patient			
General practitioner at surgery	1.97 (0.07)	2.08 (0.08)	-0.11 (-0.32, 0.09)
General practitioner at home	0.43 (0.04)	0.40 (0.03)	0.05 (-0.07, 0.13)
Practice nurse	1.57 (0.12)	1.55 (0.13)	0.02 (-0.34, 0.37)
District nurse	2.41 (0.21)	2.35 (0.24)	0.06 (-0.56, 0.68)

A&E, Accident and Emergency; CI, Confidence interval; CPAP, Continuous positive airway pressure; SE, Standard error; SVT/AF, Supraventricular tachycardia/ Atrial fibrillation; VF/VT, Ventricular fibrillation/ Ventricular tachycardia

* Included if patient randomised within four hours of surgery

Table 3: Breakdown of total average costs per patient from randomisation to three months for both trial groups

Cost component	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Restrictive versus liberal threshold Mean cost (£) difference (95% CI)
	Mean cost (£) (SE)	Mean cost (£) (SE)	
Red blood cells	277 (14)	448 (16)	-141 (-212, -130)
Inpatient episode			
Other blood products	285 (15)	273 (15)	12 (-30, 53)
Complications and SAEs	1696 (120)	1663 (128)	33 (-311, 377)
Length of stay*	5263 (197)	5332 (222)	-69 (-652, 514)
Blood saving techniques	43 (8)	36 (7)	7 (-13, 27)
Regular medications	25 (2)	29 (2)	-3 (-8, 2)
Total	7313 (287)	7333 (325)	-20 (-871, 831)
Post-discharge			
Readmissions	787 (87)	802 (79)	14 (-264, 235)
A&E visits	16 (2)	12 (2)	4 (-1, 10)
Outpatient appointments	202 (7)	220 (7)	-17 (-36, 2)
Other medical/social care	372 (14)	377 (18)	-4 (-49, 41)
Total	1378 (93)	1410 (92)	-31 (-290, 228)
Total costs	8968 (315)	9190 (348)	-222 (-1145, 700)

A&E, Accident and Emergency; CI, Confidence interval; SAE, Serious adverse event; SE, Standard error

* Includes days in another unit/hospital once transferred out of the cardiac unit

Sensitivity analyses around cost outliers

The distribution of total costs per patient is positively skewed in both transfusion groups, as seen in **Figures 5.2** and **5.3**. It is possible that a few high cost outliers are exerting influence over the mean costs in each group and the overall findings. Therefore, the existence of outliers and their effects was investigated.

There were 12 patients with costs over £80,000, of whom seven were in the liberal group and five were in the restrictive group. Patients with the five highest costs were all in the liberal group. Four patients had costs over £100,000 (£101,514; £107,598; £110,420; and one extreme outlier of £146,107). These patients did not have unexpected events; rather, they had large numbers of expected complications and stayed in hospital with a high level of care for some time. Therefore, there were no grounds for excluding these patients from the analyses. Nevertheless, it is instructive to investigate the impact they are having on cost and cost-effectiveness results since the imbalance across groups of these outliers could easily have arisen by chance.

Table 4 shows the effects on costs and cost-effectiveness results of excluding the highest cost outlier, and of excluding the four highest cost outliers with total costs over £100,000. All of these patients were in the liberal group, so results for the restrictive group are unchanged. If the patient with the highest cost is excluded from the analyses, the difference in costs between the groups reduces from -£298 to -£171. If patients with the four highest costs are excluded, the liberal group becomes less expensive than the restrictive group, the difference in costs between the groups changing from -£298 to +£94. The liberal group also becomes marginally more effective than the restrictive group and the conclusions are reversed, i.e. the liberal group dominates the restrictive group as it is both less costly and more effective. While there is much uncertainty around these findings, these four patients are clearly exerting a significant impact on the cost and cost-effectiveness results.

Table 4: Sensitivity analyses around the cost outliers

	Restrictive threshold (n=1000)		Liberal threshold (n=1003)		Restrictive versus liberal threshold		
	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (95% CI)	Mean QALY difference (95% CI)	ICER
Base case - all patients	£18092 (£338)	0.1804 (0.0015)	£18390 (£367)	0.1802 (0.0015)	-£298 (-1276, 680)	0.0001 (-0.0041, 0.0043)	Restrictive dominant (-£2,545,782)
Exclude highest cost patient	£18092 (£338)	0.1804 (0.0015)	£18263 (£345)	0.1803 (0.0015)	-£171 (-1117, 775)	0.00004 (-0.0041, 0.0042)	Restrictive dominant (-£4,656,788)
Exclude 4 highest cost patients	£18092 (£338)	0.1804 (0.0015)	£17998 (£310)	0.1806 (0.0015)	£94 (-804, 992)	-0.0002 (-0.0044, 0.0040)	Liberal dominant (-£463,568)

CI, Confidence interval; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life-year; SE, Standard error

Sensitivity analysis around the perspective

A sensitivity analysis taking a wider societal perspective (instead of the NHS and personal social services perspective taken in the base case analysis) was planned if non-NHS costs were found to differ between the trial groups. This was not found to be the case (see **Appendix 24**) and, therefore, this sensitivity analysis was not conducted.

Sensitivity analyses around QALY calculations

The results of the sensitivity analyses around alternative assumptions for calculating QALYs are shown in **Table 5**. In all of these sensitivity analyses, the difference in QALYs between the groups remained very small. When last observation carried forward until death was used, QALYs increased slightly in both groups, more so in the restrictive group since there were more deaths in this group and a greater number of patients whose QALYs were increased by this sensitivity analysis (unless their EQ-5D score was less than zero at the previous observation). When the exact timing of the six week EQ-5D questionnaire was used in the QALY calculations, the mean QALYs gained to three months were slightly higher in the liberal group than in the restrictive group, a reversal of the base case findings. Patients on average completed the six week questionnaire later than planned, at 51 days rather than 42 days.

Table 5: Results of sensitivity analyses around outcomes

Sensitivity Analysis		Restrictive threshold (n=1000) Mean (SE)	Liberal threshold (n=1003) Mean (SE)	Restrictive versus liberal threshold Mean difference (95% CI)
QALYs to 3 months				
Base case		0.1804 (0.0015)	0.1802 (0.0015)	0.0001 (-0.0041, 0.0043)
1	No adjustment for baseline utility	0.1803 (0.0018)	0.1803 (0.0017)	-0.00002 (-0.0050, 0.0049)
2	Last observation carried forward until death	0.1810 (0.0015)	0.1806 (0.0015)	0.0004 (-0.0037, 0.0044)
3	Exact time between operation and 6 week EQ-5D completion	0.1804 (0.0014)	0.1805 (0.0014)	-0.00001 (-0.0040, 0.0040)
4	From randomisation	0.1803 (0.0015)	0.1802 (0.0015)	0.0001 (-0.0041, 0.0043)

CI, Confidence interval; QALY, Quality-adjusted life-year; SE, Standard error

Life-years as an alternative outcome measure

Life-years gained from surgery up to three months are shown in **Table 6**. Given the greater number of deaths in the restrictive group, slightly fewer life-years were gained in the restrictive group than in the liberal group. The cost-effectiveness results using life-years as the outcome measure are also shown in **Table 6**. This analysis generated the typical trade-off between effectiveness and cost; the restrictive threshold was less effective but also less costly than the liberal threshold. The ICER of £109,571 is the incremental saving associated with the loss of one life-year by adopting a restrictive rather than a liberal threshold. If a decision-maker's willingness-to-accept compensation for the loss of one life-year were £20,000, then a restrictive threshold would be considered cost-effective.

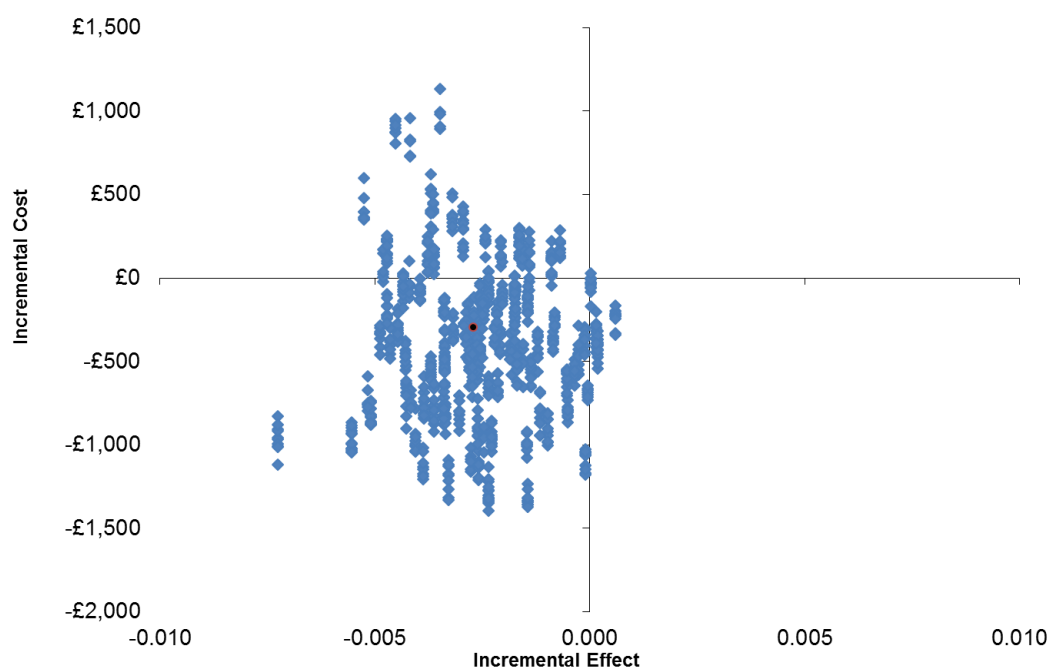
Table 6: Cost-effectiveness results for life-years

	Restrictive threshold (n=1000)	Liberal threshold (n=1003)	Difference
Total costs (95% CI)	£18092 (£17467, £18716)	£18390 (£17646, £19134)	-£298 (-£1212, £615)
Life-years gained (95% CI)	0.2428 (0.2402, 0.2454)	0.2455 (0.2438, 0.2472)	-0.0027 (-0.0057, 0.0002)
		ICER (Cost / life-year)	£109,571

CI, Confidence interval; ICER, Incremental cost-effectiveness ratio

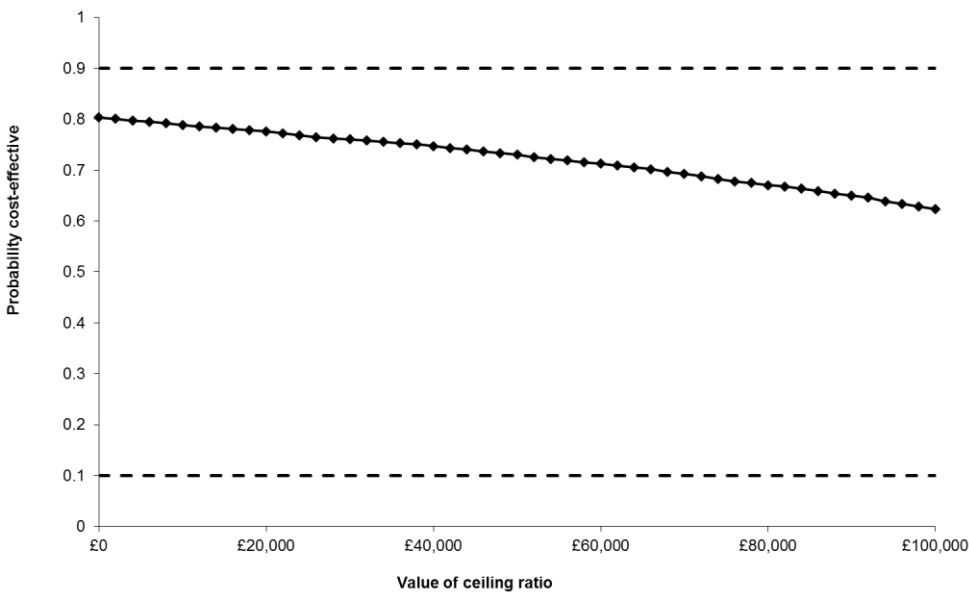
The cost-effectiveness plane for life-years (**Figure 1**) looks rather different compared to the plane for QALYs (**Figure 5.5**). In **Figure 1** many of the points are located in the bottom left quadrant of the plane (south-west quadrant), indicating that a restrictive threshold is most likely to be less effective and less costly than a liberal threshold. With the QALY analysis, most of the points on the plane were scattered around the origin showing very little difference. Compared to the cost-effectiveness plane for QALYs, the points on the cost-effectiveness plane for life-years have been pulled across to the left, as there is a clearer difference in effects, namely a reduction in the number of life-years gained in the restrictive group; the uncertainty around the difference in costs remains. In this analysis, the probability that the restrictive threshold is more effective than the liberal threshold is just 4% (not statistically significant). There is only a 4% probability that the restrictive threshold dominates the liberal threshold (i.e. is more effective and less costly), but a 19% probability of the reverse scenario, that the liberal threshold dominates the restrictive threshold.

Figure 1: Cost-effectiveness plane for life-years



The CEAC in **Figure 2** shows that if a decision-maker is willing to accept compensation of £20,000 for a life-year, then the probability that restrictive is cost-effective is 78%. As was the case for the CEAC for QALYs, there is much uncertainty around this finding. It is not possible to define 80% or even 50% confidence limits on cost-effectiveness across ceiling ratios from £0 to £100,000.

Figure 2: Cost-effectiveness acceptability curve for life-years



Appendix 24: Non-NHS costs – did these differ between trial groups?

The main non-NHS resource collected was patients' means of travel to hospital for readmissions or visits after discharge. Resource use for travel to hospital was compared between trial groups, to determine whether it differed between groups and therefore whether it was important to conduct a sensitivity analysis around this.

On the follow up questionnaire patients were asked to record how they travelled to hospital for each readmission, A&E visit, and outpatient appointment. The means of transport was recorded for 315 of the 418 readmissions recorded on the CRFs that were included in the costings, for 112 of the 144 A&E visits recorded and for 1,387 of the outpatient appointments recorded. These responses are shown in **Table 1**.

For readmissions to hospital approximately 50% of patients were taken by ambulance, the majority of other patients travelled at their own expense, most frequently being taken by a friend or relative by car. The proportion of patients travelling by each means is very similar between the trial groups. Relatively few A&E visits were recorded by patients, so while the proportion of participants travelling by different means looks to vary between the groups, the numbers are small. For outpatient appointments, 95% of patients travelled at private expense, the majority being taken by a friend or relative by car or driving themselves. The proportion of patients travelling by each means is very similar between the trial groups.

Means of transport to hospital did not appear to differ between the trial groups, therefore a sensitivity analysis taking a wider perspective was not conducted.

Table 1: Means of transport for hospital attendances post-discharge

Means of transport	Restrictive threshold	Liberal threshold	Restrictive versus liberal threshold
	Frequency (%)	Frequency (%)	% difference
Transport to readmission	n=153	n=162	
Ambulance	77 (50%)	79 (49%)	1%
Hospital provided transport	5 (3%)	8 (5%)	-2%
Hospital transport	4 (3%)	8 (5%)	-2%
Taxi (hospital paid)	1 (1%)	0 (0%)	1%
Transport at private expense	67 (44%)	75 (46%)	-2%
Friend/relative in car	62 (41%)	68 (42%)	-1%
Self-driven in car	2 (1%)	1 (1%)	0%
Taxi (self-paid)	3 (2%)	5 (3%)	-1%
Public transport	0 (0%)	1 (1%)	-1%
Other	4 (3%)¹	0 (0%)	3%
Transport to A&E	n=59	n=53	
Ambulance	24 (41%)	11 (21%)	20%
Hospital provided transport	1 (2%)	0 (0%)	2%
Hospital transport	1 (2%)	0 (0%)	2%
Taxi (hospital paid)	0 (0%)	0 (0%)	0%
Transport at private expense	34 (57%)	42 (79%)	-22%
Friend/relative in car	23 (39%)	34 (64%)	-25%
Self-driven in car	3 (5%)	6 (11%)	-6%
Taxi (self-paid)	3 (5%)	1 (2%)	3%
Public transport	5 (8%)	1 (2%)	6%
Transport to OP appointment	n=654	n=733	
Ambulance	4 (1%)	6 (1%)	0%
Hospital provided transport	19 (3%)	28 (4%)	-1%
Hospital transport	14 (2%)	22 (3%)	-1%
Taxi (hospital paid)	5 (1%)	6 (1%)	0%
Transport at private expense	624 (95%)	691 (94%)	1%
Friend/relative in car	395 (60%)	455 (62%)	-2%
Self-driven in car	141 (22%)	119 (16%)	6%
Taxi (self-paid)	24 (4%)	40 (5%)	-1%
Public transport	64 (10%)	77 (11%)	-1%
Other	7 (1%)²	8 (1%)³	0%

A&E, Accident and Emergency; OP, Outpatient

¹ 1 walked, 2 already at hospital, 1 charity

² 3 walked, 3 charity, 1 motorcycle

³ 5 walked, 2 charity, 1 hospital car

Appendix 25: Subgroup analysis results

The results of the seven subgroup analyses conducted to investigate whether cost-effectiveness results varied between patient subgroups are presented in **Table 1**. Comparing costs between subgroups as a whole, the findings are as expected: isolated CABG patients cost less than patients having other types of surgery; patients aged under 75 cost less than those aged over 75, and patients without each comorbidity before surgery cost less than those with the comorbidity (with the possible exception of pulmonary disease/asthma, but the numbers for this comorbidity were small).

The cost and QALY differences between the treatment groups within the subgroups are all small. When the impact of subgroups was evaluated using ordinary least squares regression separately for total costs and for QALYs, and considering interaction terms between treatment group and subgroup, no interaction terms were found to be significant.

Table 1: Costs, QALYs and cost-effectiveness results for each of the subgroups

	“Low risk” stratum							“High risk” stratum						
	Restrictive		Liberal		Restrictive vs Liberal			Restrictive		Liberal		Restrictive vs Liberal		
	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (95% CI)	Mean QALY difference (95% CI)	ICER	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (95% CI)	Mean QALY difference (95% CI)	ICER
1	Isolated CABG							Other operation types						
	£14771 (£366) n=408	0.1848 (0.0022)	£15409 (£418) n=408	0.1825 (0.0022)	-£638 (-£1728, 453)	0.0023 (-0.0038, 0.0085)	Restrictive dominant (-£273,070)	£20380 (£490) n=592	0.1772 (0.0020)	£20434 (£533) n=595	0.1788 (0.0020)	-£54 (£-1473, 1365)	-0.0016 (-0.0073, 0.0040)	£33,109
2	<75 years							≥75 years						
	£17296 (£373) n=714	0.1817 (0.0017)	£17507 (£447) n=680	0.1800 (0.0018)	-£211 (£1348, 925)	0.0017 (-0.0032, 0.0066)	Restrictive dominant (-£126,217)	£20079 (£711) n=286	0.1770 (0.0029)	£20249 (£636) n=323	0.1807 (0.0027)	-£170 (£-2033, 1693)	-0.0036 (-0.0115, 0.0042)	£46,711
3	No diabetes							Diet, oral medication or insulin controlled diabetes						
	£17501 (£356) n=802	0.1829 (0.0016)	£17970 (£375) n=802	0.1820 (0.0016)	-£469 (£-1483, 544)	0.0009 (-0.0036, 0.0053)	Restrictive dominant (-£528,226)	£20485 (£888) n=198	0.1700 (0.0038)	£20066 (£1052) n=201	0.1731 (0.0038)	£419 (£-2290, 3127)	-0.0031 (-0.0137, 0.0075)	Liberal dominant (-£134,521)
4	No lung disease							Chronic pulmonary disease or asthma						
	£17797 (£336) n=889	0.1833 (0.0016)	£18424 (£410) n=861	0.1810 (0.0016)	-£627 (£-1664, 410)	0.0023 (-0.0021, 0.0067)	Restrictive dominant (-£271,143)	£20451 (£1393) n=111	0.1584 (0.0046)	£18184 (£740) n=142	0.1745 (0.0042)	£2267 (£-664, 5197)	-0.0162 (-0.0284, -0.0039)	Liberal dominant (-£140,343)

	“Low risk” stratum							“High risk” stratum						
	Restrictive		Liberal		Restrictive vs Liberal			Restrictive		Liberal		Restrictive vs Liberal		
	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (95% CI)	Mean QALY difference (95% CI)	ICER	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (95% CI)	Mean QALY difference (95% CI)	ICER
5	eGFR >60ml/min							eGFR ≤60ml/min						
	£17472 (£385) n=715	0.1822 (0.0017)	£17482 (£408) n=698	0.1826 (0.0017)	£-10 (£-110, 1091)	-0.0004 (-0.0051, 0.0043)	£249,169	£19467 (£676) n=285	0.1757 (0.0031)	£20513 (£757) n=303	0.1746 (0.0030)	£-866 (£-2865, 1132)	0.0011 (-0.0074, 0.0096)	Restrictive dominant (-£774,782)
6	Males							Females						
	£18136 (£428) n=693	0.1839 (0.0018)	£18627 (£481) n=680	0.1830 (0.0018)	£-491 (£-1752, 769)	0.0009 (-0.0043, 0.0060)	Restrictive dominant (-£575,139)	£17992 (£527) n=307	0.1726 (0.0027)	£17891 (£528) n=323	0.1741 (0.0026)	£101 (£-1364, 1567)	-0.0015 (-0.0089, 0.0059)	Liberal dominant (-£67,205)
7	Good ventricular function							Moderate or poor ventricular function						
	£17812 (£378) n=787	0.1834 (0.0016)	£17830 (£415) n=771	0.1830 (0.0016)	£-18 (£-118, 1081)	0.0004 (-0.0040, 0.0048)	Restrictive dominant (-£48,537)	£19006 (£709) n=204	0.1707 (0.0038)	£20606 (£809) n=221	0.1713 (0.0038)	£-1600 (£-3727, 527)	0.0006 (-0.0112, 0.0100)	Restrictive dominant (-£2,755,940)

CABG, Coronary artery bypass grafting; CI, Confidence interval; eGFR, estimated Glomerular Filtration Rate; ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life-year; SE, Standard error

Appendix 26: COPTIC data collection forms

COPTIC STUDY DATA COLLECTION FORM

Patient Name: _____

COPTIC Screening No:

Theatre-CICU DATA COLLECTION

Time post op sample taken
(24 hr clock): :

Time admitted to CICU
(24 hr clock): :

Blood products given between post op sample collection and CICU admission

Please enter 0 if none

RBC Units

Platelets Units

Protamine doses

FFP Units

Cryoprecipitate Units

Comments:

CICU DATA COLLECTION

Chest tube drainage 6hr post CICU admission ml

12hr post CICU admission ml

Blood products given in CICU within the first 12 of admission

Please enter 0 if none

RBC Units

Platelets Units

Protamine doses

FFP Units

Cryoprecipitate Units

TEG used in theatre? Yes ☐ No ☐

TEG used in CICU ?
(first 12hrs post CICU admission) Yes ☐ No ☐

Name of person completing form (capitals): _____

Signature of person completing form: _____

Date completed: ____/____/____
d d m m y y y y

Name of person entering data* (capitals)

Date data entered (dd/mm/yyyy)

____/____/____

Version 0.1, 04/11/2010

*Names must appear on the site signature & delegation log

Appendix 27: Parameter estimates used to populate the COPTIC models

This appendix provides all the probabilities, costs, life-year and utility estimates used to populate the four base case models.

In all tables:

- ‘Treatment’ refers to protamine, platelets, clotting factors, five or more RBCs, and/or a re-operation for bleeding.
- ‘Complications’ refers to myocardial infarction, stroke, sepsis or acute kidney injury during the index hospital admission for cardiac surgery.
- ‘Group’ refers to the 12 groups of patients identified in **Figure 6.6**.

Table 1: Probabilities used to populate the base case model for TEG to one year

	Base-case value: Positive/ total	Distribution for PSA	Source
<u>Current Practice</u> Probability of ad hoc TEG	284/1802	Beta	Obs. study
<u>Current Practice, ad hoc TEG</u> Probability of ad hoc TEG positive	120/284	Beta	Obs. study
<u>Current Practice, ad hoc TEG positive</u> Probability POC test positive	13/120	Beta	Obs. study
Probability of CCB POC positive	10/13	Beta	Obs. study
Probability of treatment CCB	9/10	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	6/9	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	6/6	Beta	Obs. study
Probability alive at one year discharged	6/6	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	3/3	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	3/3	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	0/3	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	3/3	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	3/3	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	3/3	Beta	Obs. study
Probability of CCB POC negative	65/107	Beta	Obs. study
Probability of treatment CCB	59/65	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	26/59	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability discharged MI, stroke, sepsis or AKI	25/26	Beta	Obs. study
Probability alive at one year discharged	24/25	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	33/33	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	30/33	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/6	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	3/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of treatment no CCB	0/42	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	13/42	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	12/13	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	12/12	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	29/29	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	29/29	Beta	Obs. study
<u>Current Practice, ad hoc TEG negative</u>			
Probability POC test positive	0/164	Beta	Obs. study
Probability of CCB POC negative	89/164	Beta	Obs. study
Probability of treatment CCB	82/89	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	54/82	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	50/54	Beta	Obs. study
Probability alive at one year discharged	47/50	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	28/28	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	27/28	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	6/7	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability discharged MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	2/75	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	0/2	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	39/73	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	39/39	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	36/39	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
<u>Current Practice, no ad hoc TEG</u>			
Probability of POC positive	52/1518	Beta	Obs. study
Probability of CCB POC positive	15/52	Beta	Obs. study
Probability of treatment CCB	13/15	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	4/13	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability alive at one year discharged	4/4	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	9/9	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	9/9	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/2	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability of treatment no CCB	1/37	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged	1/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	13/36	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	13/13	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	13/13	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	23/23	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	23/23	Beta	Obs. study
Probability of CCB POC negative	254/1466	Beta	Obs. study
Probability of further treatment CCB	183/254	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	99/183	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	90/99	Beta	Obs. study
Probability alive at one year discharged	86/90	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	84/84	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	81/84	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	34/71	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	32/34	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	32/32	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	37/37	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	37/37	Beta	Obs. study
Probability of treatment no CCB	16/1212	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of MI, stroke, sepsis or AKI treatment	16/16	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	13/16	Beta	Obs. study
Probability alive at one year discharged	10/13	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	515/1196	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	508/515	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	492/508	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	678/681	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	673/678	Beta	Obs. study
<u>Test All for TEG</u>			
Probability of POC positive	65/1802	Beta	Obs. study
Probability of ad hoc TEG POC positive	13/65	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC positive	13/13	Beta	Obs. study
Probability of ad hoc TEG POC negative	271/1737	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC negative	107/271	Beta	Obs. study
Probability prophylactic treatment fails	154/449	Beta	Obs. study

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; MI, Myocardial infarction; Obs, Observational; POC, Point-of-care; PSA, Probabilistic sensitivity analysis

Table 2: Probabilities used to populate the base case model for ROTEM to one year

	Base-case value: Positive/ total	Distribution for PSA	Source
<u>Current Practice</u>			
Probability of ad hoc TEG	284/1802	Beta	Obs. study
<u>Current Practice, ad hoc TEG</u>			
Probability of ad hoc TEG positive	120/284	Beta	Obs. study
<u>Current Practice, ad hoc TEG positive</u>			
Probability POC test positive	21/120	Beta	Obs. study
Probability of CCB POC positive	14/21	Beta	Obs. study
Probability of treatment CCB	13/14	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	8/13	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	8/8	Beta	Obs. study
Probability alive at one year discharged	8/8	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	5/5	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	4/5	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	0/7	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	2/7	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	5/5	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	5/5	Beta	Obs. study
Probability of CCB POC negative	61/99	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of treatment CCB	55/61	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	24/55	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	23/24	Beta	Obs. study
Probability alive at one year discharged	22/23	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	31/31	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	29/31	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/6	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	3/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of treatment no CCB	0/38	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	14/38	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	13/14	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	13/13	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
<u>Current Practice, ad hoc TEG negative</u>			
Probability POC test positive	1/164	Beta	Obs. study
Probability of CCB POC positive	1/1	Beta	Obs. study
Probability of treatment CCB	1/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	0/1	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of CCB POC negative	88/163	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of treatment CCB	81/88	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	54/81	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	50/54	Beta	Obs. study
Probability alive at one year discharged	47/50	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	27/27	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	26/27	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	6/7	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	2/75	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	0/2	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	39/73	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	39/39	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	36/39	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
<u>Current Practice, no ad hoc TEG</u>			
Probability of POC positive	39/1518	Beta	Obs. study
Probability of CCB POC positive	15/39	Beta	Obs. study
Probability of treatment CCB	12/15	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of MI, stroke, sepsis or AKI treatment	11/12	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	8/11	Beta	Obs. study
Probability alive at one year discharged	8/8	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	0/3	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability of treatment no CCB	0/24	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	9/24	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	9/9	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	9/9	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	15/15	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	14/15	Beta	Obs. study
Probability of CCB POC negative	254/1479	Beta	Obs. study
Probability of further treatment CCB	184/254	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	92/184	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	86/92	Beta	Obs. study
Probability alive at one year discharged	82/86	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	92/92	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	89/92	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	35/70	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	33/35	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	33/33	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	35/35	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	35/35	Beta	Obs. study
Probability of treatment no CCB	17/1225	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	17/17	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	14/17	Beta	Obs. study
Probability alive at one year discharged	11/14	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	519/1208	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	512/519	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	496/512	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	686/689	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	682/686	Beta	Obs. study
<u>Test All for ROTEM</u>			
Probability of POC positive	61/1802	Beta	Obs. study
Probability of ad hoc TEG POC positive	22/61	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC positive	21/22	Beta	Obs. study
Probability of ad hoc TEG POC negative	262/1741	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC negative	99/262	Beta	Obs. study
Probability prophylactic treatment fails	154/449	Beta	Obs. study

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; MI, Myocardial infarction; Obs, Observational; POC, Point-of-care; PSA, Probabilistic sensitivity analysis

Table 3: Probabilities used to populate the base case model for TEG / Multiplate to one year

	Base-case value: Positive/ total	Distribution for PSA	Source
<u>Current Practice</u> Probability of ad hoc TEG	284/1802	Beta	Obs. study
<u>Current Practice, ad hoc TEG</u> Probability of ad hoc TEG positive	120/284	Beta	Obs. study
<u>Current Practice, ad hoc TEG positive</u> Probability POC test positive	16/120	Beta	Obs. study
Probability of CCB POC positive	12/16	Beta	Obs. study
Probability of treatment CCB	11/12	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	7/11	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	7/7	Beta	Obs. study
Probability alive at one year discharged	7/7	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	0/4	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/4	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability of CCB POC negative	63/104	Beta	Obs. study
Probability of treatment CCB	57/63	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	25/57	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability discharged MI, stroke, sepsis or AKI	24/25	Beta	Obs. study
Probability alive at one year discharged	23/24	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	32/32	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	29/32	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/6	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	3/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of treatment no CCB	0/38	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	14/38	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	13/14	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	13/13	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
<u>Current Practice, ad hoc TEG negative</u>			
Probability POC test positive	2/164	Beta	Obs. study
Probability of CCB POC positive	2/2	Beta	Obs. study
Probability of treatment CCB	2/2	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	1/2	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	0/1	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of CCB POC negative	87/162	Beta	Obs. study
Probability of treatment CCB	80/87	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of MI, stroke, sepsis or AKI treatment	53/80	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	50/53	Beta	Obs. study
Probability alive at one year discharged	47/50	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	27/27	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	26/27	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	6/7	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	2/75	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	0/2	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	39/73	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	39/39	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	36/39	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
<u>Current Practice, no ad hoc TEG</u>			
Probability of POC positive	73/1518	Beta	Obs. study
Probability of CCB POC positive	20/73	Beta	Obs. study
Probability of treatment CCB	17/20	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	8/17	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability discharged MI, stroke, sepsis or AKI	8/8	Beta	Obs. study
Probability alive at one year discharged	8/8	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	9/9	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	9/9	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/3	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged	1/1	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability of treatment no CCB	2/53	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	2/2	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/2	Beta	Obs. study
Probability alive at one year discharged	1/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	18/51	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	18/18	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	18/18	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	33/33	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	33/33	Beta	Obs. study
Probability of CCB POC negative	249/1445	Beta	Obs. study
Probability of further treatment CCB	179/249	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	95/179	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	86/95	Beta	Obs. study
Probability alive at one year discharged	82/86	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	84/84	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	81/84	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of MI, stroke, sepsis or AKI no treatment	34/70	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	32/34	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	32/32	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	36/36	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	36/36	Beta	Obs. study
Probability of treatment no CCB	15/1196	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	15/15	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	13/15	Beta	Obs. study
Probability alive at one year discharged	10/13	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	510/1181	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	503/510	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	487/503	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	668/671	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	663/668	Beta	Obs. study
<u>Test All for TEG / Multiplate</u>			
Probability of POC positive	91/1802	Beta	Obs. study
Probability of ad hoc TEG POC positive	18/91	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC positive	16/18	Beta	Obs. study
Probability of ad hoc TEG POC negative	266/1711	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC negative	104/266	Beta	Obs. study
Probability prophylactic treatment fails	154/449	Beta	Obs. study

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; MI, Myocardial infarction; Obs, Observational; POC, Point-of-care; PSA, Probabilistic sensitivity analysis

Table 4: Probabilities used to populate the base case model for ROTEM / Multiplate to one year

	Base-case value: Positive/ total	Distribution for PSA	Source
<u>Current Practice</u> Probability of ad hoc TEG	284/1802	Beta	Obs. study
<u>Current Practice, ad hoc TEG</u> Probability of ad hoc TEG positive	120/284	Beta	Obs. study
<u>Current Practice, ad hoc TEG positive</u> Probability POC test positive	25/120	Beta	Obs. study
Probability of CCB POC positive	16/25	Beta	Obs. study
Probability of treatment CCB	15/16	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	9/15	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	9/9	Beta	Obs. study
Probability alive at one year discharged	9/9	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	6/6	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	5/6	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	0/9	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/9	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI	4/4	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	5/5	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	5/5	Beta	Obs. study
Probability of CCB POC negative	59/95	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of treatment CCB	53/59	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	23/53	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	22/23	Beta	Obs. study
Probability alive at one year discharged	21/22	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	30/30	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	28/30	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	4/6	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	3/4	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	3/3	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of treatment no CCB	0/36	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	12/36	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	11/12	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	11/11	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	24/24	Beta	Obs. study
<u>Current Practice, ad hoc TEG negative</u>			
Probability POC test positive	3/164	Beta	Obs. study
Probability of CCB POC positive	3/3	Beta	Obs. study
Probability of treatment CCB	3/3	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	1/3	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	0/1	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of CCB POC negative	86/161	Beta	Obs. study
Probability of treatment CCB	79/86	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	53/79	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	50/53	Beta	Obs. study
Probability alive at one year discharged	47/50	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	26/26	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	25/26	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	6/7	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	6/6	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of treatment no CCB	2/75	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	0/2	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	2/2	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	39/73	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	39/39	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	36/39	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
<u>Current Practice, no ad hoc TEG</u>			
Probability of POC positive	61/1518	Beta	Obs. study
Probability of CCB POC positive	20/61	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability of treatment CCB	16/20	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	15/16	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	12/15	Beta	Obs. study
Probability alive at one year discharged	12/12	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	1/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	0/4	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	4/4	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	4/4	Beta	Obs. study
Probability of treatment no CCB	1/41	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	1/1	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	0/1	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	14/40	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	14/14	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	14/14	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	26/26	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	25/26	Beta	Obs. study
Probability of CCB POC negative	249/1457	Beta	Obs. study
Probability of further treatment CCB	180/249	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	88/180	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	82/88	Beta	Obs. study
Probability alive at one year discharged	78/82	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI	92/92	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI	89/92	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	35/69	Beta	Obs. study

	Base-case value: Positive/ total	Distribution for PSA	Source
Probability discharged MI, stroke, sepsis or AKI, no treatment	33/35	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	33/33	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	34/34	Beta	Obs. study
Probability of treatment no CCB	16/1208	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI treatment	16/16	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI	14/16	Beta	Obs. study
Probability alive at one year discharged	11/14	Beta	Obs. study
Probability of MI, stroke, sepsis or AKI no treatment	514/1192	Beta	Obs. study
Probability discharged MI, stroke, sepsis or AKI, no treatment	507/514	Beta	Obs. study
Probability alive at one year discharged, MI, stroke, sepsis or AKI, no treatment	491/507	Beta	Obs. study
Probability discharged no MI, stroke, sepsis or AKI, no treatment	675/678	Beta	Obs. study
Probability alive at one year discharged, no MI, stroke, sepsis or AKI, no treatment	671/675	Beta	Obs. study
<u>Test All for ROTEM / Multiplate</u>			
Probability of POC positive	89/1802	Beta	Obs. study
Probability of ad hoc TEG POC positive	28/89	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC positive	25/28	Beta	Obs. study
Probability of ad hoc TEG POC negative	256/1713	Beta	Obs. study
Probability of ad hoc TEG positive ad hoc TEG, POC negative	95/256	Beta	Obs. study
Probability prophylactic treatment fails	154/449	Beta	Obs. study

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; MI, Myocardial infarction; Obs, Observational; POC, Point-of-care; PSA, Probabilistic sensitivity analysis

Table 5: Pooled costs to hospital discharge used to populate the base case model for TEG to hospital discharge

Treatment	Complications	Died before discharge	n	Groups	Cost - £ Mean (Standard error)	Distribution for PSA	Source
No	No	No	805	3,7,8,9,10,11,12 4	4052 (72) 4896 (654)	Gamma Gamma	Obs. study Obs. study
			776				
			29				
No	No	Yes	3	All (12)	3370 (1345)	Gamma	Obs. study
No	Yes	No	618	1,2,3,4,7,9,10,11,12 8	5877 (169) 8576 (1026)	Gamma Gamma	Obs. study Obs. study
			579				
			39				
No	Yes	Yes	11	All (3,4,11,12)	6889 (1702)	Gamma	Obs. study
Yes	No	No	159	9,11 1,3,7,8	5179 (265) 8117 (555)	Gamma Gamma	Obs. study Obs. study
			93				
			66				
Yes	No	Yes	0				
Yes	Yes	No	189	1,3,7,9,11 10,12	10775 (617) 27096 (4138)	Gamma Gamma	Obs. study Obs. study
			175				
			14				
Yes	Yes	Yes	17	All (3,7,11,12)	22548 (3835)	Gamma	Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Table 6: Pooled costs to hospital discharge used to populate the base case model for ROTEM to hospital discharge

Treatment	Complications	Died discharge	n	Groups	Cost - £ Mean (Standard error)	Distribution for PSA	Source
No	No	No	805 781 24	2,3,7,8,9,10,11,12 4	4053 (71) 5037 (778)	Gamma Gamma	Obs. study Obs. study
No	No	Yes	3	All (12)	3370 (1345)	Gamma	Obs. study
No	Yes	No	618 579 39	1,2,3,4,7,10,11,12 8	5877 (169) 8576 (1026)	Gamma Gamma	Obs. study Obs. study
No	Yes	Yes	11	All (3,4,11,12)	6889 (1702)	Gamma	Obs. study
Yes	No	No	159 93 66	9,11 1,3,5,7,8	5179 (265) 8117 (555)	Gamma Gamma	Obs. study Obs. study
Yes	No	Yes	0				
Yes	Yes	No	189 152 23 14	1,7,9,11 3 12	10050 (597) 15568 (2341) 27096 (4138)	Gamma Gamma Gamma	Obs. study Obs. study Obs. study
Yes	Yes	Yes	17 11 6	3,7,9,12 11	18347 (3371) 30249 (8564)	Gamma Gamma	Obs. study Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Table 7: Pooled costs to hospital discharge used to populate the base case model for TEG / Multiplate to hospital discharge

Treatment	Complications	Died discharge	n	Groups	Cost - £ Mean (Standard error)	Distribution for PSA	Source
No	No	No	805	3,7,8,9,10,11,12 4	4052 (72) 4896 (654)	Gamma Gamma	Obs. study Obs. study
			776				
			29				
No	No	Yes	3	All (12)	3370 (1345)	Gamma	Obs. study
No	Yes	No	618	1,2,3,4,7,9,10,11,12 8	5877 (169) 8576 (1026)	Gamma Gamma	Obs. study Obs. study
			579				
			39				
No	Yes	Yes	11	All (3,4,11,12)	6889 (1702)	Gamma	Obs. study
Yes	No	No	159	9,11 1,3,5,7,8	5179 (265) 8117 (555)	Gamma Gamma	Obs. study Obs. study
			93				
			66				
Yes	No	Yes	0				
Yes	Yes	No	189	1,3,7,9,11 10,12	10775 (617) 27096 (4138)	Gamma Gamma	Obs. study Obs. study
			175				
			14				
Yes	Yes	Yes	17	All (3,5,7,10,11,12)	22548 (3835)	Gamma	Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Table 8: Pooled costs to hospital discharge used to populate the base case model for ROTEM / Multiplate to hospital discharge

Treatment	Complications	Died discharge	n	Groups	Cost - £ Mean (Standard error)	Distribution for PSA	Source
No	No	No	805 781 24	2,3,7,8,9,10,11,12 4	4053 (71) 5037 (778)	Gamma Gamma	Obs. study Obs. study
No	No	Yes	3	All (12)	3370 (1345)	Gamma	Obs. study
No	Yes	No	618 579 39	1,2,3,4,7,10,11,12 8	5877 (169) 8576 (1026)	Gamma Gamma	Obs. study Obs. study
No	Yes	Yes	11	All (3,4,11,12)	6889 (1702)	Gamma	Obs. study
Yes	No	No	159 93 56 10	9,11 3,7 1,5,8	5179 (265) 7352 (532) 12401 (1617)	Gamma Gamma Gamma	Obs. study Obs. study Obs. study
Yes	No	Yes	0				
Yes	Yes	No	189 153 22 14	1,7,9,11 3 12	10073 (594) 15656 (2448) 27096 (4138)	Gamma Gamma Gamma	Obs. study Obs. study Obs. study
Yes	Yes	Yes	17	All (3,5,7,9,10,11,12)	22548 (3835)	Gamma	Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Table 9: Costs beyond hospital discharge for use in all models

	Cost (£)	Source
<u>Healthcare costs after hospital discharge to one year</u>		
For all patients alive at one year	2116	See Appendix 32
For all patients who died between hospital discharge and one year	922	See Appendix 32
Additional cost for those with in-hospital complications, and alive at one year	92	See Appendix 32
Additional cost for those with in-hospital complications, and died by one year	35	See Appendix 32
<u>Healthcare costs after one year</u>		
Annual healthcare cost per patient	2173	See Appendix 33
Additional annual cost for patients who had in-hospital complications	99	See Appendix 33

Table 10: Costs of the ad hoc TEG and POC tests, and associated prophylactic treatment

Cost of the tests	Cost - £	Source	
Ad hoc TEG	64	Capital and consumable costs for TEG and ROTEM came from a published source,[165] and were provided by Roche for Multiplate. Cost calculations are described in more detail in Chapter 6.	
TEG	37		
ROTEM	32		
TEG/ Multiplate	48		
ROTEM/ Multiplate	43		
Cost of prophylactic treatment if POC test positive	Cost - £ Mean (Standard error)	Distribution for PSA	Source
TEG	224 (19)	Gamma	Obs. study
ROTEM	406 (21)	Gamma	Obs. study
TEG/ Multiplate	160 (9)	Gamma	Obs. study
ROTEM/ Multiplate	362 (16)	Gamma	Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Life-years for the base case models

All patients alive at one year (known in the observational study), accrue one life-year. For patients who die, **Table 11** summarises the life-years used in the base case models. Although patients may be in different groups in each of the models, in each case all groups could be combined for each combination of treatment/ complication and timing of death, and therefore the estimates used in each of the models are the same. For those alive at one year, **Appendix 33** describes how survival in subsequent years was estimated using life tables with additional decrements from the literature.

Table 11: Pooled life-years to one year for those who die for all base case models

Treatment	Complications	Died before discharge	Died at one year	n	Groups	Life-years: Mean (Standard error)	Distribution for PSA	Source
No	No	Yes	-	3	All	0.016 (0.007)	Beta	Obs. study
No	Yes	Yes	-	11	All	0.013 (0.005)	Beta	Obs. study
Yes	No	Yes	-	0				
Yes	Yes	Yes	-	17	All	0.060 (0.014)	Beta	Obs. study
No	No	No	Yes	5	All	0.516 (0.172)	Beta	Obs. study
No	Yes	No	Yes	19	All	0.382 (0.060)	Beta	Obs. study
Yes	No	No	Yes	7	All	0.658 (0.082)	Beta	Obs. study
Yes	Yes	No	Yes	11	All	0.488 (0.093)	Beta	Obs. study

Obs, Observational; PSA, Probabilistic sensitivity analysis

Utility weights used to quality-adjust life-years

Utility weights for the health states ‘with complications’ and ‘without complications’ were sought from the CEA Registry at Tufts University.[166] As the most frequent complication was acute kidney injury, utility weights for this complication only were sought (in line with the way survival was estimated beyond one year). The Registry was searched for utility weights using the terms ‘cardiac surgery’, and ‘acute kidney injury’. The original papers were sought to identify measures of variability about the weights provided in the Registry. **Table 12** shows the utility weights that were used in the models. For patients with complications, the utility weight for acute kidney injury of 0.69 was used through their time in the model.[212] For the first year for patients without complications and who were alive at one year, a weighted average of the utilities at baseline, one, six, and 12 months after cardiac surgery was used.[213] For patients without complications who died in the first year, an average of the utilities at baseline and one month was applied to those who died in hospital, and a weighted average of baseline, one and six months was applied to those who died between hospital discharge and one year. Beyond one year, patients without complications accrued a utility of 0.85 (listed in the table as utility three years after cardiac surgery).[213]

Table 12: Utility weights

Timing	Mean (Standard error)	Distribution for PSA
Utility at baseline after cardiac surgery	0.741 (0.191)	Beta
Utility one month after cardiac surgery	0.769 (0.171)	Beta
Utility six months after cardiac surgery	0.847 (0.153)	Beta
Utility one year after cardiac surgery	0.850 (0.158)	Beta
Utility three years after cardiac surgery	0.850 (0.161)	Beta
Utility associated with acute kidney injury	0.69 (0.15)	Beta

Appendix 28: Criteria for positive POC test results and treatments indicated

This appendix describes the criteria used to indicate positive POC test results and what treatments are assumed to be given as a result.

TEG base case criteria for a positive test result

If any of the criteria in the list below were met, a patient was considered to have a positive TEG test result in the base case analysis. In terms of treatment a patient was assumed to receive as a result of a positive test: criterion 1 was considered first and if this indicated a patient required protamine, it was assumed that they were given 50mg of protamine and that this resolved their problem, and was all that was needed. If the test did not suggest a patient required protamine, then criteria 2-5 were considered, and all treatments indicated were given.

Criteria for a positive TEG test result

1. If CK R (min) : CKH R (min) > 1.5 and if CK R (min) > 10, give protamine.
2. If CK R (min) > 10, give FFP.
3. If CK α -Angle < 37.6, give FFP and platelets.
4. If CK MA < 44, give FFP and platelets.
5. If CK LY60 > 18.75, give tranexamic acid.

where CK: citrated kaolin; CKH: citrated kaolin with heparinise; R (min): reaction time (in minutes) to initial fibrin formation; α -Angle: measures the speed of fibrin build-up; MA: maximum amplitude of the fibrin clot; LY60: percent lysis 60 minutes after MA (percentage decrease in clot amplitude).

TEG results from the COPTIC study classified 3.6% (65/1802) of the cohort as having a positive test result. The criteria for determining positive ad hoc TEG test results and positive POC test results under a 'Test All' strategy were different. Ad hoc TEGs are likely to have been given to patients who clinicians were concerned about, clinical opinion in the study research team was that these test results would be interpreted less conservatively than routine tests for all patients, many of whom give clinicians no cause for concern.

ROTEM base case criteria for a positive test result

The list below describes the criteria for a positive ROTEM test result in the base case analysis, together with the treatments indicated. As for TEG, if protamine was indicated,

then it was assumed that no further treatment was required. If protamine was not required, then the other ROTEM criteria (2-5) were considered in their entirety, and any treatments indicated would have been given.

Criteria for a positive ROTEM test result

1. If INTEM CT > 300s and HEPTTEM CT / INTEM CT < 0.64, give protamine.
2. If EXTEM CT > 100s or HEPTTEM CT > 300s, give FFP.
3. If EXTEM A10 $\leq$ 32mm and FIBTEM A10 < 8 mm, give cryoprecipitate.
4. If EXTEM A10 $\leq$ 32mm and FIBTEM A10 $\geq$ 8mm, give FFP and platelets.
5. If FIBTEM A10 < 5.6 or FIBTEM MCF < 7.2, give cryoprecipitate.

where CT: clotting time; A10: amplitude of clot firmness 10 minutes after CT; and MCF: maximum clot firmness.

Note that while TEG and ROTEM are being considered as alternatives, and EXTEM A10 is in some ways comparable to the α -Angle or MA in TEG, ROTEM has the ability to discriminate between giving FFP and platelets versus cryoprecipitate using the FIBTEM values; there is not an equivalent to this available in TEG. ROTEM results from the COPTIC study classified 3.4% (61/1802) of the cohort as having a positive test result.

TEG / ROTEM in combination with Multiplate base case criteria for a positive test result

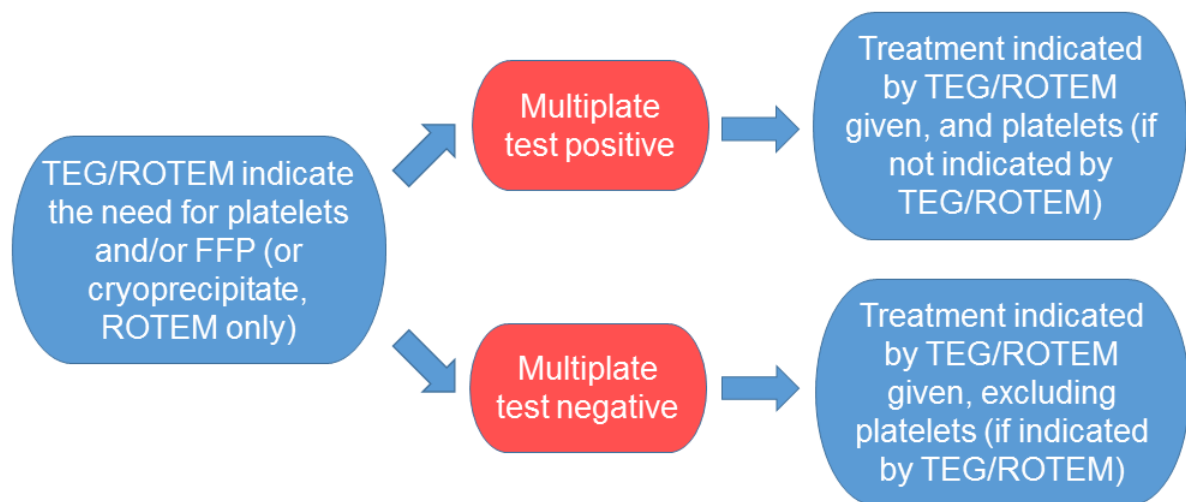
The following criteria were considered to indicate a positive Multiplate test result:

If AUC TRAP test < 50, or AUC ASPI test < 30, or AUC ADP test < 30; give platelets.

where AUC: area under the curve.

If any of the TEG/ROTEM or Multiplate criteria were met, then the combined test result was considered positive. In terms of treatment, if Multiplate was introduced alongside TEG or ROTEM, it was assumed that if the TEG or ROTEM test indicated the need for protamine, then that was all that was required and the Multiplate test result was not used. If the TEG or ROTEM test did not indicate the need for protamine, then the Multiplate criteria were considered alongside the other TEG/ROTEM criteria, as shown in **Figure 1**.

Figure 1: Treatments indicated based on TEG/ROTEM in combination with Multiplate



If Multiplate indicated the need for platelets (even if TEG/ROTEM did not) then platelets would be given alongside any other treatments indicated by TEG/ROTEM, since Multiplate would be considered more sensitive for platelet defects. If the reverse were true, and TEG/ROTEM indicated the need for platelets, but Multiplate did not, platelets were assumed not to be given. This is really the added benefit of Multiplate in practice; if abnormal TEG/ROTEM parameters indicated the need for FFP and platelets, but Multiplate was normal, it was assumed that a patient would just be given FFP, and that unnecessary treatment would have been avoided.

Test results from the COPTIC study classified 5.0% (91/1802) of the cohort as having a positive test result according to TEG and Multiplate combined, and 4.9% (89/1802) as having a positive test result according to ROTEM and Multiplate combined.

Appendix 29: Average resource use per patient in the COPTIC study

The 16 patients who had a positive ad hoc TEG and were deemed to have had successful prophylactic treatment are classed as No CCB here.

Resource / complication	All patients (n=1802)	Patients with CCB (n=433)	Patients with no CCB (n=1369)	Patients with CCB versus patients with no CCB
	Frequency (%) or Mean (SE)	Frequency (%) or Mean (SE)	Frequency (%) or Mean (SE)	% or Mean difference (95% CI)
Blood products - units/ patient				
Red blood cells	0.73 (0.04)	1.70 (0.08)	0.42 (0.05)	1.28 (1.09, 1.46)
Platelets	0.26 (0.16)	1.03 (0.02)	0.02 (0.01)	1.00 (0.95, 1.06)
Fresh frozen plasma	0.22 (0.02)	0.86 (0.03)	0.01 (0.02)	0.85 (0.78, 0.92)
Cryoprecipitate	0.01 (0.00)	0.04 (0.00)	0.00 (0.00)	0.04 (0.03, 0.06)
Length of stay – days/ patient				
Time on CICU	0.69 (0.03)	0.95 (0.07)	0.60 (0.04)	0.35 (0.20, 0.51)
Time on HDU	3.82 (0.12)	4.80 (0.24)	3.52 (0.13)	1.28 (0.75, 1.82)
Time on ward	5.05 (0.12)	5.41 (0.24)	4.94 (0.13)	0.47 (-0.06, 1.00)
Complications / additional treatments – number (%) of patients				
Protamine	121 (7%)	118 (27%)	3 (0%)	27%
rFVIIa	5 (0%)	5 (1%)	0 (0%)	1%
Re-operations	86 (5%)	65 (15%)	21 (2%)	13%
AKI stage III	122 (7%)	49 (11%)	73 (5%)	6%
Myocardial infarction	18 (1%)	4 (1%)	14 (1%)	0%
Stroke	18 (1%)	8 (2%)	10 (1%)	1%
Sepsis	100 (6%)	34 (8%)	66 (5%)	3%
IABP	5 (0%)	4 (1%)	1 (0%)	1%

AKI, Acute kidney injury; CCB, Clinical concern about bleeding; CI, Confidence interval; CICU, Cardiac intensive care unit; HDU, High dependency unit; IABP, Intra-aortic balloon pump; rFVIIa, Recombinant activated factor VII; SE, Standard error

Appendix 30: Unit costs used to value resource use in the observational study

Table 1: Unit costs

Resource	Unit cost* (£)	Reference
Blood products		
Red blood cells	122.09	NHSBT Price List 2013/14[179]
Fresh frozen plasma	27.98	NHSBT Price List 2013/14[179]
Platelets	208.09	NHSBT Price List 2013/14[179]
Cryoprecipitate	193.53	NHSBT Price List 2013/14[179]
Red blood cell administration	48.09	Costs estimated in Chapter 4, and presented in Table 4.14 , deflated to 2013/14 prices.
Fresh frozen plasma administration	37.65	Costs estimated in Chapter 4, and presented in Table 4.14 , deflated to 2013/14 prices.
Platelets administration	57.35	Costs estimated in Chapter 4, and presented in Table 4.14 , deflated to 2013/14 prices.
Cryoprecipitate administration	48.81	Costs estimated in Chapter 4, and presented in Table 4.14 , deflated to 2013/14 prices.
Excess nursing cost associated with group and screens for multiple units transfused	7.85	Costs estimated in Chapter 4, and deflated to 2013/14 prices. Methods for adjusting costs described in Section 4.6.
Inpatient stay		
Cardiac intensive care unit day	1203	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (weighted average of XC01Z - XC06Z, 1-6 organs supported).
High dependency unit day	626	NHS Reference Costs 2012/13.[138] Critical Care Services - Adult: Critical Care Unit (XC07Z, 0 organs supported).
Cardiac ward day	396	NHS Reference Costs 2012/13.[138] Weighted average of elective inpatient excess bed day costs for relevant HRGs (EA14, EA16, EA17, EA19, EA20, EA22, EA51, EA52, EC01, EC02, EC03 excluding any service codes for paediatrics).
Additional treatments		
Protamine (50mg)	2.38	eMIT[140]
Activated Factor VII (5mg intravenously)	2514.30	Oxford University Hospitals NHS Foundation Trust, 2013
Reoperation	8390	NHS Reference Costs 2012/13.[138] Elective inpatients. HRG code EA20 for service codes 170 (Cardiothoracic surgery) and 172 (Cardiac surgery). For each code, the costs associated with the average LOS reported were subtracted at a cost of £392 per day (cardiac ward day cost above before inflation to 2013/14 prices), and £1421 was subtracted for blood products based on data from an audit of blood transfusion in cardiac surgery.[93] An average cost for the codes was then generated, weighted by activity.
Intra-aortic balloon pump	2807	NICE Medical technology guidance 8.[207]

HRG, Healthcare resource group; LOS, Length of stay; NHSBT, NHS Blood and Transplant; NICE, National Institute for Health and Care Excellence

*Unit costs not in 2013/2014 prices have been inflated to 2013/2014 prices using the hospital and community health services inflation index.[105]

Table 2: Resource use assumed for complications and costs

Complication	Treatment/action assumed	Cost* (£)	Reference
Sepsis	Antibiotics (piperacillin/tazobactam, 4.5g IV 3xday for 5 days)	28.72	eMIT[140]
Permanent stroke	Rehabilitation	141	NHS Reference Costs 2012/13.[138] Elective inpatients. DZ30Z Chest Physiotherapy. 340 Respiratory Medicine.
	CT scan	63	NHS Reference Costs 2012/13.[138] Diagnostic Imaging - Direct Access. RA08A Computerised Tomography Scan, one area, no contrast, 19 years and over. 100 General surgery.
	Total	204	
Suspected myocardial infarction	Emergency angiography	1713	NHS Reference Costs 2012/13.[138]
	Transthoracic echo	122	NHS Reference Costs 2012/13.[138] Diagnostic Imaging – Outpatients. RA60A Simple Echocardiogram, 19 years and over. 172 Cardiac Surgery
	ECG	54	NHS Reference Costs 2012/13.[138] Directly Accessed Diagnostic Services. EA47Z Electrocardiogram Monitoring and stress testing.
	Total	1889	
Acute kidney injury - stage 3 only	Haemofiltration (treatment for 2 days)	1454	NHS Reference Costs 2012/13.[138] Renal Dialysis at Base. LE01A. Haemodialysis for Acute Kidney Injury, 19 years and over.

CT, Computed tomography; ECG, Electrocardiography; eMIT, electronic Marketing Information Tool; IV, Intravenous

*Unit costs not in 2013/2014 prices have been inflated to 2013/2014 prices using the hospital and community health services inflation index.[105]

Appendix 31: Populating the model with observed healthcare costs to hospital discharge

This appendix describes how the observed healthcare costs for patients in the COPTIC study were used to populate the model with healthcare costs to hospital discharge. Regression analysis was used to pool patients whose costs were not statistically significantly different, across individual pathways in the model to generate the cost inputs required.

In **Figure 6.6**, 12 groups of patients were identified, based on their ad hoc test and POC test results, six with CCB and six without CCB. These 12 groups of patients are then divided into whether they had treatment in the form of protamine, platelets, clotting factors, five or more units of RBCs or a reoperation, whether they developed complications and whether they were alive at hospital discharge. For each of the eight different combinations of treatment/ no treatment, complications/ no complications, and alive at discharge/ died in hospital, regression was used to determine whether the costs to discharge were similar across some or all of the 12 groups of patients, and for which groups costs could be pooled.

Initially ordinary least squares (OLS) regression was conducted, with healthcare costs as the dependent variable and dummy variables included for 11 of the 12 groups of patients (**Figure 6.6**). Group 12, patients with no ad hoc test, and a negative POC test was taken as the base group, since this was the largest group of patients. Any of groups 1-11 were considered suitable to be pooled with group 12 if their coefficient was not statistically significantly different from group 12. If several groups were significantly different to group 12, Wald tests (which test the significance of particular explanatory variables, in this case dummy variables for groups) were conducted to determine whether these groups could be combined.

Since the cost data were skewed, alternatives to OLS regression (and the Normal distribution) were considered. A gamma distribution is positively skewed and often fits cost data well; a generalised linear model (GLM) with a gamma family, and a log link was also conducted. Since the results from the OLS and GLM models were not always identical, a modified Parks test was conducted for each regression to determine the most appropriate family,[214] and a Box Cox test was performed to determine the most appropriate link function.[215] Results from the GLM with the most appropriate family and link function were

used to determine which groups could be combined. Generally many groups could be combined, and only one or two pooled cost estimates were required for each of the eight different combinations of treatment, complications, and outcome at discharge, thus successfully increasing the sample size for each cost estimate. All cost estimates used in the models are reported in **Appendix 27 (Tables 5-8)**.

Appendix 32: Healthcare costs from hospital discharge to one year

Healthcare costs from hospital discharge to one year were based on the Office of Health Economics estimate of the annual cost per person of NHS care inflated to 2013/14 prices using the hospital and community health services inflation index, multiplied by the proportion of the first year that was not part of the index admission (based on the average length of stay of patients alive at one year).[105, 216] All patients who survived to one year after their surgery were assumed to incur healthcare costs of £2116 between hospital discharge and one year. Patients who died in the first year were assumed to incur healthcare costs of £922 after hospital discharge, based on the same annual cost, and the average proportion of one year for which they were alive and which was not part of the index admission.

For patients who had complications during their index admission, an additional cost was assigned between hospital discharge and one year. MI and stroke were assumed to be associated with continuing care costs. These annual costs were taken from Greenhalgh *et al.* (2011),[217] and inflated to 2013/14 prices. Separate costs were provided for disabling and non-disabling stroke; according to Davies *et al.* (2006) 58% of strokes are disabling,[148] and this percentage was used to weight the two continuing care costs for stroke. An annual cost associated with complications was calculated by weighting estimates of the annual costs of MI and stroke by the number of patients alive at hospital discharge with these complications across the number of patients alive at discharge with any complications. Costs associated with complications between hospital discharge and one year were then calculated separately for patients alive at one year and for those who had died by one year, based on the proportion of the year for which they were alive and not in hospital for the index admission. Continuing care costs across all patients with complications were estimated to be £92 for patients alive at one year, and £35 for patients who had died by one year.

Appendix 33: Populating the model beyond one year

This appendix describes the methods for extrapolating survival to a longer time horizon and the calculation of annual healthcare costs.

Survival beyond one year

Age and gender adjusted population life tables need to be adjusted to account for the increased risk of death in patients who have had cardiac surgery compared to the general population.[167] A further adjustment is required for patients who experienced complications, since these patients are known to be at an increased risk of death compared to patients without complications.

Adjusting for increased mortality after cardiac surgery

Data on the proportion of patients surviving each year after cardiac surgery from the National Adult Cardiac Surgery Audit (NACSA) were used to adjust for the increased risk of mortality after cardiac surgery compared to the general population.[85] Using the separate survival curves for CABG, mitral valve and aortic valve surgery available on the audit website, the proportion of patients surviving each year after surgery (up to 12 years) was read off the graphs. A weighted average of the proportion of patients surviving each year after surgery was calculated for all cardiac surgery, based on the proportion of the different types of surgery included in the audit.

To estimate the additional risk of mortality associated with having had cardiac surgery, the odds of dying each year after surgery were calculated for the NACSA population and for an age and gender matched population from life tables. The odds ratio (OR) of the increased odds of dying in the cardiac surgery population compared to the general population was then calculated for each subsequent year after surgery. The OR was estimated to be 3.0 in the second year after surgery, and it gradually reduced to 2.2 by five years after surgery (the OR for the first year after surgery was not required, since survival to one year was available for patients in the observational study). These ORs were used to adjust the life table estimates for the increased risk of mortality after cardiac surgery for all patients in the model; life table probabilities were converted to odds to be adjusted, and then converted back to probabilities.

It is recognised that this is likely to underestimate survival slightly for patients without complications, since the NACSA data includes patients with and without complications. However this underestimation will affect both the Current Practice arm of the model and the Test All arm, so should not affect the differences between treatment options.

Adjusting for increased mortality with complications after cardiac surgery

A second adjustment to survival is required for patients who experienced complications. Of the 777 patients alive at one year who experienced complications during their index admission, 749 had AKI (of whom 543 had stage 1, 113 had stage 2 and 93 had stage 3 according to AKI Network criteria for AKI),[218] 83 had sepsis, 17 had a stroke and 15 had an MI (these are not mutually exclusive events). As the figures are dominated by AKI, rather than adjusting mortality for a number of different complications, mortality was adjusted for AKI only.

As individual patient data are available on survival to one year, it is important that estimates of increased mortality in patients with AKI (compared to those without AKI) from other sources do not include mortality in the first year after surgery along with longer term mortality, otherwise mortality in the first year will be double counted. In a review of long-term outcomes after AKI, Sawhney *et al.* (2015) identify two papers which compare mortality with and without AKI and look at the timing of outcomes.[219] Of the two papers reported, one is not specific to cardiac surgery,[220] but the other reports hazard ratios for mortality from 12, 24, 36 and 60 months after cardiac surgery with and without AKI.[168] Hazard ratios for their Group III, (50-99% creatinine increase from baseline) correspond with stage 1 AKI here. This slightly underestimates mortality for COPTIC patients with AKI, since they are a mix of Stage 1/2/3, but a sensitivity analysis was also conducted using hazard ratios for their Group IV, (>100% creatinine increase from baseline). Hazard ratios were used to adjust survival for patients who experienced complications based on rates and then converted back to probabilities.

Healthcare costs beyond one year

These costs were calculated using the unit costs used to estimate healthcare costs between hospital discharge and one year (see **Appendix 32**). Annual healthcare costs for patients alive in a subsequent year were estimated to be £2173, and an additional annual cost of £99 was assigned to patients alive in a subsequent year who experienced a complication during their index admission.

Appendix 34: Further details on sensitivity analyses conducted

Further details are provided on some of the one-way sensitivity analyses (SA) conducted.

Probability of a positive test result (SA1)

While the POC test results were available for each patient, there is uncertainty around the threshold at which a test parameter indicates a positive test, and the need for prophylactic treatment. These thresholds still need to be validated. Less conservative thresholds for treatment were therefore considered in sensitivity analyses. The base case thresholds were approximately 80% of normal ranges, 100% of normal ranges were used to consider less conservative thresholds for treatment.

For TEG, the following less conservative criteria were used to indicate positive test results (these are the same criteria as used to identify positive ad hoc test results):

1. If CK R (min) : CKH R (min) > 1.5 and if CK R (min) > 8, give protamine.
2. If CK R (min) > 8, give FFP.
3. If CK α -Angle < 47, give FFP and platelets.
4. If CK MA < 55, give FFP and platelets.
5. If CK LY60 > 15, give tranexamic acid.

Based on these criteria, 32.8% (591/1802) of patients were classified as having a positive TEG test result, and the average cost (SE) of their prophylactic treatment indicated was £342 (5).

For ROTEM, the following less conservative criteria were used to indicate positive test results:

1. If INTEM CT > 240s and HEPTTEM CT / INTEM CT < 0.8, give protamine.
2. If EXTEM CT > 80s or HEPTTEM CT > 240s, give FFP.
3. If EXTEM A10 $\leq$ 40mm and FIBTEM A10 < 10mm, give cryoprecipitate.
4. If EXTEM A10 $\leq$ 40mm and FIBTEM A10 $\geq$ 10mm, give FFP and platelets.
5. If FIBTEM A10 < 7 or FIBTEM MCF < 9, give cryoprecipitate.

Based on these criteria, 10.6% (191/1802) of patients were classified as having a positive ROTEM test result, and the average cost (SE) of their prophylactic treatment indicated was £358 (14).

For Multiplate, the base case criteria were increased by 25% to give the following less conservative criteria for determining positive test results:

If AUC TRAP test < 62.5, or AUC ASPI test < 37.5, or AUC ADP test < 37.5; give platelets.

Based on less conservative criteria, 34.1% (615/1802) of patients were classified as having a positive TEG/Multiplate test result, and the average cost (SE) of their prophylactic treatment indicated was £142 (2); and 12.5% (225/1802) of patients were classified as having a positive ROTEM/Multiplate result with an average cost (SE) of prophylactic treatment of £356 (12).

Probability that the prophylactic treatment prevents the development of CCB (SA2)

There is considerable uncertainty around the probability that the prophylactic treatment indicated by a positive test result is successful and prevents the development of CCB; this is a key parameter in the model. The base case failure rate of 34.3% was varied by +/-25% in sensitivity analyses.

Probability of CCB for patients in the Test All arm, with a positive ad hoc TEG and a negative POC test (SA4)

In the Test All arm, it was not possible to 'take out' the effect of a positive ad hoc TEG for patients who had a negative POC test. This was crudely attempted in a sensitivity analysis by shifting some of these patients from no CCB to CCB on the basis that these patients would not have had prophylactic treatment as a result of a positive ad hoc test, and more of them may have developed CCB. Specifically, the probability of being in the No CCB group for patients with a positive ad hoc test but a negative POC test (group four in **Figure 6.6**) was multiplied by the probability that the prophylactic treatment failed.

Appendix 35: Probabilistic sensitivity analyses

Since the majority of parameters in the model were estimated from COPTIC rather than the whole population of patients undergoing cardiac surgery, uncertainty exists around these parameter estimates. Parameter uncertainty was investigated using probabilistic sensitivity analysis (PSA), which enabled the joint impact on cost-effectiveness results of all the uncertain parameters in the model to be assessed simultaneously.[60, 221, 222] Rather than taking fixed values, model parameters were assigned probability distributions to describe the range of plausible values they could take based on the precision of the estimates available. The type of distribution assigned was matched to the nature of the parameter, for example a beta distribution lies between zero and one and is therefore appropriate for parameterising the probability of two mutually exclusive events, and a gamma distribution is positive and continuous and was used to parameterise costs. The type of distribution assigned to each parameter is shown in **Appendix 27**.

Randomly selected values from each distribution for each model parameter were simultaneously generated using Monte Carlo simulation; this was repeated 1000 times, and the results were calculated for each run of the model, generating a distribution of costs and effects which were used to calculate 95% CIs around the cost and QALY differences between strategies, enabling the effect of the parameter uncertainty on conclusions to be investigated. Results are presented on the cost-effectiveness plane and also are expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that a POC test is cost-effective for different amounts that healthcare decision-makers are willing to pay for an additional QALY.[67]

Appendix 36: Sensitivity analysis results

The results of the sensitivity analyses are shown in **Table 1**. Sensitivity analysis one, which considered less stringent criteria for determining whether a POC test result was positive had the greatest impact on results for TEG and TEG/ Multiplate. With these criteria, point estimates suggest these tests are more costly than Current Practice as in the base case, but are now more effective; the ICERs are less than £9,000 per QALY and suggest the tests would be considered cost-effective. Neither of the differences in costs or QALYs are statistically significant, and the uncertainty around results remains.

Under an extreme sensitivity analysis (SA3) assuming that prophylactic treatment was always successful, ROTEM became marginally less costly than Current Practice (by £1), and the point estimate of the ICER suggests that ROTEM dominates Current Practice, but there is huge uncertainty around this result, as demonstrated by the CIs around the cost and QALY differences compared to Current Practice.

When an attempt was made to ‘take out’ the effect of a positive ad hoc test result for patients in the Test All arm with a negative POC test (SA4), costs under each of the POC strategies increased, QALYs decreased, and ROTEM and ROTEM/ Multiplate were no longer likely to be considered cost-effective.

The sensitivity analysis around the cost of blood administration had very little effect. When no costs associated with blood administration were included, average costs in each group reduced by approximately £60 in each group but the cost difference between each POC strategy and current practice was virtually unchanged.

All other sensitivity analyses had very little impact on results. In most cases there was little impact on the average costs and QALYs in each group, and therefore little impact on the differences between groups and the ICERs. Altering bed day costs by $\pm 25\%$ did alter average costs by approximately £1,300, but this effect was seen under all strategies and therefore there was virtually no change in the mean difference in costs between the POC tests and Current Practice. Based on the point estimates, TEG and TEG/ Multiplate remain dominated by Current Practice, while ROTEM and ROTEM/ Multiplate are likely to be cost-effective (all ICERs less than £10,000 per QALY except in extreme SA4); but as in the base case, differences are tiny and results are very uncertain.

Table 1: One-way sensitivity analysis results

		Costs £	QALYs	Difference in costs	Difference in QALYs	ICER £ – compared to
		Mean (SE)	Mean (SE)	to Current Practice	to Current Practice	Current Practice (CP)
				Mean (95% CI)	Mean (95% CI)	
Base case	Current practice	16108 (134)	3.5617 (0.4377)			
	TEG	16134 (135)	3.5615 (0.4324)	26 (-34, 89)	-0.0002 (-0.0070, 0.0069)	CP dominant (-132153)
	ROTEM	16118 (134)	3.5660 (0.4380)	10 (-58, 81)	0.0043 (-0.0030, 0.0149)	2318
	TEG & Multiplate	16143 (135)	3.5617 (0.4398)	35 (-25, 102)	-0.00002 (-0.0079, 0.0090)	CP dominant (-2088098)
	ROTEM & Multiplate	16127 (131)	3.5663 (0.4537)	19 (-50, 86)	0.0046 (-0.0042, 0.0149)	4251
SA1	TEG	16175 (129)	3.5691 (0.4307)	67 (2, 130)	0.0074 (-0.0031, 0.0204)	8966
	ROTEM	16117 (128)	3.5654 (0.4606)	9 (-66, 83)	0.0037 (-0.0046, 0.0130)	2412
	TEG & Multiplate	16141 (129)	3.5690 (0.4387)	33 (-44, 101)	0.0073 (-0.0044, 0.0203)	4505
	ROTEM & Multiplate	16121 (128)	3.5670 (0.4517)	13 (-66, 92)	0.0053 (-0.0038, 0.0171)	2438
SA2 -25%	TEG	16133 (135)	3.5615 (0.4324)	25 (-35, 89)	-0.0002 (-0.0073, 0.0070)	CP dominant (-112709)
	ROTEM	16115 (134)	3.5665 (0.4381)	7 (-61, 78)	0.0048 (-0.0027, 0.0160)	1487
	TEG & Multiplate	16141 (135)	3.5617 (0.4398)	33 (-27, 99)	-0.00002 (-0.0079, 0.0091)	CP dominant (-1741462)
	ROTEM & Multiplate	16123 (136)	3.5669 (0.4505)	15 (-55, 88)	0.0051 (-0.0036, 0.0164)	2953
SA2 +25%	TEG	16135 (135)	3.5616 (0.4324)	27 (-33, 89)	-0.0002 (-0.0070, 0.0069)	CP dominant (-157433)
	ROTEM	16121 (134)	3.5654 (0.4380)	13 (-55, 84)	0.0037 (-0.0033, 0.0135)	3398
	TEG & Multiplate	16145 (135)	3.5617 (0.4398)	37 (-24, 103)	-0.00001 (-0.0079, 0.0090)	CP dominant (-2538792)
	ROTEM & Multiplate	16132 (136)	3.5657 (0.4504)	24 (-44, 95)	0.0040 (-0.0039, 0.0140)	5938

		Costs £ Mean (SE)	QALYs Mean (SE)	Difference in costs to Current Practice Mean (95% CI)	Difference in QALYs to Current Practice Mean (95% CI)	ICER £ – compared to Current Practice (CP)
SA3	TEG	16131 (136)	3.5614 (0.4324)	22 (-39, 86)	-0.0003 (-0.0079, 0.0071)	CP dominant (-74384)
	ROTEM	16107 (133)	3.5682 (0.4382)	-1 (-72, 69)	0.0065 (-0.0026, 0.0194)	ROTEM dominant (-151)
	TEG & Multiplate	16135 (135)	3.5617 (0.4398)	27 (-33, 95)	-0.00003 (-0.0085, 0.0099)	CP dominant (-1058226)
	ROTEM & Multiplate	16111 (135)	3.5687 (0.4506)	3 (-73, 79)	0.0069 (-0.0031, 0.0207)	396
SA4	TEG	16184 (139)	3.5561 (0.4321)	76 (6, 146)	-0.0056 (-0.0177, 0.0034)	CP dominant (-13620)
	ROTEM	16187 (140)	3.5624 (0.4378)	78 (1, 161)	0.0007 (-0.0102, 0.0114)	112019
	TEG & Multiplate	16192 (138)	3.5561 (0.4396)	84 (16, 161)	-0.0056 (-0.0163, 0.0038)	CP dominant (-14965)
	ROTEM & Multiplate	16188 (142)	3.5625 (0.4500)	80 (2, 171)	0.0008 (-0.0088, 0.0116)	105635
SA5	Current practice	16106 (133)	3.5617 (0.4324)			
-25%	TEG	16134 (135)	3.5615 (0.4324)	29 (-31, 91)	-0.0002 (-0.0070, 0.0069)	CP dominant (-144877)
	ROTEM	16118 (134)	3.5660 (0.4380)	12 (-55, 83)	0.0043 (-0.0030, 0.0149)	2909
	TEG & Multiplate	16143 (135)	3.5617 (0.4398)	38 (-23, 104)	-0.00002 (-0.0079, 0.0090)	CP dominant (-2238344)
	ROTEM & Multiplate	16127 (131)	3.5663 (0.4537)	22 (-46, 94)	0.0046 (-0.0042, 0.0149)	4805
SA5	Current practice	16111 (133)	3.5617 (0.4324)			
+25%	TEG	16134 (135)	3.5615 (0.4324)	24 (-37, 87)	-0.0002 (-0.0070, 0.0069)	CP dominant (-119428)
	ROTEM	16118 (134)	3.5660 (0.4380)	7 (-60, 78)	0.0043 (-0.0030, 0.0149)	1727
	TEG & Multiplate	16143 (135)	3.5617 (0.4398)	33 (-28, 100)	-0.00002 (-0.0079, 0.0090)	CP dominant (-1937852)
	ROTEM & Multiplate	16127 (131)	3.5663 (0.4537)	17 (-52, 89)	0.0046 (-0.0042, 0.0149)	3697

		Costs £ Mean (SE)	QALYs Mean (SE)	Difference in costs to Current Practice Mean (95% CI)	Difference in QALYs to Current Practice Mean (95% CI)	ICER £ – compared to Current Practice (CP)
SA6	TEG	16125 (135)	3.5615 (0.4324)	17 (-43, 80)	-0.0002 (-0.0070, 0.0069)	CP dominant (-85475)
-25%	ROTEM	16110 (134)	3.5660 (0.4380)	2 (-66, 73)	0.0043 (-0.0030, 0.0149)	442
	TEG & Multiplate	16130 (165)	3.5617 (0.4398)	22 (-39, 89)	-0.00002 (-0.0079, 0.0090)	CP dominant (-1283731)
	ROTEM & Multiplate	16115 (136)	3.5663 (0.4537)	7 (-61, 79)	0.0046 (-0.0042, 0.0149)	1560
SA6	TEG	16144 (135)	3.5615 (0.4324)	35 (-25, 98)	-0.0002 (-0.0070, 0.0069)	CP dominant (-178830)
+25%	ROTEM	16126 (134)	3.5660 (0.4380)	18 (-50, 89)	0.0043 (-0.0030, 0.0149)	4194
	TEG & Multiplate	16157 (135)	3.5617 (0.4398)	49 (-12, 116)	-0.00002 (-0.0079, 0.0090)	CP dominant (-289265)
	ROTEM & Multiplate	16140 (136)	3.5663 (0.4537)	32 (-37, 104)	0.0046 (-0.0042, 0.0149)	6942
SA7	TEG	16133 (135)	3.5615 (0.4324)	25 (-35, 88)	-0.0002 (-0.0070, 0.0069)	CP dominant (-123998)
-25%	ROTEM	16116 (134)	3.5660 (0.4380)	8 (-59, 78)	0.0043 (-0.0030, 0.0149)	1803
	TEG & Multiplate	16142 (135)	3.5617 (0.4398)	33 (-27, 100)	-0.00002 (-0.0079, 0.0090)	CP dominant (-1991549)
	ROTEM & Multiplate	16124 (136)	3.5663 (0.4537)	16 (-52, 89)	0.0046 (-0.0042, 0.0149)	3578
SA7	TEG	16136 (135)	3.5615 (0.4324)	28 (-32, 91)	-0.0002 (-0.0070, 0.0069)	CP dominant (-140307)
+25%	ROTEM	16120 (134)	3.5660 (0.4380)	12 (-55, 83)	0.0043 (-0.0030, 0.0149)	2833
	TEG & Multiplate	16145 (125)	3.5617 (0.4398)	37 (-23, 104)	-0.00002 (-0.0079, 0.0090)	CP dominant (-2184647)
	ROTEM & Multiplate	16130 (136)	3.5663 (0.4537)	22 (-46, 94)	0.0046 (-0.0042, 0.0149)	4924

		Costs £ Mean (SE)	QALYs Mean (SE)	Difference in costs to Current Practice Mean (95% CI)	Difference in QALYs to Current Practice Mean (95% CI)	ICER £ – compared to Current Practice (CP)
SA8	Current practice	16108 (134)	2.8566 (0.3362)			
-25%	TEG	16134 (135)	2.8815 (0.3399)	26 (-34, 89)	0.0249 (0.0126, 0.0349)	1053
	ROTEM	16118 (134)	2.8600 (0.3415)	10 (-58, 81)	0.0034 (-0.0023, 0.0119)	2892
	TEG & Multiplate	16143 (135)	2.8566 (0.3423)	35 (-25, 102)	-0.00002 (-0.0062, 0.0072)	CP dominant (-2040601)
	ROTEM & Multiplate	16127 (131)	2.8602 (0.3496)	19 (-50, 86)	0.0036 (-0.0029, 0.0120)	5319
SA8	Current practice	16108 (134)	4.2668 (0.5292)			
+25%	TEG	16134 (135)	4.2666 (0.5262)	26 (-34, 89)	-0.0002 (-0.0087, 0.0084)	CP dominant (-109361)
	ROTEM	16118 (134)	4.2720 (0.5352)	10 (-58, 81)	0.0051 (-0.0037, 0.0178)	1934
	TEG & Multiplate	16143 (135)	4.2668 (0.5319)	35 (-25, 102)	-0.00002 (-0.0095, 0.0109)	CP dominant (-2137858)
	ROTEM & Multiplate	16127 (131)	4.2723 (0.5519)	19 (-50, 86)	0.0055 (-0.0045, 0.0185)	3540
SA9	Current practice	16108 (134)	3.2846 (0.3947)			
	TEG	16134 (135)	3.2843 (0.3946)	26 (-34, 89)	-0.0004 (-0.0091, 0.0081)	CP dominant (-73466)
	ROTEM	16118 (134)	3.2895 (0.4005)	10 (-58, 81)	0.0048 (-0.0033, 0.0160)	2050
	TEG & Multiplate	16143 (135)	3.2851 (0.4020)	35 (-25, 102)	0.0004 (-0.0087, 0.0110)	85059
	ROTEM & Multiplate	16127 (131)	3.2904 (0.4142)	19 (-50, 86)	0.0058 (-0.0033, 0.0176)	3357
SA10	Current practice	16108 (134)	4.5917 (0.0232)			
	TEG	16134 (135)	4.5917 (0.0233)	26 (-34, 89)	-0.00002 (-0.0050, 0.0041)	CP dominant (-1212055)
	ROTEM	16118 (134)	4.5960 (0.0240)	10 (-58, 81)	0.0043 (-0.0031, 0.0137)	2302
	TEG & Multiplate	16143 (135)	4.5911 (0.0250)	35 (-25, 102)	-0.0006 (-0.0084, 0.0066)	CP dominant (-58860)

		Costs £ Mean (SE)	QALYs Mean (SE)	Difference in costs to Current Practice Mean (95% CI)	Difference in QALYs to Current Practice Mean (95% CI)	ICER £ – compared to Current Practice (CP)
	ROTEM & Multiplate	16127 (131)	4.5955 (0.0243)	19 (-50, 86)	0.0038 (-0.0046, 0.0131)	5154
SA11	Current practice	16048 (131)	3.5617 (0.4377)			
	TEG	16072 (134)	3.5615 (0.4324)	24 (-34, 85)	-0.0002 (-0.0070, 0.0069)	CP dominant (-122481)
	ROTEM	16056 (132)	3.5660 (0.4380)	9 (-55, 77)	0.0043 (-0.0030, 0.0149)	2080
	TEG & Multiplate	16081 (133)	3.5617 (0.4398)	33 (-25, 97)	-0.00002 (-0.0079, 0.0090)	CP dominant (-1986262)
	ROTEM & Multiplate	16065 (132)	3.5663 (0.4537)	18 (-48, 87)	0.0046 (-0.0042, 0.0149)	3915
SA12	Current practice	16108 (134)	3.5343 (0.4288)			
	TEG	16134 (135)	3.5341 (0.4288)	26 (-34, 89)	-0.0002 (-0.0072, 0.0071)	CP dominant (-122219)
	ROTEM	16118 (134)	3.5389 (0.4343)	10 (-58, 81)	0.0043 (-0.0030, 0.0150)	2330
	TEG & Multiplate	16143 (135)	3.5345 (0.4362)	35 (-25, 102)	0.00003 (-0.0081, 0.0091)	1369068
	ROTEM & Multiplate	16127 (131)	3.5389 (0.4470)	19 (-50, 86)	0.0047 (-0.0037, 0.0154)	4226
SA13	Current practice	22002 (153)	5.6427 (0.7196)			
	TEG	22028 (154)	5.6424 (0.7195)	26 (-31, 86)	-0.0004 (-0.0122, 0.0119)	CP dominant (-72655)
	ROTEM	22018 (160)	5.6497 (0.7262)	16 (-48, 79)	0.0070 (-0.0051, 0.0244)	2245
	TEG & Multiplate	22037 (159)	5.6428 (0.7308)	34 (-23, 97)	0.0000 (-0.0132, 0.0151)	425728
	ROTEM & Multiplate	22027 (161)	5.6503 (0.7512)	25 (-40, 93)	0.0076 (-0.0061, 0.0255)	3241

CI, Confidence interval; ICER, Incremental cost-effectiveness ratio; SA, Sensitivity analysis; SE, Standard error
Note: all costs and ICERs are rounded to nearest pound.

Appendix 37: Methods and results of the literature review of studies comparing resource use from routine data with an alternative source

Aims and methods

A literature review was undertaken to identify references which compare the validity of resource use from routine or administrative data with an alternative source to establish what is known in this field, and to place the empirical work in Chapter 7 into context. To inform search strategies, the keywords and Medical Subject Headings (MeSH) of known papers in this field were reviewed.[174, 175, 223-226] No common MeSH headings were identified from these papers, and therefore the search strategies were based on keywords only. The electronic databases Medline and Embase were searched through Ovid on 10 September 2016, (see **Appendix 38** for the electronic search strategies for each database). The Cochrane Library was not searched as economic evaluation papers were not expected to meet the inclusion criteria, (this was confirmed by an exploratory search of the NHS Economic Evaluation Database and the Health Technology Assessment Database within the Cochrane Library using the Medline search strategy which did not identify any relevant references). In addition to the database searches, papers discussed at the most recent three Health Economists' Study Group (HESG) meetings (June 2015, January 2016 and June 2016) were hand searched for relevant papers which have not yet been published in peer-reviewed journals. Searches were limited to references published from 2000 onwards. A systematic review of discharge coding found that the accuracy of routine data was improving over time,[227] and the introduction of Payment by Results from 2003/04 has led to improved coding within hospitals. It was therefore felt that references before 2000 would not be relevant to today. Searches were also limited to the English language to ensure that papers could be reviewed in detail. Conference abstracts were excluded since these are not likely to contain sufficient detail on the methods or results for comparative purposes.

Papers were sought which compared resource use from routine or administrative datasets in the UK with an alternative source, for the purposes of economic evaluation. A broad definition of routine data was taken, so this included patient paper based case notes as well as electronic medical records, and large electronic national datasets.

Titles and abstracts of all references returned were reviewed for relevance. Potentially eligible studies were identified and full text papers obtained. Full texts were also obtained

for references where it was not possible to determine relevance from the title and abstract; these papers were reviewed and a decision made on the inclusion or exclusion of each. The reference lists of papers included in the review were also reviewed to identify any further relevant literature.

For papers meeting the inclusion criteria, information was extracted on the country of origin, year of data collection, study population, data sources and resource use being compared, and the measure(s) used to compare sources and the results. Where possible, comparisons based on resource use rather than costs were extracted, where comparisons were made based on the costs of resource use only, this was extracted along with the price year.

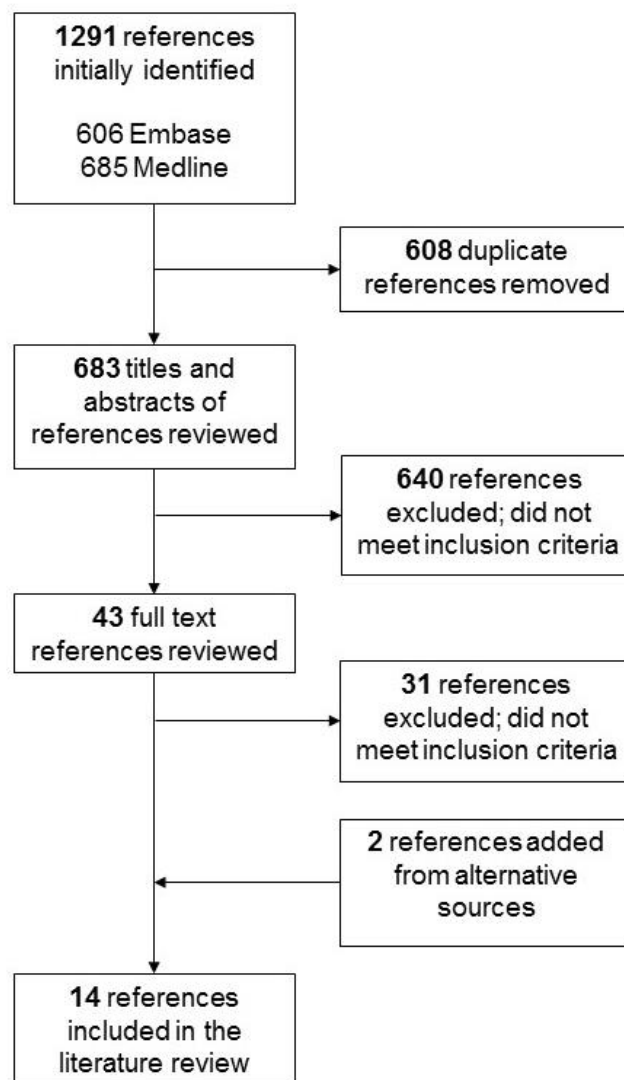
The quality of included studies was assessed using a checklist (**Appendix 39, Table 1**). This checklist was based on a tool developed by Noben *et al.* to assess the methodological quality of studies comparing validation evidence for self-reported healthcare resource use data compared to administrative data,[172] and was supplemented by items from another quality checklist.[228] For each item on the checklist, a study scored one if it was fully reported, 0.5 if it was partially reported and zero if it was only poorly reported or not reported at all. An overall summary score for each study was then generated by expressing the total score as a percentage.

Results

Figure 1 summarises the references identified in the literature review. 1,291 references were initially identified, which reduced to 683 once duplicates had been removed. Twelve references met the inclusion criteria and two further relevant papers were identified from the references of included papers, so 14 papers in total were included in the review (**Appendix 40** provides a complete list). Most of the papers excluded at the title and abstract review stage did not compare resource use from alternative sources or were conducted outside of the UK; many of the papers excluded during the full-text review included no primary data, or were very clinically focused, for example assessing agreement between sources for comorbidities or clinical codes for complications, rather than focusing on resource use. One Health Technology Assessment report which replicated four RCTs with data from routine sources was excluded since only the difference between trial groups for the two different sources was presented, it was therefore not possible to assess the agreement between the routine and designed data collection methods.[182] One feasibility study in dementia was excluded as the resource use from the alternative data collection methods was not compared.[229] Two HESG papers were obtained in full for closer

inspection, but neither reference met the inclusion criteria. One interesting paper considered agreement between cost-effectiveness results estimated using alternative sources of resource use data. However, only total costs from alternative sources were presented with no breakdown of resource use or cost, since this was not the focus of the applied example presented, and therefore it was not possible to assess the level of agreement between the sources in any detail, and hence the paper was excluded.[230]

Figure 1: References identified in the literature review



The study characteristics extracted from the 14 papers are summarised in **Table 1**, and reported in full in **Appendix 41** (where studies are grouped according to the sources of resource use data that were compared). Nine (64%) studies compared patient self-reported data from questionnaires or interviews with medical records. Studies compared resource use for a diverse range of patient populations, from primary care attenders presenting with

mental health problems or knee pain, to secondary care users with leukaemia or prostate cancer. Studies were fairly evenly split between comparing primary or community care, secondary care or both. Eight (57%) studies compared just one or two resource items (for example the number of GP visits or outpatient appointments), the remaining six studies compared a broad range of healthcare resource use. Resource use was compared in natural units in 12 (86%) studies, in two (14%) studies comparisons were made in costs only.

Table 1: Summary of the characteristics of studies included in the literature review

Characteristic	Categories	Number (%) of studies
Data sources compared	Patient self-report versus medical records	9 (64)
	Case report forms versus medical records	1 (7)
	Registry data versus medical records	1 (7)
	Hospital Episode Statistics versus medical records	2 (14)
	Clinical database versus Hospital Episode Statistics	1 (7)
Resource use compared	Primary and/or community care	4 (29)
	Secondary care	5 (36)
	Primary and/or community care, and secondary care	5 (36)
Results reported	Resource use	9 (64)
	Resource use and costs	3 (21)
	Costs	2 (14)

The findings from studies comparing resource use from alternative sources are summarised in **Table 2**. There were mixed findings from the nine (64%) papers which compared patient self-reported data with medical records. Four studies found that patients under-reported resource use,[225, 231-233] while three studies found that medical records under-reported resource use compared to patient self-report,[224, 234, 235] one study found very good agreement between the two sources (although only considered GP visits),[223] and the final study concluded that GP records were more accurate for GP-based contacts but patient self-reported resource use was more reliable for other resource use.[226] Studies in which patients were thought to have under-reported resource use were not limited to those which included older patients and/ or a long recall period (12 months), two factors which are thought to be associated with under-reporting. Although medical records were often treated as the gold standard, there was frequently an acknowledgement that neither source was necessarily more accurate, and there were likely to be limitations with both sources.

Table 2: Summary of evidence reported in the papers comparing resource use from routine data with an alternative source

	First author and publication year	Statistical methods for comparing sources	Summary of evidence reported
Patient self-report versus medical records	Byford (2007)	Mean resource use and mean total costs; mean difference (95% CI); Lin's concordance correlation coefficient (ρ_c); 95% limits of agreement	Patient self-report data available for 397/480 (83%) patients, and GP record data available for 272/397 (69%) patients. Number of GP and nurse contacts are higher from GP records than patient self-report, on average all other resource use is higher from patient self-report than GP records High level of agreement for GP contacts ($\rho_c=0.63$), accident and emergency attendances ($\rho_c=0.76$) and total inpatient days ($\rho_c=0.66$) but low ($\rho_c<0.4$) for outpatient appointments and other community contacts
	Chishti (2013)	Mean (SD) resource use and range; mean difference (95% CI)	Electronic records obtained for 87/115 (76%) patients who completed the questionnaire. GP records versus self-report: GP consultations: mean 7.2 versus 5.7, difference 1.6, 95% CI (0.5, 2.7) Nurse consultations: mean 1.9 versus 1.4, difference 0.5, 95% CI (-0.2, 1.2)
	Houweling (2014)	Mean (SD) resource use and mean difference (95% CI); percentage of patients over-reporting and under-reporting; intraclass correlation coefficient (ICC) and 95% CI; 95% limits of agreement	Data available from both sources for 89/238 (37%) patients. Patient files versus self-report: Chiropractor visits: 5.3 versus 4.6, difference 0.6, 95% CI (0.25, 1.01) ICC 0.83, 95% CI (0.75, 0.88).

	First author and publication year	Statistical methods for comparing sources	Summary of evidence reported
	Jordan (2006)	Cross tabulation of each source reporting resource use; kappa (κ) and 95% CI	Only 40% of self-reported consultants could be verified in medical records. Low rate of incorrect reporting of non-consultation: only 3% of self-reported non-consulters had a knee code or text mentioned in medical records. Based on read codes: $\kappa=0.30$, 95% CI (0.27, 0.34). Based on read codes/text: $\kappa=0.43$, 95% CI (0.39, 0.47).
	Kennedy (2002)	Mean (SD) resource use and mean differences (95% CI); intraclass correlation coefficient (ICC) (95% CI); 95% limits of agreement	Data available for 96/315 (30%) patients from hospital records and self-report data available for 150/315 (48%) patients; data available from both sources for n=52. Hospital records versus self-report: Physiotherapy appointments: mean 4.3 versus 5.6, mean difference -1.3, 95% CI (-2.2, -0.4). ICC 0.54, 95% CI (0.31, 0.70)
	Mistry (2005)	Mean resource use; weighted kappa (κ_w); mean costs	Of 324/327 (99%) patients with complete GP records, 85 (26%) had complete self-report data. Number of contacts are higher for each category from self-report than GP records, overall self-report versus GP records 17.2 versus 12.64 visits. Agreement classed as moderate for GP visits at home ($\kappa_w=0.485$) and other hospital and specialist services ($\kappa_w=0.430$), fair for GP visits at surgery ($\kappa_w=0.370$) and psychiatric hospital and community services ($\kappa_w=0.278$), poor for social services ($\kappa_w=0.021$), and moderate for overall total contacts ($\kappa_w=0.465$).

	First author and publication year	Statistical methods for comparing sources	Summary of evidence reported
	Patel (2005)	Mean (SD) resource use and costs, mean difference (95% CI); paired sample <i>t</i> tests; Lin's concordance correlation coefficient (ρ_c); 95% limits of agreement	GP record data available for 274/303 (90%) patients, and patient self-report data available for 229/303 (76%) patients. GP records versus self-report: GP visits: mean 3.03 versus 2.99, difference 0.03, 95% CI (-0.29, 0.36) High level of agreement between sources ($\rho_c=0.756$).
	Petrou (2002)	Mean (SD) difference; percentage of under, accurate and over-reporting; Wilcoxon sign-rank test to identify significant differences between the 2 distributions	Medical records versus self-report, mean (SD) difference: 0.92 (1.53) for GP visits in months 1-4, and 1.88 (2.65) in months 5-12; 0.28 (3.45) for community midwife visits in months 1-4. Negligible differences for secondary care. Statistically significant differences for GP visits for both recall periods ($p<0.001$).
	Richards (2003)	Percentage crude agreement; (quadratic) weighted kappa (κ_w) and 95% CI	Of 219 eligible patients, self-report data available for 190 and 185 patients at 4 and 12 weeks respectively, routine hospital and community data available for the majority of patients, routine GP data available for 179 patients. Number of hospital readmissions (85.7%, κ_w 0.42) Number of GP surgery visits (83.0%, κ_w 0.61) Number of patient-requested GP home visits (41.7%, κ_w 0.59) Number of routine GP home visits (71.0%, κ_w 0.71)

	First author and publication year	Statistical methods for comparing sources	Summary of evidence reported
Case report forms versus medical records	Standaert (2002)	Mean costs (in 1998 prices) in trial groups; percentage of costs in CRFs versus patient files	Medical records versus case report forms: For trial filgrastim group for induction and consolidation cycle combined: Hospital stay: £7721 versus £7721 Anti-infective drugs: £600 versus £600 Haematology and biochemistry tests: £660 versus £463 Platelets: £1959 versus £2242 Total: £14861 versus £12463 Total costs: £16146 versus £12876 for placebo group for combined cycle, and £9701 versus £7881, and £10611 versus £8058 for the first induction cycle for the filgrastim and placebo groups respectively. Costs based on CRF data captured 76% - 84% of costs captured in patient files (for different trial groups and induction/combined cycles) Some differences in the detail of resource use captured from each source, and wider range of resource use captured from patient files

	First author and publication year	Statistical methods for comparing sources	Summary of evidence reported
Registry data versus medical records	Strobl (2003)	Percentage of verified records with disagreements	Extent of data verified: all data items 55%, 75-99% of data – 17%, 50-74% of data – 16%, 1-49% of data – 5%, no data – 7%. Disagreements: 1.3% for lung function test date 0.4% for dornase alfa use 0.6% for start date 10.5% for stop date 3.7% for hospital admissions
HES versus medical records	Thorn (2016a)	Proportions matching (based on appointment date) and 95% CI	4922 outpatient appointments extracted from medical records. HES outpatient dataset included 12,154 appointments since HES covers all outpatient appointments, not just those related to prostate cancer. 4088/4922 (83.1%) appointments in medical records were identified in HES, 95% CI (82.0%, 84.1%).
	Thorn (2016b)	Event identification: definition of a single event not comparable between datasets. Number of cases where events captured in one source only reported. Mean (95% CI) costs (in 2010/11 prices) over the final year of life	Zero events: 11 (3.8%) men had events reported in HES which were missing from medical records; 7 (2.4%) men had events in medical records which were missing from HES. Medical records: £11122, 95% CI (£9083, £13161), HES: £10223, 95% CI (£8880, £11565)
Clinical database versus HES	Nikiphorou (2015)	Length of stay: spearman's correlation (ρ), and kappa (κ) when analysed as 4 categories. Procedure: percentage matching	Length of stay: $\rho=0.924$ ($p<0.001$), $\kappa=0.712$ ($p<0.001$). Procedure coding: 89% match

CI, confidence interval; GP, general practitioner; HES, Hospital Episodes Statistics; ICC, intraclass correlation coefficient; SD, standard deviation

While the focus here was on the agreement between sources, no source is going to be reliable for the purposes of economic evaluation if it is frequently incomplete or very difficult to obtain. Mistry *et al.* found that self-reported data were only available for 26% of their cohort, whereas 99% of their cohort had complete GP records; the incompleteness of patient questionnaires necessitated a reliance on GP records even though these were found to under-report some categories of resource use compared to patient self-report.[224] Kennedy *et al.* reported data being available for a greater proportion of patients from self-reported questionnaires than hospital records (48% compared to 30%), although neither percentage is high, and both would raise concerns should either source be used in an economic evaluation.[234] While routine data is a source that already exists, it may be time consuming to obtain; Chishti *et al.* found it took an average of six contacts with general practice staff and six weeks to collect primary care resource use directly from practices.[232]

There was only one study which compared resource use from CRFs to an alternative source, which is most closely related to the comparisons later in Chapter 7.[173] Unfortunately the CRFs were not designed to capture resource use, they were designed for the clinical aspects of the trial only, so did not capture all relevant resource use and therefore it is not surprising that resource use was lower from this source than patients' medical records.

Two recent studies compared Hospital Episode Statistics (HES) data to medical records for older men diagnosed with prostate cancer.[174, 175] In this patient group, HES inpatient and outpatient data was found to be valid for the purposes of economic evaluation, although in the study of the outpatient data the authors noted that the scope of the evaluation would need to include all resource use, and not just appointments relating to prostate cancer for example, since the reason for the appointment cannot be accurately identified from HES.[174]

The assessment of study quality is reported in **Appendix 39 (Table 2)** and indicates that key information was generally well reported, overall studies met 84% of the quality criteria. There were several areas that were frequently less well reported however. Only eight (57%) of the studies described methods for capturing the routine data clearly and in detail. Missing data were not well reported in half of the studies, both in terms of data sources completely missing (i.e. the number of responses to a survey or request to GPs for information on patients) and of missing data within sources (non-response to particular questions).

Appendix 38: Search strategies used to identify references which compare resource use from routine data with an alternative source

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1. (administrative data*5 or routine data*5 or hospital episode statistics or electronic records or electronic health records or GP records or general practitioner records or GPRD or general practice research database or CPRD or clinical practice research datalink or hospital records or medical records).ti,ab.
2. (accuracy or valid*5 or agree*5).ti,ab.
3. (economic* or cost-effectiveness).ti,ab.
4. 1 and 2 and 3
5. health technology assessment.ti,ab.
6. 1 and 5
7. ((compar*5 and methods) or (alternative and methods)).ti,ab.
8. ((collect*3 or measur*3) adj3 ("resource use" or service utili*ation or resource utili*ation or economic data or cost data or (healthcare adj2 data))).ti,ab.
9. 7 and 8
10. ("resource use" or service utili*ation or resource utili*ation).ti,ab.
11. accuracy.ti,ab.
12. 3 and 10 and 11
13. 4 or 6 or 9 or 12
14. editorial.pt.
15. letter.pt.
16. 14 or 15
17. 13 not 16
18. animals/ not (animals/ and humans/)
19. 17 not 18
20. limit 19 to english language
21. limit 20 to yr="2000-Current"

Embase 1996 to 2016 Week 37

1. (administrative data*5 or routine data*5 or hospital episode statistics or electronic records or electronic health records or GP records or general practitioner records or GPRD or general practice research database or CPRD or clinical practice research datalink or hospital records or medical records).ti,ab.
2. (accuracy or valid*5 or agree*5).ti,ab.
3. (economic* or cost-effectiveness).ti,ab.
4. 1 and 2 and 3
5. health technology assessment.ti,ab.
6. 1 and 5
7. ((compar*5 and methods) or (alternative and methods)).ti,ab.
8. ((collect*3 or measur*3) adj3 ("resource use" or service utili*ation or resource utili*ation or economic data or cost data or (healthcare adj2 data))).ti,ab.
9. 7 and 8
10. ("resource use" or service utili*ation or resource utili*ation).ti,ab.
11. accuracy.ti,ab.
12. 3 and 10 and 11
13. 4 or 6 or 9 or 12
14. conference.pt.
15. note.pt.
16. editorial.pt.
17. letter.pt.
18. or/14-17
19. 13 not 18
20. exp animals/
21. exp humans/
22. 20 not (20 and 21)
23. 19 not 22
24. limit 23 to english language
25. limit 24 to yr="2000-Current"

Appendix 39: Assessing the quality of studies comparing resource use from routine data with an alternative source

Table 1: Checklist for the quality assessment of studies comparing resource use

Item	Criteria
1	Explicit identification of the study as an evaluation of the reliability, agreement, or validity (accuracy) of health care resource use measured using routine / administrative data with health care resource use measured by an alternative source
2	Items of resource use specified
3	Rationale for relationship between the administrative data and alternative source
4	Methods or measurement procedures for the routine / administrative data
5	Methods or measurement procedures for the alternative data source
6	Time interval for which resource use data sought
7	Population characteristics (including sampling methods, recruitment)
8	Missing data and number of patients included in analyses reported
9	Statistical methods for validation estimates defined
10	Validation estimates reported
11	Methods for statistical uncertainty defined and estimates presented
12	Conclusions follow from the validation evidence
13	Source of funding stated and, if funded by a commercial company, were the analyses conducted independently of the funder?

Table 2: Quality assessment for each study included in the literature review

First author and publication year	Checklist item													Total score	Percentage
	1	2	3	4	5	6	7	8	9	10	11	12	13		
Byford (2007)	1	1	1	0.5	1	1	1	0.5	1	1	1	1	1	12.0	92
Chishti (2013)	1	1	1	1	1	1	1	1	0.5	1	1	1	1	12.5	96
Houweling (2014)	1	1	1	1	1	1	1	0.5	1	1	1	1	1	12.5	96
Jordan (2006)	1	1	1	1	1	1	1	1	1	1	1	1	1	13.0	100
Kennedy (2002)	1	1	1	1	1	1	1	1	1	1	1	1	0	12.0	92
Mistry (2005)	1	1	1	0.5	1	1	1	0.5	1	1	0	1	1	11.0	85
Nikiphorou (2015)	0.5	1	1	0.5	0.5	0	0.5	0	1	1	0	0.5	0	6.5	50
Patel (2005)	0.5	1	1	1	1	0.5	1	1	1	1	1	1	1	12.0	92
Petrou (2002)	1	1	1	1	1	1	0.5	0	1	1	0.5	1	1	11.0	85
Richards (2003)	1	1	1	1	1	1	1	0	1	1	1	1	1	12.0	92
Standaert (2002)	0.5	1	0.5	0.5	1	0.5	0.5	1	0	0.5	0	1	1	8.0	62
Strobl (2003)	0.5	1	1	0.5	0.5	0	0.5	0.5	0.5	0.5	0	0.5	1	7.0	54
Thorn (2016a)	1	1	1	1	1	0.5	1	1	1	1	1	1	1	12.5	96
Thorn (2016b)	1	0.5	1	0.5	1	1	0.5	1	0.5	0.5	0.5	1	1	10.0	76

Appendix 40: References included in the literature review comparing resource use from routine data with an alternative source

1. Byford S, Leese M, Knapp M, Seivewright H, Cameron S, Jones V, et al. (2007) Comparison of alternative methods of collection of service use data for the economic evaluation health care interventions. *Health Economics* 16(5):531-6.
2. Chishti T, Harris T, Conroy R, Oakeshott P, Tulloch J, Coster D, et al. (2013) How reliable are stroke patients' reports of their numbers of general practice consultations over 12 months? *Family Practice* 30(1):119-22.
3. Houweling T, Bolton J, Newell D (2014) Comparison of two methods of collecting healthcare usage data in chiropractic clinics: patient-report versus documentation in patient files. *Chiropractic & manual therapies* 22(1):32.
4. Jordan K, Jinks C, Croft P (2006) Health care utilization: measurement using primary care records and patient recall both showed bias. *J Clin Epidemiol* 59(8):791-7.
5. Kennedy ADM, Leigh-Brown AP, Torgerson DJ, Campbell J, Grant A (2002) Resource use data by patient report or hospital records: Do they agree? *BMC Health Services Research* 2:1-5.
6. Mistry H, Buxton M, Longworth L, Chatwin J, Peveler R (2005) Comparison of general practitioner records and patient self-report questionnaires for estimation of costs. *European Journal of Health Economics* 6(3):261-6.
7. Nikiphorou E, Morris S, Dixey J, Williams PL, Kiely P, Walsh DA, et al. (2015) The Effect of Disease Severity and Comorbidity on Length of Stay for Orthopedic Surgery in Rheumatoid Arthritis: Results from 2 UK Inception Cohorts, 1986-2012. *The Journal of Rheumatology* 42(5):778-85.
8. Patel A, Rendu A, Moran P, Leese M, Mann A, Knapp M (2005) A comparison of two methods of collecting economic data in primary care. *Family Practice* 22(3):323-7.
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12. Strobl J, Enzer I, Bagust A, Haycox A, Smyth R, Ashby D, et al. (2003) Using disease registries for pharmacoepidemiological research: A case study of data from a cystic fibrosis registry. *Pharmacoepidemiology and Drug Safety* 12(6):467-73.
13. Thorn JC, Turner E, Hounscome L, Walsh E, Donovan JL, Verne J, et al. (2016a) Validation of the Hospital Episode Statistics Outpatient Dataset in England. *Pharmacoeconomics* 34(2):161-8.
14. Thorn JC, Turner EL, Hounscome L, Walsh E, Down L, Verne J, et al. (2016b) Validating the use of Hospital Episode Statistics data and comparison of costing methodologies for economic evaluation: an end-of-life case study from the Cluster randomised trial of PSA testing for Prostate cancer (CAP). *BMJ Open* 6(4):e011063.

Appendix 41: Characteristics of the studies included in the literature review comparing resource use from routine data with an alternative source

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
Patient self-report versus medical records	Byford (2007)	England and Scotland	1998-2001	RCT	Patients presenting with recurrent deliberate self-harm (n=480)	Number of inpatient days, outpatient and accident and emergency attendance, contacts with GPs, practice nurses, community psychologists, community psychiatric nurses and occupational therapists	GP records	Patient self-report (in interview using a modified version of the Client Service Receipt Inventory (CSRI)) 6 and 12 months after trial entry	Retrospective – 12 months
	Chishti (2013)	England (London)	2008-2009	RCT	Hypertensive stroke patients (n=115)	Number of primary care consultations (doctor or nurse)	Electronic primary care records	Patient self-report (questionnaire posted to patients and collected at home visit)	Retrospective – 12 months
	Houweling (2014)	UK	2010-2011	Cohort	Patients with low back pain undergoing chiropractic treatment (n=238)	Number of chiropractor visits in three month follow up period	Patient files	Patient self-report (postal questionnaire)	Retrospective – 3 months

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
	Jordan (2006)	England (North Staffordshire)	Not reported	Cohort	Adults registered at 3 general practices aged 50 and over responding to a general population survey and reporting knee pain (n=2414)	Number of GP consultations	Primary care electronic medical records (based on read codes, and read codes and text)	Patient self-report (questionnaire)	Retrospective – 12 months
	Kennedy (2002)	Scotland	1993-1994	RCT	Adults attending an orthopaedics outpatient appointment with a 'non-surgical' musculo-skeletal condition (n=315)	Number of NHS physiotherapy appointments	Hospital record data (outpatient and physiotherapy department records)	Patient self-report (postal questionnaire mailed 3 and 12 months after initial outpatient appointment)	Retrospective – 6 months (1-3 and 9-12 months after the initial appointment)

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
	Mistry (2005)	England	1999-2003	RCT	Patients in 73 GP practices, presenting to their GP with a new episode of depressive illness (n=327)	Number of contacts with GP and other practice staff, contacts with community mental health teams, and psychiatric and general hospital contacts, including accident and emergency departments.	GP records (either computer-based or manual records)	Patient self-report (postal questionnaire mailed monthly for 3 months after randomisation, and then every 3 months to 1 year)	Retrospective – 12 months
	Patel (2005)	England (London)	1997-1998	Cohort	Random sample of primary care attenders (n=303)	Number of GP visits	GP records	Patient self-report (postal questionnaire - a modified version of the Client Service Receipt Inventory (CSRI))	Retrospective – 6 months

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
	Petrou (2002)	Great Britain	Not reported	RCT	Primiparous women at risk of developing postnatal depression, allocated to the routine care arm of an RCT (n=82)	Number of GP visits, community midwife visits (N/A at 8 months), inpatient admissions, outpatient and emergency department attendances	Medical records – by accessing electronic or paper records from NHS hospital and community health service providers in the town where the trial was conducted	Patient self-report in two face-to-face interviews 4 and 12 months postpartum	Retrospective – 12 months
	Richards (2003)	England (Bristol)	1994-1996	RCT	Acute ward patients aged 60 years and over (n=185)	Number of hospital admissions, GP visits	Healthcare providers (Patient administration system, Integrated community system, GP questionnaire)	Patient self-report (interviewer-administered questionnaire at 4 and 12 weeks follow up)	Retrospective – 12 weeks
Case report forms versus medical records	Standaert (2002)	England (Manchester)	1992-1994	RCT	Adult patients with newly diagnosed, de novo, acute myeloid leukaemia (n=30)	Hospital stay (days), drugs, diagnostic tests, blood products, filgrastim use (days)	Patient medical charts	Case report forms	Data collected for first induction cycle, and for the first induction and first consolidation cycle combined

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
Registry data versus medical records	Strobl (2003)	UK	1994-1999	Cohort	Patients with cystic fibrosis (n=230)	Lung function test date, dornase alfa use and start and stop dates, hospital admissions	Epidemiologic Registry of Cystic Fibrosis (ERCF)	Hospital records	Retrospective - assume data from record entry to the registry to time of verification were compared, unclear how long this was or when verification took place
Hospital Episode Statistics versus medical records	Thorn (2016a)	England	2003-2012	RCT	Men diagnosed with prostate cancer (n=370)	Number of outpatient visits	Hospital Episode Statistics Outpatient dataset	Medical records	Retrospective - assume all outpatients appointments between 2003 and 2012
	Thorn (2016b)	England	2003-2012	RCT	Men diagnosed with prostate cancer, who died at least a year after first being investigated for prostate cancer (n=292)	Inpatient resource use, costed using national reference costs (in 2011/12 prices)	Hospital Episode Statistics inpatient dataset	Medical records	Retrospective – 12 months

	First author and publication year	Country (Region)	Year of data	Study design	Study population (sample size)	Resource elements	Routine data source	Alternative data source	Data collection period
Clinical database versus HES	Nikiphorou (2015)	England	1997-? (at least 2012)	Cohort	Patients recruited to an inception cohort of early rheumatoid arthritis from 9 rheumatology centres between 1986-1999 who had orthopaedic surgery (n unclear)	Orthopaedic length of stay (episodes post-1997), orthopaedic procedure	Early RA Study (ERAS) clinical database	Hospital Episode Statistics (HES)	Unclear

GP, general practitioner; HES, Hospital Episodes Statistics; RCT, randomised controlled trial