HEALTH TECHNOLOGY ASSESSMENT

VOLUME 20 ISSUE 60 AUGUST 2016
ISSN 1366-5278

A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2)

Barnaby C Reeves, Katie Pike, Chris A Rogers, Rachel CM Brierley, Elizabeth A Stokes, Sarah Wordsworth, Rachel L Nash, Alice Miles, Andrew D Mumford, Alan Cohen, Gianni D Angelini and Gavin J Murphy on behalf of the TITRe2 investigators

National Institute for Health Research

DOI 10.3310/hta20600

A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2)

Barnaby C Reeves,[1]* Katie Pike,[1] Chris A Rogers,[1] Rachel CM Brierley,[1] Elizabeth A Stokes,[2] Sarah Wordsworth,[2] Rachel L Nash,[1] Alice Miles,[1] Andrew D Mumford,[3] Alan Cohen,[4] Gianni D Angelini[5] and Gavin J Murphy[6] on behalf of the TITRe2 investigators†

[1]Clinical Trials and Evaluation Unit, School of Clinical Sciences, University of Bristol, Bristol, UK
[2]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK
[4]Division of Specialised Services, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[5]Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol, UK
[6]Department of Cardiovascular Sciences and National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular Medicine, University of Leicester, Leicester, UK

*Corresponding author
†Transfusion Indication Threshold Reduction (TITRe2) investigators are listed in *Appendix 1*

Declared competing interests of authors: Rachel CM Brierley, Alan Cohen, Alice Miles, Andrew D Mumford, Gavin J Murphy (up to 31 August 2012), Rachel L Nash, Katie Pike, Sarah Wordsworth, Elizabeth A Stokes and Barnaby C Reeves had varying percentages of their salaries paid for by the grant awarded for the trial. Some or all of the time contributed by Gianni D Angelini, Gavin J Murphy (from 1 September 2012) and Chris A Rogers was paid for by the British Heart Foundation. Barnaby C Reeves is a member of the National Institute for Health Research Health Technology Assessment Commissioning Board, Systematic Reviews Programme Advisory Board and the Efficient Studies Design Board.

Published August 2016
DOI: 10.3310/hta20600

This report should be referenced as follows:

Reeves BC, Pike K, Rogers CA, Brierley RCM, Stokes EA, Wordsworth S, *et al*. A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2). *Health Technol Assess* 2016;**20**(60).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.058

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the ISI Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

The HTA programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

For more information about the HTA programme please visit the website: http://www.nets.nihr.ac.uk/programmes/hta

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 06/402/94. The contractual start date was in December 2008. The draft report began editorial review in September 2014 and was accepted for publication in January 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).

Abstract

A multicentre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and health-care resource use following cardiac surgery (TITRe2)

Barnaby C Reeves,[1]* Katie Pike,[1] Chris A Rogers,[1] Rachel CM Brierley,[1] Elizabeth A Stokes,[2] Sarah Wordsworth,[2] Rachel L Nash,[1] Alice Miles,[1] Andrew D Mumford,[3] Alan Cohen,[4] Gianni D Angelini[5] and Gavin J Murphy[6] on behalf of the TITRe2 investigators†

[1]Clinical Trials and Evaluation Unit, School of Clinical Sciences, University of Bristol, Bristol, UK
[2]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[3]School of Cellular and Molecular Medicine, University of Bristol, Bristol, UK
[4]Division of Specialised Services, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[5]Bristol Heart Institute, School of Clinical Sciences, University of Bristol, Bristol, UK
[6]Department of Cardiovascular Sciences and National Institute for Health Research Leicester Biomedical Research Unit in Cardiovascular Medicine, University of Leicester, Leicester, UK

*Corresponding author barney.reeves@bristol.ac.uk
†Transfusion Indication Threshold Reduction (TITRe2) investigators are listed in *Appendix 1*

Background: Uncertainty about optimal red blood cell transfusion thresholds in cardiac surgery is reflected in widely varying transfusion rates between surgeons and cardiac centres.

Objective: To test the hypothesis that a restrictive compared with a liberal threshold for red blood cell transfusion after cardiac surgery reduces post-operative morbidity and health-care costs.

Design: Multicentre, parallel randomised controlled trial and within-trial cost–utility analysis from a UK NHS and Personal Social Services perspective. We could not blind health-care staff but tried to blind participants. Random allocations were generated by computer and minimised by centre and operation.

Setting: Seventeen specialist cardiac surgery centres in UK NHS hospitals.

Participants: Patients aged > 16 years undergoing non-emergency cardiac surgery with post-operative haemoglobin < 9 g/dl. Exclusion criteria were: unwilling to have transfusion owing to beliefs; platelet, red blood cell or clotting disorder; ongoing or recurrent sepsis; and critical limb ischaemia.

Interventions: Participants in the liberal group were eligible for transfusion immediately after randomisation (post-operative haemoglobin < 9 g/dl); participants in the restrictive group were eligible for transfusion if their post-operative haemoglobin fell to < 7.5 g/dl during the index hospital stay.

Main outcome measures: The primary outcome was a composite outcome of any serious infectious (sepsis or wound infection) or ischaemic event (permanent stroke, myocardial infarction, gut infarction or acute kidney injury) during the 3 months after randomisation. Events were verified or adjudicated by blinded personnel. Secondary outcomes included blood products transfused; infectious events; ischaemic events; quality of life (European Quality of Life-5 Dimensions); duration of intensive care or high-dependency unit stay; duration of hospital stay; significant pulmonary morbidity; all-cause mortality; resource use, costs and cost-effectiveness.

Results: We randomised 2007 participants between 15 July 2009 and 18 February 2013; four withdrew, leaving 1000 and 1003 in the restrictive and liberal groups, respectively. Transfusion rates after randomisation were 53.4% (534/1000) and 92.2% (925/1003). The primary outcome occurred in 35.1% (331/944) and 33.0% (317/962) of participants in the restrictive and liberal groups [odds ratio (OR) 1.11, 95% confidence interval (CI) 0.91 to 1.34; $p = 0.30$], respectively. There were no subgroup effects for the primary outcome, although some sensitivity analyses substantially altered the estimated OR. There were no differences for secondary clinical outcomes except for mortality, with more deaths in the restrictive group (4.2%, 42/1000 vs. 2.6%, 26/1003; hazard ratio 1.64, 95% CI 1.00 to 2.67; $p = 0.045$). Serious post-operative complications excluding primary outcome events occurred in 35.7% (354/991) and 34.2% (339/991) of participants in the restrictive and liberal groups, respectively. The total cost per participant from surgery to 3 months postoperatively differed little by group, just £182 less (standard error £488) in the restrictive group, largely owing to the difference in red blood cells cost. In the base-case cost-effectiveness results, the point estimate suggested that the restrictive threshold was cost-effective; however, this result was very uncertain partly owing to the negligible difference in quality-adjusted life-years gained.

Conclusions: A restrictive transfusion threshold is not superior to a liberal threshold after cardiac surgery. This finding supports restrictive transfusion due to reduced consumption and costs of red blood cells. However, secondary findings create uncertainty about recommending restrictive transfusion and prompt a new hypothesis that liberal transfusion may be superior after cardiac surgery. Reanalyses of existing trial datasets, excluding all participants who did not breach the liberal threshold, followed by a meta-analysis of the reanalysed results are the most obvious research steps to address the new hypothesis about the possible harm of red blood cell transfusion.

Trial registration: Current Controlled Trials ISRCTN70923932.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 20, No. 60. See the NIHR Journals Library website for further project information.

Contents

List of tables

List of figures

List of abbreviations

AE	adverse event
AKI	acute kidney injury
ARDS	acute respiratory distress syndrome
ASEPSIS	additional treatment, serious discharge, erythema, purulent exudate, separation of deep tissues, isolation of bacteria, stay duration as inpatient
BNF	*British National Formulary*
CABG	coronary artery bypass graft
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CICU	cardiac intensive care unit
CPAP	continuous positive airway pressure
CPB	cardiopulmonary bypass
CRF	case report form
CT	computerised tomography
DMEC	Data Monitoring and Ethics Committee
ECG	echocardiogram
ED	emergency department
eGFR	estimated glomerular filtration rate
eMIT	electronic marketing information tool
EQ-5D-3L	European Quality of Life-5 Dimensions-3 Level
EuroSCORE	European System for Cardiac Operative Risk Evaluation
FFP	fresh frozen plasma
GI	gastrointestinal
GMR	geometric mean ratio
GP	general practitioner
HCHS	Hospital and Community Health Services
HDU	high-dependency unit
HR	hazard ratio
HRG	Healthcare Resource Group
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IQR	interquartile range
ITT	intention to treat
IV	instrumental variable
LOS	length of stay
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
NHSBT	NHS Blood and Transplant
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OR	odds ratio
PIL	patient information leaflet
PPI	patient and public involvement
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
TITRe2	Transfusion Indication Threshold Reduction
TSC	Trial Steering Committee
VAS	visual analogue scale

Plain English summary

When patients lose blood during cardiac surgery, the oxygen-carrying capacity of the blood (haemoglobin) drops. Blood transfusion is thought to restore the oxygen-carrying capacity and a patient's haemoglobin usually guides doctors' decisions about when to give a transfusion. However, different hospitals and surgeons give transfusions at different levels of haemoglobin. The study investigated whether or not giving fewer transfusions (by allowing the haemoglobin to fall lower) reduces the risk of serious post-operative complications previously associated with transfusion.

Just over 2000 patients took part. They were allocated by chance into groups who were transfused at 'low' or 'high' haemoglobins. Almost all patients in the high group (92%), but only half of the patients in the low group (53%), had a transfusion. Slightly more patients in the low group experienced serious complications (infections, heart attacks, strokes, kidney and serious bowel problems) than in the high group (35% vs. 33%), but this was a small difference. However, more patients died in the low group than in the high group (4.2% vs. 2.6%, respectively). We found no substantial differences between groups in other aspects of patients' recovery, including the duration of hospital stay, quality of life reported by patients or lung complications.

Contrary to our original expectation, the trial showed that waiting to transfuse until lower haemoglobin is reached might, in fact, be worse. It is particularly worrying that more patients died in the lower haemoglobin group. We have recommended that more research be done to understand the reasons for this finding.

Scientific summary

Background

Perioperative anaemia is common after cardiac surgery and is associated with an increased risk of morbidity and mortality. Transfusion of allogeneic red blood cells is the preferred treatment for acute anaemia but an 'acceptable' level of anaemia, and the risks and benefits of red blood cell transfusion, are unclear. Defining what constitutes a safe and effective red blood cell transfusion strategy is important; observational analyses suggest that reversing anaemia by transfusing red blood cells may worsen outcome, yet > 50% of cardiac surgery patients are transfused. Randomised controlled trials (RCTs) have sought to answer the question by comparing restrictive (lower haemoglobin) with liberal (higher haemoglobin) transfusion thresholds. However, RCTs in cardiac surgery populations have had insufficient power and RCTs in non-cardiac surgery populations, although generally supportive of restrictive practice, have recruited very low proportions of patients with unstable cardiac disease. Transfusion guidelines increasingly recommend restrictive transfusion but uncertainty about the safety of this strategy for cardiac surgery patients persists and is reflected in large variations in transfusion practice.

Objective

The Transfusion Indication Threshold Reduction (TITRe2) RCT tested the hypothesis that a restrictive threshold for red blood cell transfusion reduces post-operative morbidity and health-care costs compared with a liberal threshold.

Methods

Study design

A multicentre parallel-group RCT with an economic evaluation.

Settings and participants

Seventeen specialist cardiac surgery centres in UK NHS hospitals took part. Patients aged > 16 years undergoing non-emergency cardiac surgery were eligible if the haemoglobin fell < 9 g/dl post-operatively. Exclusion criteria were: patients unwilling to have transfusion owing to beliefs; platelets, red blood cell or clotting disorders; ongoing or recurrent sepsis; critical limb ischaemia; inability to give full informed consent; and participation in another interventional research study. Participants gave written informed consent before surgery and were only randomised after admission to intensive care units (ICUs) after surgery, if the haemoglobin fell < 9 g/dl. Participants were followed up by post or telephone 3 months after randomisation.

Interventions

Participants were randomised to a restrictive (transfuse if haemoglobin falls < 7.5 g/dl) or liberal threshold (transfuse if haemoglobin falls < 9 g/dl), which was applied during hospitalisation after surgery. One red blood cell unit was transfused, the haemoglobin rechecked and a second unit transfused only if the haemoglobin remained below the relevant threshold. Physicians could transfuse, or refuse to transfuse, in contravention of the allocated threshold but had to document the reason and the haemoglobin level.

Randomisation and blinding

Randomisation was achieved with a secure internet-based system that generated the allocation using cohort minimisation to balance allocations by centre and operation type, and concealed allocation until a participant's details were recorded. Physicians and nurses were not blinded to the allocation. We tried to blind participants and tested whether or not this was successful by asking if they knew their allocation.

Outcomes

The primary outcome was a composite of a serious infectious (sepsis or wound infection) or ischaemic event [permanent stroke, myocardial infarction, gut infarction or acute kidney injury (AKI)] in the 3 months after randomisation.

Secondary outcomes were: red blood cells and other blood products transfused; infectious events; ischaemic events; quality of life [European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L)]; duration of ICU and high-dependency unit (HDU) stay; duration of hospital stay; significant pulmonary morbidity; all-cause mortality; resource use, costs and cost-effectiveness.

Protocol adherence

Non-adherence was defined as (1) failing to transfuse red blood cells within 24 hours of breaching the allocated threshold or (2) transfusing red blood cells when the haemoglobin level was above the allocated threshold. Non-adherence was considered severe when it changed the classification of a participant as transfused or not.

Sample size

The primary outcome frequency was estimated to be 17% and 11% in the liberal and restrictive groups, respectively. A sample size of 1468 was required to detect this difference with 90% power and 5% significance (two-sided test). The target sample size was inflated to 2000 to allow for uncertainty about non-adherence, as higher than expected non-adherence would reduce power.

Statistical methods

All analyses were performed on an intention-to-treat basis and directed by a pre-specified analysis plan. All outcomes were compared using mixed-effects methods, adjusting for operation type and centre. Binary outcomes were analysed by logistic regression, time-to-event outcomes using Cox proportional hazards models and EQ-5D-3L scores using mixed-effects mixed-distribution models.

Primary outcome frequencies in pre-specified subgroups were compared by estimating allocation by subgroup interactions. Sensitivity analyses were performed for the primary outcome and for mortality. Pre-specified observational analyses adjusting for potential confounding by conventional regression and instrumental variable (IV) methods (using allocation as the instrument) investigated relationships between number of red blood cells units transfused, minimum haemoglobin and red blood cell storage time with morbidity and mortality.

A 5% significance level (two-sided) was applied for main treatment effects and subgroup analyses, and a 10% level for interactions between allocated group and time in longitudinal models. Likelihood ratio tests were used. We did not adjust for multiple testing or a planned interim analysis.

Economic evaluation

A within-trial cost–utility analysis assessed the incremental cost and cost-effectiveness of a restrictive compared with liberal transfusion threshold from the perspective of the UK NHS and Personal Social Services. The primary outcome was quality-adjusted life-years (QALYs) estimated using the EQ-5D-3L. Resource use was collected for all participants from surgery to 3 months postoperatively. The restrictive haemoglobin threshold was considered as cost-effective if the incremental cost-effectiveness ratio fell below £20,000.

Results

Trial cohort

Between July 2009 and February 2013, 11,483 patients were screened; 3565 consented to take part and 2007 were randomised. Four participants asked for their data to be excluded, giving an analysis population of 2003 participants (1000 and 1003 in the restrictive and liberal groups, respectively). Treatment of 47 participants (28 and 19 in the restrictive and liberal groups, respectively) was discontinued. Twenty-five participants (1.2%) could not be followed up.

Participant characteristics

Baseline characteristics were similar in the two randomised groups. Median age was 70.3 years [interquartile range (IQR) 63.5–76.4 years] and 68.5% were men. Median European System for Cardiac Operative Risk Evaluation was 5 (IQR 3–7). Most participants had undergone coronary artery bypass grafting (CABG) (40.7%) or valve (30.5%) surgery. One-quarter of participants had a red blood cell transfusion before randomisation (25.7%).

Success of blinding

At discharge, 15.1% of participants thought they knew their allocation, of whom 115 (75.6%) were correct. At 3 months, more participants thought they knew their allocation (27.5%) but fewer (56.6%) were correct.

Haemoglobin levels and transfusions

After randomisation, the mean nadir haemoglobin level was lower in the restrictive than the liberal group by approximately 1 g/dl; 53.4% and 92.2% of participants in the restrictive and liberal groups, respectively, were transfused after randomisation [risk ratio (RR) 0.58, 95% confidence interval (CI) 0.54 to 0.62; $p < 0.0001$]. The median numbers of red blood cell units transfused were 1 unit (IQR 0–2 units) and 2 units (IQR 1–3 units) in the restrictive and liberal groups, respectively. Use of other blood products was similar across groups.

Non-adherence

One or more instance of non-adherence was documented in 30.0% and 45.2% of participants in the restrictive and liberal groups, respectively. Severe non-adherence was reported for 9.7% and 6.2% in the restrictive and liberal groups, respectively.

Primary outcome

The primary outcome occurred in 35.1% and 33.0% of participants in the restrictive and liberal groups, respectively [odds ratio (OR) 1.11, 95% CI 0.91 to 1.34; $p = 0.30$]. Sensitivity analyses tested the robustness of this result. When participants transfused before randomisation were excluded, the OR increased (OR 1.23, 95% CI 0.97 to 1.54; $p = 0.084$). Including additional AKI events, identified from routinely collected creatinine data, as primary outcome events increased the treatment effect (OR 1.20, 95% CI 1.00 to 1.44; $p = 0.045$). Two sensitivity analyses, excluding primary outcome events in the first 24 hours after randomisation and excluding AKI events not supported by a creatinine rise, did not change the result. Restricting the primary outcome to serious events decreased the treatment effect (OR 0.99, 95% CI 0.77 to 1.27; $p = 0.94$). A further sensitivity analysis showed little heterogeneity between sites ($p = 0.65$) and no indication that the OR tended to the null with increasing severe non-adherence. There were no subgroup effects.

Secondary outcomes

There were more deaths in the restrictive than the liberal group [4.2% vs. 2.6%, respectively; hazard ratio (HR) 1.64, 95% CI 1.00 to 2.67; $p = 0.045$]; two sensitivity analyses, excluding participants transfused before randomisation and deaths within 24 hours of randomisation, shifted the HR away from the null. Percentages of participants with significant pulmonary morbidity, duration of ICU/HDU and hospital stay and EQ-5D-3L scores were similar across groups. Serious post-operative complications (excluding primary outcome events) occurred in 35.7% (664 events) and 34.2% (648 events) of participants in the restrictive and liberal groups.

Meta-analysis

A meta-analysis of mortality for TITRe2 and five earlier RCTs suggest an increased risk of death in the restrictive group, of borderline statistical significance (RR 1.41, 95% CI 0.98 to 2.04).

Economic evaluation

Mean QALYs to 3 months were 0.18 in both groups (restrictive minus liberal difference = 0.0004, 95% CI –0.0037 to 0.0045). The total costs from surgery up to 3 months were £17,945 and £18,127 in the restrictive and liberal groups, respectively (mean difference –£182, 95% CI –£1108 to £744); the cost difference was largely attributable to the difference in the costs of red blood cells. Several outliers substantially influenced the average cost of participants in the liberal group, altering the direction of the differences between groups when they were excluded.

In the base-case cost-effectiveness analysis, the point estimate suggested that the restrictive group was more effective and less costly than the liberal group (i.e. dominant) and, therefore, cost-effective. However, there was great uncertainty around these results partly owing to the negligible differences in QALYs gained. Bootstrap replicates of the cost and QALY differences covered all four quadrants of the cost-effectiveness plane, which shows that there is not a movement in one direction rather than another. There was a 43% probability that the restrictive group dominated the liberal group but also a 20% probability of the reverse scenario. There was a 65% chance that the restrictive group was cost-effective at a £20,000/QALY ceiling ratio. One subgroup effect was significant; participants in the restrictive group with chronic pulmonary disease or asthma gained a reduced number of QALYs compared with other participants ($p = 0.003$).

Observational analyses

A dose–response relationship between the number of red blood cell units transfused and occurrence of the primary outcome or death was apparent in a conventional multivariable regression model (OR 1.19, 95% CI 1.06 to 1.35). However, an IV analysis contradicted this result (OR 0.89, 95% CI 0.75 to 1.06). A multivariable regression model suggested that increasing haemoglobin level reduced the risk of primary outcome or death, particularly for non-CABG patients (estimate for valve patients; OR 0.62, 95% CI 0.48 to 0.79). An IV analysis estimated a reduced effect for all surgery types (OR 0.83, 95% CI 0.64 to 1.08). The third analysis investigating the effect of red blood cell storage time was infeasible.

Discussion

Main findings: study results

The frequency of the primary outcome did not differ between the restrictive and liberal groups. Subgroup analyses showed no differences, contrary to beliefs that 'at risk' groups should be transfused at different haemoglobin thresholds. More participants died in the restrictive group than the liberal group (4.2% vs. 2.6%, respectively). There were no differences in other secondary outcomes, including cost, between the two groups. In the economic evaluation, differences in cost and effect between the two groups were small. The cost-effectiveness result was very uncertain, although the restrictive threshold appeared to be dominant (more effective and less costly).

Strengths and limitations

There was better than expected power with TITRe2 because the outcome frequency was higher than expected. In addition, unlike previous trials, the trial only randomised participants who breached the liberal threshold, preventing any dilution of the treatment effect by including similar numbers of untransfused participants in both groups. TITRe2 was pragmatic and, therefore, should directly inform red blood cell transfusion practice in cardiac surgery patients with haemoglobin levels < 9 g/dl in similar settings. Transfusion thresholds were successfully implemented and there were few missing outcome data.

The main limitation was our inability to blind health-care staff. However, the use of objective end points or adjudication by blinded personnel protected against detection bias. The nature of protocol non-adherence differed by group but only affected the overall transfusion rate in a small percentage of participants. A second limitation was the unexpected way in which sepsis and AKI, less severe events, dominated the primary composite outcome. A third limitation was that prospective data collection failed to identify AKI events that were apparent from routinely collected serial creatinine data. The effects of the final two limitations were investigated in sensitivity analyses.

Lessons for the future

The results of the trial lead us to reject the hypothesis that restrictive transfusion is superior to more liberal transfusion in cardiac surgery. Our main analysis indicates no difference between the two strategies, although, given the increased cost of more liberal transfusion, these results are still supportive of restrictive practice. However, the results of our primary analysis notwithstanding, the secondary analyses create new uncertainty about recommending restrictive transfusion after cardiac surgery. Importantly, the risk of death was higher in the restrictive group and this finding strengthened in sensitivity analyses, although the trial does not provide a clear explanation for this finding. Causes of death and severe adverse events that preceded death did not suggest a mechanism. In addition to the mortality finding, a benefit from more liberal transfusion was also suggested by sensitivity analyses of the primary outcome, excluding participants who had received transfusion prior to randomisation and including AKI events based on serial creatinine data. These findings do not lead us to recommend using a liberal threshold after cardiac surgery; however, we believe that, collectively, they should lead to a new hypothesis that more liberal transfusion may be beneficial.

This hypothesis is clinically plausible. Unlike previous trials, all participants in TITRe2 had symptomatic cardiovascular disease, the principal indication for cardiac surgery, and a significant proportion will have developed oxygen supply dependency in the immediate post-operative period. As cardiac surgery patients are often at the limits of their cardiovascular reserve, they may constitute a high-risk group in whom more liberal transfusion is beneficial.

Conclusion

A restrictive threshold is not superior to a liberal threshold after cardiac surgery.

Implications for health care

Our primary finding supports use of either transfusion threshold evaluated in the trial. In practice, it is likely to lead to wider application of a restrictive strategy because this will reduce the consumption and cost of allogeneic red blood cells.

Recommendations for research

Our findings show that transfusion is safe but uncertainty remains as to the correct haemoglobin threshold or indication for transfusion at which the benefits outweigh the risks. We suggest that a more liberal transfusion threshold of approximately 9 g/dl may benefit cardiac surgery patients and that this hypothesis should be tested in a pragmatic trial. Identifying when the benefits of transfusion outweigh the risks is not straightforward because red blood cell transfusion is inevitably associated with haemoglobin level and the nadir haemoglobin level does not necessarily precede transfusion.

Trial registration

This trial is registered as ISRCTN70923932.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Perioperative anaemia is strongly associated with adverse outcomes in cardiac surgery patients.[1–3] Transfusion of allogenic red blood cells is the preferred treatment to reverse acute anaemia and, on average, > 50% of adult cardiac surgery patients receive a perioperative transfusion.[4,5]

Cardiac surgery consumes a substantial proportion of blood supplies – > 6% of all red blood cell use in the UK occurs in cardiac surgery.[6] Red blood cell transfusion is essential in some cardiac surgical patients for the management of life-threatening haemorrhage. In most cases, however, decisions to give a red blood cell transfusion are made because the haemoglobin concentration has fallen to a level or threshold at which the physician is uncomfortable.[2,7,8] The transfusion threshold varies across different cardiac surgery units and between different surgeons, which contributes to the wide variation in blood usage observed in cardiac surgical units (25% to 95%).[4,5,9] The threshold variation stems from a lack of evidence regarding what constitutes a safe level of anaemia following cardiac surgery.

Background and rationale

The clinical benefits of red blood cell transfusion beyond increasing circulating haemoglobin concentrations are unclear. Observational analyses suggest that transfusion after cardiac surgery may not, in fact, improve outcome where, in an apparent paradox, reversal of anaemia with transfusion has been shown to be consistently associated with increased infection, low cardiac output state, acute kidney injury (AKI) and death.[2,10,11] In contrast, randomised controlled trials (RCTs) comparing a restrictive red blood cell transfusion threshold (allowing a participant's haemoglobin level to drop to a lower level before transfusing) with a more liberal strategy (transfusing a participant at a higher haemoglobin level) have not demonstrated adverse effects directly attributable to transfusion in patients undergoing major surgery or in the critically ill.[12–14]

The absence of harm from restrictive practice in RCTs combined with the evidence from observational studies has been interpreted as being supportive of restrictive transfusion practice.[15] Alongside the well-documented risks of more liberal transfusion (including haemolytic and non-haemolytic transfusion reactions and transfusion-associated lung injury,[16] increasing demands on blood services[17] as well as additional and important cost implications associated with the storage, handling and administration of red blood cell units[18]), this evidence has led to an emphasis on restrictive transfusion in contemporary blood management guidelines[19–21] and increasingly in health policy.[22,23]

The Transfusion Indication Threshold Reduction (TITRe2) trial was designed in 2006 and was prompted by the widely varying transfusion thresholds that were being applied at the time and by a detailed observational analysis of data from the hospital in which the triallists worked.[2] Existing RCTs at the time that had compared liberal with restrictive transfusion in cardiac surgery, including our own pilot trial, had lacked sufficient statistical power to demonstrate clinical benefits attributable to restrictive transfusion.[24–26] A contemporary systematic review of RCTs of liberal compared with restrictive transfusion, most of which were not conducted in cardiac surgery, also concluded that there is uncertainty as to the benefits of more restrictive transfusion in patients with unstable cardiac disease.[12]

Aims and objectives

To address this uncertainty, we undertook the TITRe2 RCT. The trial was designed to test the hypothesis that a restrictive threshold for red blood cell transfusion (haemoglobin 7.5 g/dl and/or haematocrit 22%) would reduce post-operative morbidity and health service costs compared with a liberal threshold (haemoglobin 9 g/dl and/or haematocrit 27%).

Specific objectives of the TITRe2 trial were:

- to estimate the difference in the risk of a post-operative infection or ischaemic event between restrictive and liberal transfusion thresholds
- to compare the effects of restrictive and liberal transfusion thresholds with respect to a range of secondary outcomes
- to estimate the cost-effectiveness of a restrictive compared with a liberal haemoglobin transfusion threshold.

Chapter 2 Methods

Study design

The study was a multicentre RCT. The objectives were addressed by randomising participants to either a restrictive (transfuse if post-operative haemoglobin dropped below 7.5 g/dl, or haematocrit below 22%) or a liberal (transfuse if post-operative haemoglobin dropped below 9 g/dl, or haematocrit below 27%) strategy for red blood cell transfusion. The trial is registered, number ISRCTN70923932.

Participants provided written, informed consent pre-operatively but only became eligible for randomisation if their haemoglobin fell below 9 g/dl, or haematocrit below 27%, at some point postoperatively. Therefore, postoperatively, haemoglobin/haematocrit levels were monitored according to usual care and if the relevant threshold was breached at any time on the cardiac unit the participant was randomised as soon as possible, at the latest within 24 hours. (Note: thresholds were expressed as haemoglobin or haematocrit, and randomisation or transfusion was indicated if either value fell below the allocated threshold. Hereinafter, haemoglobin should be interpreted as haemoglobin or haematocrit.) A UK NHS Research Ethics Committee approved the study (08/H0606/125). Full details of all methods are reported elsewhere.[7]

Changes to study design after commencement of the study

There were no major changes to the study design after commencement. Some changes were made to eligibility criteria and outcomes, which are discussed in *Changes to study eligibility criteria after commencement of the study* and *Changes to study outcomes after commencement of the study*, respectively.

Participants

Eligibility criteria

The study inclusion criteria were:

- adults of either sex, aged ≥ 16 years, undergoing cardiac surgery [defined as coronary artery bypass grafting (CABG), heart valve replacement or repair, aortic surgery or surgical correction of congenital cardiac disease]
- post-operative haemoglobin level < 9 g/dl at any stage during the patient's post-operative hospital stay [i.e. on cardiac intensive care unit (CICU) or cardiac surgical ward]
- written informed consent.

The exclusion criteria were:

- patients undergoing emergency cardiac surgery
- patients prevented from having blood and blood products according to a system of beliefs (e.g. Jehovah's Witnesses)
- patients with congenital or acquired platelet, red blood cell or clotting disorders
- patients with ongoing or recurrent sepsis
- patients with critical limb ischaemia
- patients unable to give full informed consent for the study (e.g. learning or language difficulties)
- patients already participating in another interventional research study.

Changes to study eligibility criteria after commencement of the study

In April 2009 (before starting recruitment to the study), two exclusion criteria were removed:

- patients with a critical carotid artery stenosis (> 75%)
- patients with flow limiting (> 70% luminal stenosis) coronary artery disease not undergoing complete revascularisation.

These exclusion criteria were included originally on the basis of the exclusion criteria used in the pilot study for this trial.[26] The pilot study used different thresholds, notably a lower haemoglobin threshold of 7 g/dl for the restrictive group. At the time of designing the pilot study it was felt that, because patients entering the pilot study could potentially experience haemoglobin levels as low as 7 g/dl, these exclusion criteria were needed to avoid non-adherence by intensivists, who might consider such patients to be more at risk of experiencing ischaemic adverse effects. TITRe2 used the higher haemoglobin level of 7.5 g/dl for the restrictive threshold and this threshold was already used routinely at some centres for all patients. Therefore, after discussing these exclusion criteria again, the study team believed they were not necessary for TITRe2.

In August 2010, the previously stated upper age limit of 80 years for the inclusion of participants was removed. This decision was a result of feedback from sites that they did not consider older age to be a contraindication for randomisation to the study and that the exclusion would substantially limit the pool of eligible patients for the study. After removal of this criterion surgeons were still able to refuse to include patients aged > 80 years on a case-by-case basis.

Settings

Patients were recruited to the trial in 17 specialist cardiac surgery centres in UK NHS hospitals.

Interventions

The trial compared two thresholds for blood transfusion, liberal and restrictive. The thresholds were defined as follows:

- Liberal group: participants randomised to this group were eligible for transfusion if their post-operative haemoglobin level fell < 9 g/dl at any time during their post-operative hospital stay on the CICU or cardiac surgical ward. Therefore, all participants in this group should have received one red blood cell unit soon after randomisation. The objective was to maintain the haemoglobin level at or above 9 g/dl.
- Restrictive group: participants randomised to this group were eligible for transfusion if their post-operative haemoglobin level fell < 7.5 g/dl at any time during their post-operative hospital stay on the CICU or cardiac surgery ward. The objective was to maintain the haemoglobin level ≥ 7.5 g/dl.

The protocol specified that, in both groups, one red blood cell unit should be transfused, the haemoglobin rechecked and a second unit transfused only if the haemoglobin remained below the relevant threshold. Clinicians were allowed to transfuse, or refuse to transfuse, in contravention of the allocated threshold but were required to document their reason for doing this and the haemoglobin level at the time. Furthermore, a clinician could decide it was in the best interests of a participant to permanently discontinue treatment according to the allocated group, which did not constitute a withdrawal and the participant was followed up as normal. Other aspects of post-operative care were provided in accordance with the institution's usual care.

The duration of intervention in the trial was the duration of the participant's care under the consultant cardiac surgeon or a maximum of 3 months after the date of randomisation, whichever was shorter. Almost always, the duration of care under the cardiac surgeon was the period of hospitalisation after surgery. However, a few participants who developed serious complications were transferred to the care of another consultant in the same hospital, at which time the interventional period for the study ended.

Outcomes

Primary outcome

The primary outcome was a binary composite outcome of any serious infectious (sepsis or wound infection) or ischaemic event [permanent stroke, myocardial infarction (MI), gut infarction or AKI] in the first 3 months after randomisation. The qualifying events listed in *Table 1* were included; the table also describes the manner in which each qualifying event was verified.

Events occurring after discharge only contributed to the primary outcome if the potentially qualifying event resulted in admission to hospital or death. Wound infection identified as a result of adding post-discharge information was the only exception to this rule. For example, information ascertained using the additional treatment, serous discharge, erythema, purulent exudate, separation of deep tissues, isolation of bacteria, and stay duration as inpatient (ASEPSIS) post-discharge surveillance assessment questionnaire (see *Table 1*), when added to the ASEPSIS score derived for the index admission, sometimes resulted in a total ASEPSIS score for the index admission that was > 20. Other suspected infectious events treated in the community that did not cause readmission to hospital were not recorded as they could not be validated and are less serious than perioperative infections.

Events suspected to qualify for the primary outcome but that were not supported by objective evidence were referred to an independent adjudication committee. In practice, the adjudication committee only considered suspected MIs because documentary objective evidence for sepsis, stroke, AKI and gut infarction was verified by research nurses at the co-ordinating centre who were blinded to the random allocation. The adjudication committee consisted of a cardiac surgeon, cardiologist and anaesthetist who were blinded to allocation and each other's assessments. They were required to classify a suspected MI as definite or not based on participant's medical history, echocardiograms (ECGs) (both pre-operatively and at the time of the suspected MI) and troponin levels at the time of the suspected MI. Agreement between at least two of the three specialists was required to reach a final adjudicated classification.

Death was not included as a component of the primary composite outcome because, if death occurred following a qualifying event, the event would precede death itself. Deaths that occurred for other reasons were not hypothesised to increase because of red blood cell transfusion.

TABLE 1 Definition of serious infectious/ischaemic primary outcome events

Infectious events	Definition/method of verification
Sepsis	During index admission: • Defined by the following two conditions: antibiotic treatment for suspected infection and the presence of SIRS within 24 hours prior to the start of antibiotic treatment • SIRS was defined as two or more of the following conditions: temperature > 38 °C or < 36 °C; heart rate > 90 beats/minute; respiratory rate > 20 breaths/minute or $PaCO_2$ < 32 mmHg or < 4.3 kPa; white blood cell count > 12,000 mm^3 or < 4000 mm^3 In follow-up period: • Hospital admission for treatment with antibiotic therapy
Wound infection	ASEPSIS score of > 20.[27] Two scores were calculated and summed: • An in-hospital score from assessment of wounds between one and three times during a participant's index hospital admission A follow-up score derived from the in-hospital score and a questionnaire either posted for self-completion or administered by telephone, at 3 months post randomisation[28,29]
Ischaemic events	**Definition/method of verification**
Permanent stroke	Clinical report of brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit (defined as a deficit in motor, sensory or co-ordination function)
MI	Elevated post-operative peak serum troponin I or T, verified by an adjudication committee. Further details are given in *Primary outcome*
Gut infarction	Documented reason for laparotomy or post-mortem report
AKI	AKI network criteria for AKI, stage one, two or three:[30] Stage one: • Serum creatinine increase ≥ 0.3 mg/dl (≥ 26.4 µmol/l), or • > 1.5 and ≤ 2-fold serum creatinine increase compared with the pre-operative serum creatinine (baseline) value, or • urine output < 0.5 ml/kg for 6 hours Stage two: • > 2 and ≤ threefold serum creatinine increase compared with the pre-operative serum creatinine (baseline) value, or • urine output < 0.5 ml/kg for > 12 hours Stage three: • > threefold serum creatinine increase compared with the pre-operative serum creatinine (baseline) value, 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 • urine output < 0.3 ml/kg per hour for 24 hours or anuria for 12 hours, or • need for RRT irrespective of AKI stage at time of RRT • the AKI stage recorded was the highest stage reached by the participant after randomisation

CT, computerised tomography; MRI, magnetic resonance imaging; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome.

Secondary outcomes

All secondary outcomes were collected in the time between randomisation and 3-month follow-up, unless otherwise stated.

- Units of red blood cells and other blood components [fresh frozen plasma (FFP), platelets, cryoprecipitate, activated factor VI (NovoSeven, Novo Nordisk) and Beriplex® (CSL Behring UK Ltd)] transfused during a participant's hospital stay. Red blood cells transfused pre-randomisation (either intraoperatively or postoperatively but prior to randomisation) were collected and described separately. However, it was only possible to collect information about other blood components transfused over the pre-randomisation and post-randomisation periods combined.
- Occurrence of an infectious qualifying event, defined as sepsis or wound infection.
- Occurrence of an ischaemic qualifying event, defined as permanent stroke, MI, AKI or gut infarction.
- Quality of life measured using European Quality of Life-5 Dimensions-3 Level (EQ-5D-3L),[31] assessed pre-operatively and at 6 weeks and 3 months post randomisation.
- Duration of intensive care unit (ICU) or high-dependency unit (HDU) stay; calculated as the total time between randomisation and discharge from the cardiac unit that the participant was in either the CICU, HDU or general ICU wards, including any periods of readmission to that area.
- Duration of hospital stay, calculated as the time between randomisation and discharge from the cardiac unit.
- Significant pulmonary morbidity, comprising initiation of non-invasive ventilation [e.g. continuous positive airway pressure (CPAP) ventilation], reintubation/ventilation or tracheostomy.
- All-cause mortality.
- Health and Personal Social Services resource use and their costs.

(Durations of ICU, HDU and hospital stay were originally specified as 'postoperative'. We specified randomisation as the time origin for these durations in the analysis plan, for consistency with the primary and other secondary outcomes.)

Changes to study outcomes after commencement of the study

The following changes were made to study outcomes after the trial had commenced.

- In April 2009, before starting recruitment, there were some amendments made to the definitions of infectious and ischaemic events that qualified for the primary outcome.
- In March 2010, an amendment was made to include troponin T in addition to troponin I in defining MI. This amendment was required after discovering that some participating centres habitually used troponin T rather than I. In addition, as part of this change, the troponin threshold for MI that was previously stated was removed; the decision was made, instead, to collect the highest troponin reading for all participants with suspected MI and to adjudicate suspected MIs (see *Primary outcome*).
- In March 2011, the secondary outcome 'significant pulmonary morbidity' was added. This was initially named transfusion-associated circulatory overload and then subsequently renamed. The outcome was added because information from the haematology community had highlighted pulmonary morbidity as a potentially important outcome for patients receiving blood transfusions. The outcome was defined with respect to data already being collected on the study case report forms (CRFs) before the amendment so that the outcome could be identified consistently across the entire duration of the trial.
- Furthermore, in March 2011, 'A&E [accident and emergency] admission' was removed from the primary outcome as qualifying event. This change arose from discussion with clinicians on the Trial Steering Committee (TSC) who agreed that a participant experiencing any element of the primary outcome would be admitted to hospital if they attended the emergency department (ED) within the follow-up period.

Adverse events

Expected adverse events (AEs) were specified in the study protocol and captured via the study CRFs, both for the post-operative in-hospital period (serious and non-serious), and at the 3-month follow-up (serious only).

A serious adverse events (SAE) is any untoward medical occurrence that either results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly/birth defect.

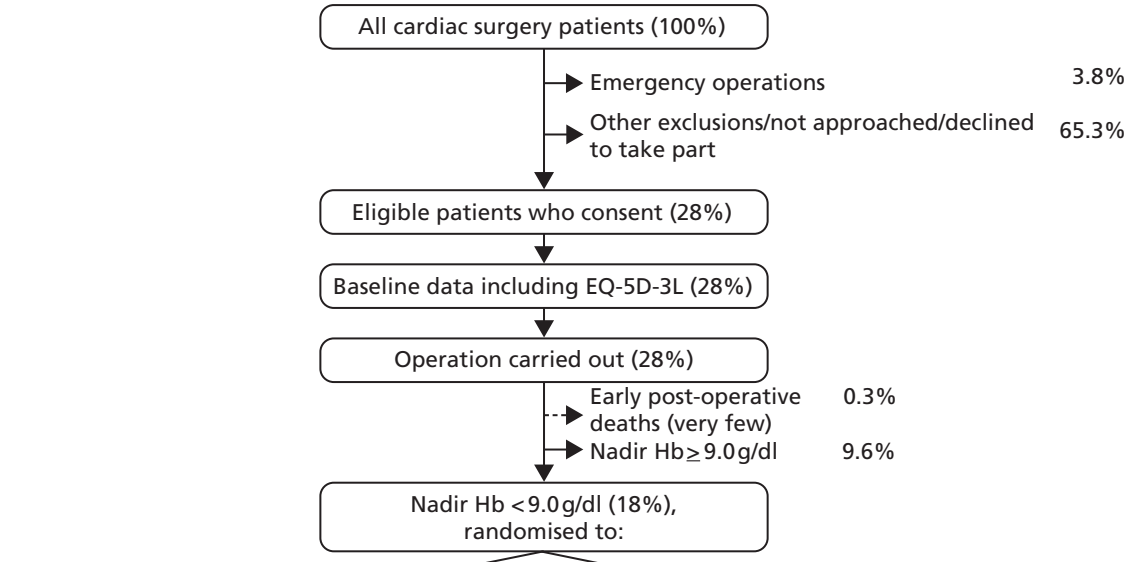
All other AEs were considered unexpected, any such events satisfying one or more criteria for classification as serious were recorded in detail on purpose-designed SAE forms. Unexpected SAEs were coded using the Medical Dictionary for Regulatory Activities version 14.1 (MedDRA; McLean, VA, USA) independently by two research nurses blinded to randomised allocation. Any discrepancies were resolved by a consultant cardiac surgeon also blinded to allocation.

Sample size

The trial was designed to answer superiority questions. The following steps were taken to calculate the sample size.

- From observational data, we assumed that approximately 65% of patients would breach the threshold of 9 g/dl and 20% would breach the 7.5 g/dl threshold.[2] Therefore, with complete adherence to the transfusion protocol, we assumed that transfusion rates should be 100% in the liberal group and ≈30% (0.20/0.65) in the restrictive group.
- In the observational analysis,[2] 63% of patients with a nadir haematocrit between 22.5% and 27%, and 93% of patients with a nadir haematocrit below 22.5%, were transfused. Therefore, in combination with the proportions of patients expected to breach the liberal and restrictive thresholds, these figures were used to estimate conservative transfusion rates of 74% for the liberal group and ≤ 35% for the restrictive group. These percentages reflected the rates of transfusion documented in the observational study (*Figure 1*) and assumed non-adherence with the transfusion protocol of approximately 26% in the liberal group and 5% in the restrictive group.
- The observational frequencies of infectious and ischaemic events for transfused and non-transfused patients were adjusted to reflect the estimated transfusion rates in the two groups (i.e. 74% and ≤ 35%), giving event rates for the proposed composite outcome of 17% in the liberal threshold group and 11% in the restrictive threshold group. A sample size of 1468 was required to detect this risk difference of 6% with 90% power and 5% significance (two-sided test), using a sample size estimate for a chi-squared test comparing two independent proportions (applying a normal approximation correction for continuity) in Stata version 9 (StataCorp LP, College Station, TX, USA).
- The target sample size was inflated to 2000 participants (i.e. 1000 in each group) to allow for uncertainty about non-adherence and the estimated proportions of participants experiencing the primary outcome. We regarded these parameter estimates as uncertain because (1) they were estimated from observational data, (2) they were based on the red blood cell transfusion rate only in Bristol, (3) they were based on routinely collected data, using definitions for elements of the composite primary outcome which are not identical to those proposed for the trial, and (4) they were based on any compared with no red blood cell transfusion, rather than on the number of units of red blood cells likely to be transfused in participants who breach the liberal threshold. No adjustment was made for withdrawals or loss to follow-up, as both rates were expected to be very low.

We expected approximately two-thirds of participants to breach the haemoglobin threshold for eligibility.[2] Therefore, we predicted that we needed to register approximately 3000 participants into the study as a whole to allow 2000 participants to be randomised into the main study.



	Transfusion threshold		
	Nadir Hb <7.5 g/dl	Nadir Hb 7.5 to <9.0 g/dl	Total
Transfused	96%	62%	74%
Not transfused	4%	38%	26%

	Transfusion threshold		
	Nadir Hb <7.5 g/dl	Nadir Hb 7.5 to <9.0 g/dl	Total
Transfused	96%	<5%	<35%
Not transfused	4%	≥95%	≥65%

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram summarising TITRe2 trial design. Percentages are based on data from the cardiac surgery registry in Bristol for the period January to September 2007. An unknown percentage of patients are excluded by the exclusion criteria because the registry does not contain sufficient detail to apply the definitions proposed for the trial. However, patients meeting one or more of these criteria are extremely rare and we expected all of the exclusion criteria to account for a maximum of 5% of cardiac surgery patients. Hb, haemoglobin.

The main outcome measure for the economic evaluation was quality-adjusted life-years (QALYs), which are derived from EQ-5D-3L utilities measured on a continuous scale and time under observation. The analysis of QALYs requires baseline utility to be modelled as a covariate; the correlation between baseline and 3-month EQ-5D-3L utilities was assumed to be ≥ 0.3. With a total sample size of 2000, the trial had more than 95% power to detect a standardised difference in continuous outcomes between groups of 0.2 with 1% significance (two-sided test). This magnitude of difference is conventionally considered to be 'small'.[32]

Interim analyses

One formal, pre-specified interim analysis was carried out in June 2012 after 50% of the participants had been recruited and followed up for 3 months. Extreme criteria for stopping the trial ($p \leq 0.001$) were set and, therefore, no adjustment was made to the sample size and statistical significance levels for this interim analysis.

Randomisation

Participants were randomly allocated to either the liberal or restrictive transfusion strategies using cohort minimisation to achieve balance across the two arms of the trial; minimisation factors were centre and operation type (CABG, valve, CABG and valve combined, or other cardiac surgery). Participants were

randomly assigned in a 1 : 1 ratio. Allocations were generated by computer and concealed using an internet-based system provided by Sealed Envelope Ltd (London, UK). Staff in participating centres were able to gain secure limited access to the system using a password and PIN (personal identification number). Information to identify a participant uniquely and to confirm eligibility had to be entered before the system assigned the randomised treatment allocation, ensuring concealment of allocations. Randomisation occurred postoperatively and as soon as possible after the participant's haemoglobin level fell below 9 g/dl (at the latest within 24 hours). If randomisation did not occur within 24 hours, the patient was considered to have become ineligible and should not have been randomised unless the haemoglobin fell below 9 g/dl again (when the clock for the '24 hour rule' was restarted; see *Non-adherence with randomisation protocol*).

Blinding

It was not possible to blind clinicians, research staff and other NHS staff caring for participants to the randomised allocation. However, outcomes were defined on the basis of objective criteria as far as possible, in order to minimise susceptibility to bias. Furthermore, both the research nurses reviewing the documentary evidence relating to primary outcome events and the adjudication committee assessing MIs were blinded to treatment allocation.

Every effort was made to blind participants to their allocation. The success of blinding was checked by asking participants if they knew what their allocation was at the time of discharge from hospital and their 3-month post-randomisation follow-up.

Data collection

In-hospital data collection (see *Appendix 4* for the CRFs) included the following elements.

- Screening log of all non-emergency patients having cardiac surgery
  - distinguishing patients but without recording identifiable data electronically
  - whether or not a patient information leaflet (PIL) was sent
  - whether or not a patient was approached for the trial
  - assessment of eligibility; if ineligible, reasons for ineligibility
  - whether or not a patient was asked to give written informed consent for the trial.
- For all registered participants (randomised and non-randomised)
  - pre-operative characteristics, including operation category
  - a summary of blood products received
  - daily haemoglobin levels to check compliance with protocol.
- For all randomised participants
  - date and time when the haemoglobin fell below 9 g/dl
  - operative details, including duration of surgery and use of any blood products
  - observations required for the primary and secondary outcomes, including dates and times of relevant events
  - other key resource use
  - any AEs
  - information about whether or not a participant was blinded to allocation at discharge.

Research staff in participating centres collected data on the trial screening log and pre-printed CRFs. These data were transferred promptly to a secure computerised database maintained on a NHS computer, allowing data to be checked centrally. Queries about specific data items were listed on the database and were immediately apparent to centre staff when they logged on.

Post-operative haemoglobin levels in consented participants were measured at regular intervals and the lowest level observed on each post-operative day was recorded on the CRF. After randomisation, the threshold to which a participant had been randomised was communicated to attending medical and nursing staff and recorded on the CRF. Centres used varying methods to highlight to staff that a participant had been randomised. Details of red blood cell transfusions were recorded and haemoglobin levels continued to be monitored. If a non-adherent transfusion decision was made for a randomised participant (i.e. a decision which did not adhere to the allocated protocol, see *Non-adherence with transfusion protocol*), the attending doctor was required to give a reason for the decision. This reason was documented on the CRF.

Data collection after hospital discharge consisted of the following elements.

- The EQ-5D-3L was posted to randomised participants at 6 weeks and 3 months after randomisation. Participants who consented to the study but were not randomised also received a postal EQ-5D-3L 3 months after their operation.
- Three months after the operation, a questionnaire was posted for self-completion, or administered by telephone (if a participant elected to be telephoned or failed to return the postal questionnaire), by staff at the co-ordinating centre. The questionnaire was composed of items eliciting information about:
    - AEs occurring after discharge, with further details of any event suspected to contribute to the primary outcome or meet the definition of a SAE sought from either the admitting hospital or the participant's general practitioner (GP).
    - surgical wound infections occurring after discharge (ASEPSIS post-discharge surveillance questionnaire).[28,29]
    - resource use after discharge from hospital.
    - a participant's awareness of his/her random allocation.
- Occasionally data collection was delayed beyond the planned follow-up times; when this occurred the following rules were used to determine whether or not data should be included in analyses:
    - EQ-5D-3L – the time between questionnaire completion and operation date was examined by group, blinded to allocation, separately for each time point. The distributions did not differ; therefore, data corresponding to times that were extreme outliers (identified by eye) were excluded but all other data included.
    - Three-month telephone/postal questionnaire – questionnaire items were phrased specifically in relation to the 3-month post-operative period and staff completing the telephone questionnaires were trained only to record information regarding this period. Therefore, data from all questionnaires were used.

Data collection is summarised in *Table 2*.

TABLE 2 Schedule of data collection

Data collected	Pre-surgery	Day of surgery	At randomisation	In CICU/ward	At discharge	6 weeks after randomisation	3 months after randomisation
Eligibility	✓[a]						
Written consent	✓[a]						
Demographics and medical history	✓[a]						
EQ-5D-3L questionnaire	✓[a]					✓[b]	✓[a,b]
Operative details		✓					
Haemoglobin/haematocrit level	✓[a]	✓[a]	✓	✓[a]			
Summary of blood components transfused				✓[a]			
Details of red blood cell transfusion		✓		✓			
Randomised allocation			✓				
Surgical complications and AEs				✓			✓[c]
ASEPSIS assessment of wound infection				✓			
Resource use data		✓		✓			✓[c]
ASEPSIS post-discharge surveillance							✓[c]
Check participant blinded to allocation					✓		✓[c]

a Data collected for all registered participants (all other data collected for randomised participants only).
b Assessed via postal questionnaire.
c Data collected via 3-month follow-up postal questionnaire. This information was obtained by telephone if the participant did not respond to the postal questionnaire or preferred to be contacted by telephone.

Adherence

Non-adherence with randomisation protocol

Non-adherence with the randomisation protocol was defined as any of the following:

- Participant did not meet one or more of the pre-consent study eligibility criteria but was consented into the study. Any randomised participant to whom this applies was classified as 'randomised in error' and excluded from the analysis population.
- Participant consented and met the post-consent inclusion criteria (i.e. haemoglobin dropped below 9 g/dl) but was not randomised. Any randomised participant to whom this applies was not randomised and, therefore, was excluded from the analysis population.
- Participant did not meet the post-consent eligibility criteria (i.e. haemoglobin did not drop below 9 g/dl) but was randomised. Any randomised participant to whom this applies was classified as 'randomised in error' and excluded from the analysis population.
- Participant was randomised more than 24 hours after meeting the post-consent inclusion criteria (i.e. randomised more than 24 hours after haemoglobin dropping below 9 g/dl). Any participant to whom this applies was classified as non-adherent with the randomisation protocol, but was included in the analysis population.

Non-adherence with transfusion protocol

Measuring and assessing adherence with the transfusion protocol was identified as a critical element of the study owing to the assumptions about adherence made in the sample size calculation.[33] The Data Monitoring and Ethics Committee (DMEC) also highlighted the importance of non-adherence, as they had concern that doctors might otherwise make transfusion decisions in different ways in the two groups. For example, a decision to transfuse in the liberal group could be delayed up to 24 hours without contravening the protocol and such behaviour would have been missed if data about haemoglobin levels measured during this period, their times and consequent actions had not been recorded.

Two types of non-adherence were defined: (1) a participant received a red blood cell transfusion outside of protocol ('extra' transfusion) and (2) a participant was not given a red blood cell transfusion that, according to the protocol, should have been given ('withheld' transfusion). Adherence was assessed for the period from randomisation to hospital discharge so multiple instances of non-adherence could be documented for a participant. If a participant withdrew or had their treatment according to their allocation discontinued, adherence after the time of withdrawal/discontinuation was not assessed. For both of the above types of non-adherence, instances were classified into mild, moderate or severe (*Table 3*). Non-adherence was classified as severe only if the non-adherent instant changed the participant's overall classification as transfused or not.

TABLE 3 Non-adherence with the transfusion protocol

Non-adherence type	'Extra' transfusion outside of protocol	'Withheld' transfusion according to protocol
Mild	N/A	A transfusion took place, but more than 24 hours after the relevant breach of the transfusion threshold
Moderate	Participant transfused outside of protocol, but participant breached the threshold for transfusion at least once postoperatively	Participant was not transfused following a breach, but the participant had previously had at least one post-randomisation transfusion
Severe	Participant transfused outside of protocol and participant did not breach the threshold for transfusion at any point postoperatively	Participant was not transfused following a breach and participant had no post-randomisation transfusions

N/A, not applicable.
A participant could breach the relevant threshold for transfusion multiple times and so there could be more than one case of non-adherence per participant.

In addition to describing the amount of non-adherence, work has been done to further describe and characterise non-adherence, including:

- characteristics of each instance of non-adherence (including reasons, haemoglobin levels and timing) have been described
- logistic regression models were fitted to identify predictors of non-adherence
- non-adherence trends both by centre and over the course of the trial have been described.

Statistical methods

The analysis and safety populations consisted of all participants randomised into the study, excluding participants who withdrew and who were unwilling for the data already collected to be used. All analyses were performed on an intention-to-treat (ITT) basis and were directed by a pre-specified analysis plan.[34] Continuous variables were summarised via the mean and standard deviation (SD), or median and interquartile range (IQR) if distributions were skewed. Categorical data were summarised as a number and percentage. Pre-randomisation characteristics were described by allocated treatment. Similarly, pre-operative and intraoperative characteristics, transfusions, EQ-5D-3L scores and mortality of randomised and non-randomised (but consented) participants were described but no formal comparisons made.

Comparisons of outcomes

All outcomes were analysed using mixed-effects regression models, adjusting for all factors included in the cohort minimisation: operation type as a fixed effect and centre as a random effect (or a shared frailty term in time-to-event models). The primary outcome and other binary outcomes (numbers of participants experiencing infectious or ischaemic events, any transfusions of red blood cells and non-red blood cell products and significant pulmonary morbidity) were analysed using logistic regression, with treatment estimates presented as odds ratios (OR) and 95% confidence intervals (CI). For the analysis of the transfusion of any red blood cells, treatment estimates were analysed using unadjusted logistic regression, with results presented as a risk ratio (RR) and 95% CI, as the OR proved difficult to interpret and an adjusted model did not converge. Time-to-event outcomes were analysed using Cox proportional hazards models and treatment estimates presented as hazard ratios (HR) and 95% CI. Durations of ICU/HDU stay and hospital stay were censored at the time of death if the participant died before discharge from hospital. All-cause mortality was censored at the time of last follow-up for survivors. A secondary analysis of the primary outcome, analysing the time to first occurrence of the primary outcome, was also undertaken using a Cox proportional hazards model, censoring at the time of last follow-up or death.

Longitudinal data (EQ-5D-3L scores) were analysed using mixed-effects mixed-distribution models;[35] this method was used because the distribution of the data was non-monotonic, with many participants scoring perfect health. Both types of score (utility and visual analogue scores) were dichotomised into less than perfect health compared with perfect health. There were two-parts to each fitted model: (1) an occurrence model, a logistic regression model for the occurrence of less than perfect health compared with perfect health, and (2) an intensity model, a log-linear model for the score, conditional on a non-perfect health score. Correlated participant-term random effects (for occurrence and intensity) were included in each model to allow for the repeated measures. Separate parameter estimates were incorporated into models for the mean baseline response across both treatment groups and for each treatment post intervention, avoiding the necessity to either exclude cases with missing baseline measures or to impute missing baseline values. A time by allocation interaction (post intervention) was added to each of the models; an overall treatment effect is reported unless the interaction was statistically significant at the 10% level, in which case separate treatment effects at each post-intervention time are given.

Safety data

The AEs and SAEs were described by allocated treatment but no formal comparisons made.

Subgroup analyses

Pre-planned subgroup analyses were specified because of clinical opinion that transfusion decisions should be influenced by patients' characteristics, notably that 'at-risk' patients should be transfused at a different threshold. The subgroups defined in the protocol were: operation type (isolated CABG vs. other operation types), age (< 75 years vs. ≥ 75 years), pre-operative diagnosis of diabetes (none vs. diet, oral medication or insulin controlled), pre-operative diagnosis of lung disease (none vs. chronic pulmonary disease or asthma), pre-operative renal impairment [estimated glomerular filtration rate (eGFR) > 60 ml/minute vs. eGFR ≤ 60 ml/minute], sex (males vs. females) and ventricular function (good vs. moderate or poor). Such analyses were implemented by adding a relevant treatment allocation by subgroup interaction term into the primary outcome model; the hypothesis for all subgroup analyses was that there would be no interaction. The pre-operative renal impairment subgroup analysis was defined in the study protocol as pre-operative creatinine ≤ 177 µmol/l versus creatinine > 177 µmol/l. However, during the course of the trial, use of pre-operative creatinine for risk stratification was superseded by estimated eGFR and, therefore, the subgroup analysis for renal impairment was based on eGFR as described above (this change was not covered by a protocol amendment).

Sensitivity analyses

A number of sensitivity analyses were pre-specified for the primary outcome in the analysis plan, although such analyses were not specified in the study protocol.

(a) Examining treatment effect estimates for the primary outcome by site, ordering sites by rates of severe non-adherence with the transfusion protocol. This was implemented by a forest plot displaying site-specific treatment estimates. It provided a way of assessing the effect of non-adherence on the overall treatment estimate for the primary outcome, without excluding non-adherent participants. (We considered that an analysis excluding non-adherent participants would be inappropriate because it would be very likely to be biased as non-adherent participants were hypothesised to be the sicker participants in the restrictive group and the healthier participants in the liberal group.) As non-adherence represents a dilution of the allocated intervention, we hypothesised that the treatment effect would tend towards the null with increasing non-adherence.

(b) Excluding all events that occurred in the first 24 hours after randomisation. The rationale was that such events could have an onset that actually preceded randomisation and, hence, be unrelated to the intervention. Therefore, we hypothesised that the treatment effect would tend away from the null with exclusion of these events.

(c) Excluding participants who were transfused before randomisation. The rationale was that transfusions before randomisation, expected to occur with similar frequency in both groups, would dilute any effect of a difference between groups in the number of transfusions after randomisation. Therefore, we hypothesised that the treatment effect would tend away from the null with exclusion of pre-randomisation transfusions.

(d) In collecting AKI data it became apparent that prospective data collection by research nurses in centres failed to identify AKI events that were apparent from routinely collected serial creatinine data. We attribute this discrepancy to differences between centres in the 'baseline' creatinine value used to define AKI, which can be confusing to implement as the specified creatinine rise should occur in a 48-hour period.[30,36] However, highest daily creatinine levels were recorded separately, so the following sensitivity analyses were planned:

- excluding AKI events when the clinical diagnosis was not verified by routinely recorded creatinine levels. This analysis would exclude potentially 'false' AKI events, although AKI events in these participants may have been 'true' events classified on the basis of urine output (which was not documented routinely).
- including additional AKI events when the participant was reported not to have had AKI according to clinical judgement but when highest daily creatinine levels supported a diagnosis of AKI. This analysis would include AKI events that were missed, assuming that the creatinine levels recorded for usual hospital care were accurately transcribed on to the CRF.

Assuming that false AKI events would arise in proportion to the incidence of true AKI events, they would not bias the treatment effect. Therefore, we hypothesised that the effect in the first analysis would reduce precision but not shift the estimate predictably either towards or away from the null. Similarly, assuming that missed AKI events would arise in proportion to the incidence of true AKI events, they would also not bias the treatment effect. Therefore, we hypothesised that the effect in the second analysis would increase precision but not shift the estimate predictably.

(e) Including only 'serious' primary outcome events, defined as either stroke, MI, gut infarction, AKI stage three events, pre-discharge sepsis plus organ failure [MI, stroke, laparotomy for gut infarction and one or more of reintubation, acute respiratory distress syndrome (ARDS), low cardiac output and/or tracheostomy] and/or post-discharge sepsis that required hospital readmission. This analysis arose from the pre-planned interim analysis that showed a higher primary outcome event frequency than was anticipated when the study was designed, with a large majority of qualifying events arising from sepsis and AKI, which were considered to be clinically less serious. We considered that this sensitivity analysis would better reflect our original intention in formulating the composite outcome and the outcome events that were included in the observational analysis, which led to the superiority hypothesis for the trial. This analysis would necessarily have less precision but we did not have a strong hypothesis about the way in which the treatment effect might be affected. If transfusion were to have the same effect on more and less serious events, the treatment effect should be unaltered; if transfusion were to have a differential effect on more and less serious events, the treatment effect should be moved towards or away from the null in a manner consistent with the differential effect.

Post-hoc analyses

In addition, a secondary post-hoc analysis of severe in hospital events was performed, which involved refitting the primary outcome model with an outcome of death, severe sepsis [as defined in sensitivity analysis (e) above], ARDS, tracheostomy, low cardiac output, MI, AKI stage three, gut infarction and/or stroke. This analysis was performed because it was judged to be of key interest to hospital-based clinicians caring for patients. As for analysis (e) above, it would necessarily have less precision but we did not hypothesise that the treatment effect would be moved towards or away from the null.

Two further post-hoc sensitivity analyses were carried out for the secondary outcome of mortality; these comprised analyses (b) and (c) above (i.e. excluding deaths within 24 hours of randomisation and participants transfused before randomisation). These were suggested during the peer review process, on account of the seriousness of the outcome, and we agreed that they were worthwhile. Our (post hoc) hypotheses were the same as that for the corresponding sensitivity analyses of the primary outcome. These were the only additional analyses requested in this way, the decision to perform them was made without knowing the results and the results are fully reported.

Observational analyses

Three observational analyses were pre-specified in the study protocol.

(a) Estimating the relationship between the number of red blood cell units transfused and the risk of mortality and morbidity, stratified by trial arm.
(b) Investigating the relationship between percentage decline in haemoglobin from the pre-operative level and the risk of primary and secondary outcomes, taking into account the number of red blood cell units transfused.
(c) Investigating whether or not red blood cell age (i.e. time since donation and processing) is associated with the risk of primary and secondary outcomes, achieved by linking batch numbers of all red blood cells transfused to a blood bank database and determining the age of each unit donation and transfusion dates.

For the purposes of these observational analyses, a composite outcome of the trial primary outcome or death was defined in the statistical analysis plan (SAP). In addition, all red blood cell units transfused or haemoglobin levels recorded after the time of the first occurrence of the primary outcome (or censoring) were excluded to ensure the relevant exposure occurred before the outcome. (More complex methods to deal with this issue were outlined in the SAP but these have not been attempted owing to the complexity of the analyses.) For all three analyses, pre-operative and intraoperative characteristics and trial outcomes were described by exposure [i.e. any red blood cells vs. no red blood cells, minimum haemoglobin < 7.5 g/dl vs. ≥ 7.5 g/dl, and transfusion of any red blood cells aged over 21 days old (median age) vs. only younger blood (< 21 days) vs. no red blood cell transfusions].

For analyses (b) and (c), the exposure definitions differ slightly from those used in the protocol/SAP. With respect to analysis (b), the protocol stated that haemoglobin would be defined in terms of percentage decline; however, exploratory analyses suggested this was not sensible (e.g. a participant with pre-operative haemoglobin 12 g/dl and post-randomisation haemoglobin 6 g/dl would be treated in the same way as a participant with pre-operative haemoglobin 18 g/dl and post-randomisation haemoglobin 9 g/dl, as the percentage decline is 50% in both cases) and that it would be more informative to include both pre-operative and post-randomisation haemoglobin levels in any analysis model. For analysis (c), various methods of defining age of blood were described in the SAP (using the age of the 'oldest' red blood cell unit given, the mean age of all red blood cells, the use of any red blood cells more than 14 days old, the number or percentage of red blood cells given over 14 days old, the use of red blood cells older than the median age of all red blood cells transfused) and it was stated that the age of the oldest unit would be used as the primary analysis. Owing to the large volume of missing data for age of blood, it was decided instead only to provide descriptive analyses by the receipt of any red blood cells older than the median age.

For parts (a) and (b), further analyses have been undertaken. Univariate analyses exploring the relationship between exposures and the outcome were performed. Two separate adjusted models [one for analysis (a) and one for analysis (b)] were then fitted adjusting for the following, if found to be potential confounders: operation type, centre (as a random effect), European System for Cardiac Operative Risk Evaluation (EuroSCORE), age, sex and pre-randomisation red blood cell transfusions [for analysis (a) only]. A model building strategy was used whereby variables were sequentially added to the model, at each step including the variable that improved the model fit the most (as determined by a likelihood ratio test). Variables were included in the model if they were (1) associated with both the exposure and the outcome but did not lie on the causal pathway between the exposure and outcome, and (2) significantly contributed to the relevant multivariate model (defined by a likelihood ratio $p < 0.05$ or modifying the effect estimate by greater than 10%). If pairs of variables were considered to be collinear or strongly related (e.g. EuroSCORE and age), only one of the pair was included. In addition, interaction terms were included in models if significant at the 5% level. The parameterisation of the exposure variable (e.g. continuous linear, continuous

including additional power terms, ordinal categorical or binary) was explored using fractional polynomial models and likelihood ratio tests to compare nested models. Marginal plots were used to describe interactions between continuous and categorical covariates graphically. Models were refitted separately within each randomised group. Finally, instrumental variable (IV) methods were used to estimate the associations of interest free from confounding, separately for analyses (a) and (b); models used the multiplicative generalised method of moments estimation (the ivpoisson command in Stata).

Meta-analysis

A meta-analysis was performed analysing mortality from TITRe2 and all other RCTs that have compared liberal and restrictive red blood cell transfusion strategies in patients undergoing cardiac surgery. This analysis was undertaken to place the findings of TITRe2 in the context of the evidence base. Eligible RCTs[24–26,37,38] were identified from a previous review of RCTs comparing restrictive versus liberal transfusion thresholds[12] and an on-going review comparing RCT and observational evidence about the effects of red blood cell transfusion in cardiac surgery patients.[39] The previous Cochrane review searched multiple databases including the Cochrane Injuries Group's Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and ISI Web of Science (both the Science and Conference Proceedings Citation Indices). The review included RCTs with a concurrent control group in which participants were assigned to groups with different transfusion triggers or thresholds, for which the thresholds were defined by a haemoglobin or haematocrit level that a participant had to reach before a red blood cell transfusion could be administered. For the purposes of the current meta-analysis, we included RCTs identified from either review that were deemed to have taken place in the context of cardiac surgery. Therefore, we included RCTs with different group-specific transfusion thresholds to those used in TITRe2 and which included all participants, irrespective of whether or not the liberal threshold was breached (i.e. without the post-operative eligibility criterion adopted in the TITRe2 trial). When writing the SAP, we also intended to perform a meta-analysis for the primary outcome; however, outcomes were too dissimilar between included RCTs. The meta-analysis was performed using standard meta-analysis methods for binary outcomes with a random effects model.

Missing data

Missing data are indicated in all of the tables. Rules for imputing missing data were outlined in the analysis plan, dependent on the level of missing data. However, the majority of outcomes had levels of missing data below the defined thresholds in the plan (5% for outcomes measured at one time point and 20% for longitudinal data) and imputation methods were not generally used. The first exception was for the infectious events secondary outcome (5.6% missing), whereby separate estimates were made prior to hospital discharge and overall. A second exception was the in-hospital component of the ASEPSIS score from which wound infection events were identified; this was one of the rarer components of the primary outcome but the in-hospital component of the score was the outcome data item that was most likely to be missing. If the in-hospital ASEPSIS score was missing, the participant was assumed not to have had a serious wound infection if the following criteria were met: participant did not have antibiotics for suspected wound infection prescribed in hospital and follow-up was completed, and the participant reported no problems with the healing of chest, leg and/or arm wound up to 3 months after the operation.

Significance levels

For hypothesis tests, two-tailed p-values of < 0.05 were considered statistically significant, with the exception of tests for interactions between group and time in longitudinal models when a 10% significance level was used. Likelihood ratio tests were used in preference to Wald tests. No formal adjustment was made for multiple testing. When interpreting the results, consideration has been given to the number of tests performed and the consistency, magnitude and direction of estimates for different outcomes.[40] All data management and analyses were performed in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) or Stata version 12.1 or 13.1 (StataCorp LP, College Station, TX, USA).

Health economics

Aims and objectives

The economic evaluation aimed to estimate the cost-effectiveness of the restrictive compared with the liberal haemoglobin transfusion threshold as compared in TITRe2. Our main objective was to estimate the incremental cost and the incremental cost-effectiveness of the restrictive compared with the liberal haemoglobin transfusion threshold after cardiac surgery.

Economic evaluation methods overview

A cost–utility analysis was conducted, with outcomes measured using the EQ-5D-3L. The restrictive haemoglobin threshold was considered as cost-effective if the incremental cost-effectiveness ratio (ICER) fell below £20,000, which is generally considered as the threshold at which the National Institute for Health and Care Excellence (NICE) considers an intervention to be cost-effective.[41] Good practice guidelines on the conduct of economic evaluations were followed for the economic evaluation.[42–44] *Table 4* summarises the methods for the economic evaluation, with further details provided in the text following the table.

TABLE 4 Summary of methods used in the economic evaluation

Aspect of methodology	Strategy used in base-case analysis
Form of economic evaluation	Cost–utility analysis for comparison between restrictive and liberal transfusion thresholds
Perspective	NHS and Personal Social Services
Time horizon	A within-trial analysis, taking a 3-month time horizon (up to the primary clinical time point)
Population	All randomised participants were included, except those randomised in error
Costs included in analysis	Index admission • Surgery • Blood products • Length of stay by ward type (including ICU and HDU) • Medications • Reoperations • Investigations and treatments relating to complications, including renal replacement therapy, and SAEs Post discharge • Readmissions to hospital • Other hospital ED 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 6 weeks and 3 months postoperatively)
QALY calculations	Assume that participants' utility changes linearly between utility measurements
Adjustment for baseline utility	Regression used to adjust QALY calculations for differences in baseline utility
Missing data	Mean imputation and multiple imputation

Form of analysis and primary outcome measure

The primary outcome measure for the economic evaluation was QALYs, as advocated by NICE.[44] This outcome combines quantity and quality of life into a single measure. Our evaluation took the form of a cost–utility analysis in which the difference in mean costs between the two transfusion threshold groups is divided by the difference in mean QALYs between the two groups to calculate an ICER and, specifically, the incremental cost per QALY gained by switching from using a liberal threshold to using a restrictive threshold.

Perspective

The primary perspective of the evaluation was that of the UK NHS and Personal Social Services, as recommended by NICE.[44] However, data were collected on some types of non-NHS costs including expenditure incurred by a participant when travelling to hospital. We planned to include these costs in a wider perspective in a sensitivity analysis, if resource use for these non-NHS costs differed between the trial groups. The perspective for outcomes was that of the participants undergoing treatment.

Time horizon

A within-trial analysis, taking a 3-month time horizon, was conducted. It was anticipated that all major resource use would occur within this timeframe and, therefore, be captured. The start of our 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. Our time horizon continued until 3 months postoperatively. Ideally, the time point for baseline costs and outcomes should be the same; however, the EQ-5D-3L was collected pre-operatively whereas detailed resource use collection began on the day of surgery.

Population

Our base-case analysis included all participants randomised into the trial except those randomised in error, which is consistent with the main effectiveness analyses. Analyses were performed on an ITT basis.

Collection of resource use and cost data

Resource use data were collected on all significant health service resource inputs for the trial participants up to the point of the 3-month follow-up. The main resource use categories that were costed are listed in the first column of *Table 5*, along with the 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 participants to trial groups.

Initial cardiac surgery and blood products

As the type of surgery itself was not the main factor being assessed within the trial, we used published cardiac surgery costs rather than performing a detailed microcosting. We used cost figures from the cardiac surgery Healthcare Resource Group (HRG) codes from the elective inpatient spreadsheet in the National Reference Costs database[45] and subtracted costs relating to length of stay (LOS) and blood products to calculate the cost of the surgery itself.

The LOS in hospital was removed by using the average LOS associated with each HRG and each specialty (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 3*, *Table 60* 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 Reference Costs was for procedures involving multiple valves[45] but in TITRe2 this proportion is only 10%. To reflect this fact, we created a weighted average of the costs of single- and multiple-valve procedures, with the weighting being according to the proportion of these types of participants recruited to TITRe2.

TABLE 5 Resource use categories and sources of resource use and unit cost information

Resource category	Sources for resource use information[a]	Sources for unit cost information
Initial cardiac surgery	CRF C1	National Schedule of Reference Costs (2012–13);[45] NHSBT National Comparative Audit of Blood Transfusion;[5] NHSBT price list[46]
Blood products	CRFs B1, B2	NHSBT price list;[46] primary data collection for the costs of administering blood products (further details in *Appendix 3*, *Table 60*)
Initial stay in hospital post surgery	CRFs D1, H5	National Schedule of Reference Costs (2012–13)[45]
Medications	CRF D2	eMIT;[47] BNF[48]
Complications, including re-operations; SAEs	CRFs C1, C2–C4, C5, C6, C7, F1–F3, H5, X1	National Schedule of Reference Costs (2012–13);[45] eMIT;[47] BNF[48]
Hospital readmissions	CRF X1, 3-month follow-up questionnaire – section 2a	National Schedule of Reference Costs (2012–13)[45]
Outpatient attendances and visits to ED	3-month follow-up questionnaire – sections 2b, 2c	National Schedule of Reference Costs (2012–13)[45]
Community health and social care contacts	3-month follow-up questionnaire – section 3	National Schedule of Reference Costs (2012–13);[45] Unit Costs of Health and Social Care[49]

BNF, *British National Formulary*; eMIT, electronic marketing information tool; NHSBT, NHS Blood and Transplant.
a B1–X1 are labels used to distinguish CRFs (see *Appendix 4*).

The costs of blood products (red blood cells, 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 NHS Blood and Transplant (NHSBT) national audit in 2011,[5] and valued using published NHSBT prices. For our surgery category of 'other', the costs of average blood products were removed by applying the information used for CABG and valve participants because the average operation time for 'other' was lengthy and most similar to the CABG and valve group.

The total number of red blood cells transfused each day was recorded on the trial CRFs. The costs of administering red blood cell transfusions were added to the costs of the units of red blood cells. The costs of administering transfusions were based on primary data collection of the nursing time and consumables associated with administering transfusions collected by the authors as part of another study (see *Appendix 3*, *Table 60* for more information).

Initial post-surgery hospital stay

In terms of hospital stay following the actual surgery, LOS was collected for CICU/HDU, general 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. Participants had an initial extubation date and time recorded in the trial, along with the dates and times of any further intubations and extubations. If data were missing on extubation date/time, we assumed that for those who died before discharge, that they were intubated until death. For participants without a tracheostomy, and no indication that they were not extubated, we assumed an average intubation duration, based on information from participants with available data. For participants who went on to have a tracheostomy, we calculated their time to tracheostomy and time to discharge and assumed the average intubation time for participants with intubation durations between these two times. Similar assumptions were made for any reintubations. CICU and HDU costs were taken from NHS Reference Costs.[45] To cost time on a cardiac ward, an average bed-day cost was created by weighting the cost of relevant cardiac procedures excess bed-day costs according to activity from the elective inpatient spreadsheet in Reference Costs[45] (see *Appendix 3*, *Table 60* for further details).

Medications and fluids

Medications and fluids given during surgery or intensive care, such as inotropes, were costed for each participant. Information on whether or not participants received these medications were collected on pre-specified yes/no tick boxes on the trial CRFs (Form D2). In order to cost these interventions, a member of the trial research team provided an estimate of the likely quantity of fluids a participant 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 participants were readmitted (up to 3 months). The names of specific antibiotics were reported on the trial CRF (Form C5) as free text with the route and duration of the course. We established the most likely dose with the TITRe2 research team. If information was missing on the route of administration (oral or intravenous) or frequency of drugs, we clarified this information with the trial research team and conducted sensitivity analyses around alternative scenarios and drug costs for antibiotic treatment. The costs of antibiotics were included in the costs of complications.

In addition, the regular medications that participants were taking, such as beta-blockers, statins and warfarin, were recorded as on the medication or not by pre-specified tick boxes (yes/no) on CRF Form D2. This was recorded for two time points: at baseline – on admission to the cardiac surgery unit – and at discharge from the cardiac surgery unit. A member of the trial research team estimated the name, dose and mode of delivery (oral or intravenous) for the regular medications that participants were taking at baseline and discharge. We assumed that participants took any medications recorded at discharge for the 3-month follow-up and costed these medications for 3 months. In a separate analysis, we also costed the regular medications participants were taking at baseline and at discharge for a period of one week. Comparisons were then made between the costs of these medications taken at baseline and at discharge from hospital, to determine whether or not there were significant changes in this resource before and after surgery.

Treatment complications and serious adverse events

Primary outcome complications that were costed included serious infection, permanent stroke, MI, gut infarction and AKI. Details of these complications were recorded on CRF Forms C5 and C6. We also included the costs of any procedures or tests required to verify the complications, such as computerised tomography (CT) or magnetic resonance imaging (MRI) scans for permanent stroke, laparotomy for gut infarction and ECG for suspected MIs. For all participants suspected to have had a MI, the costs of diagnostic investigations were included. The costs of all other post-operative complications recorded on CRF C7 were calculated; examples include pacing (both temporary and permanent pacing), CPAP ventilation, tracheostomy and transient ischaemic attack. Cardiac surgery reoperations were also included in complication costs. Care was taken to avoid double counting of complication costs. For example, resource use associated with both ARDS and reintubation was assumed to be a transoesophageal echo and three chest X-rays. If a participant had both complications on the same day, only one echo and three chest X-rays were costed to avoid probable double counting. The trial CRFs were used to gather the types and amounts of complications the participants had experienced and also to capture resource use around SAEs. SAEs were individually reviewed and additional resources were costed if not already captured in complication costs, again to avoid double counting. *Tables 64*, *65*, *67* and *68* in *Appendix 3* show all the complications, the corresponding diagnostic tests and treatments assumed, and their unit costs.

Hospital readmissions

The costs of hospital readmissions include all expected and unexpected cardiac surgery and transfusion complications, in terms of AEs and SAEs, but excluded all unexpected unrelated complications. For example, our analysis included the cost of readmissions for hypertension and angina, but excluded the cost of readmissions for cancer treatment. 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 by weighting the non-elective inpatient excess bed-days across all specialties according to activity. The cost of an ED attendance was included if a participant was admitted via ED or referred by their GP (and assumed to be admitted via ED). If participants travelled to hospital via ambulance, this was also costed.

Outpatient attendances, emergency department 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 include cardiac surgery, cardiology (non-surgical), renal/dialysis unit, stroke clinic or 'other'. If participants specified 'other', we discussed with the trial research team whether or not these were likely to be linked to the surgery, in order to avoid costing any outpatient visits that were totally unlinked to the trial. Information on the number of ED 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 participants were reviewed and any unrelated activity excluded. Information was also collected on how the participant travelled to ED to ensure any ambulance costs were captured. Primary care contacts with GPs and practice nurses, whether at the GP surgery or participant'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 questionnaires (see section 3 of the questionnaire).

Attaching unit costs to resource use

Unit costs for hospital and community health-care resource use were largely obtained from national sources, for example, NHSBT price lists for blood products, the National Schedule of 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.[45,46,49] Resources were valued in 2012/13 pounds sterling (£); if any unit costs were in pre-2012/13 prices, they have been inflated to 2012/13 using the Hospital and Community Health Services (HCHS) inflation index.[49] Costs of drugs given in hospital were taken from the electronic marketing information tool (eMIT)[47] when possible, which provides the reduced prices paid for generic drugs in hospital; other drug costs were taken from the *British National Formulary* (BNF).[48] *Tables 63* and *64* in *Appendix 3* lists all the medications and their costs used for the trial; further details on all unit costs and their source can be found in *Appendix 3*, *Unit costs and resource use assumed for complications*.

Measurement of health-related quality of life and quality-adjusted life-years

Measurement of health-related quality of life

The EQ-5D-3L questionnaire, advocated for use in economic evaluations by NICE,[44] was used to measure health-related quality of life.[31] The EQ-5D-3L 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 are converted into a single-index value using the UK valuation set, valuations from approximately 3000 members of the UK general population elicited using the time trade-off method;[50] scores are then used to facilitate the calculation of QALYs in health economic evaluations. The EQ-5D-3L was used for TITRe2 as the 5-level version was not available at the start of the trial. Our trial participants completed the EQ-5D-3L questionnaire at three time points: in hospital pre-operatively and by post/telephone at 6 weeks and 3 months postoperatively.

Calculation of quality-adjusted life-years

The QALY profile for each participant up to 3 months postoperatively was estimated and the area under the curve of utility measurements used to calculate the number of QALYs accrued by each participant. QALYs were calculated assuming that each participant's utility changed linearly between each of the time points (pre-operatively, 6 weeks and 3 months postoperatively). For participants 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 participants from death onwards.

Total QALYs gained were calculated for each participant by adding together QALYs gained from baseline to 6 weeks and from 6 weeks to 3 months. QALYs gained from baseline to 6 weeks were calculated by averaging a participant's EQ-5D-3L scores at baseline and 6 weeks and multiplying by 42 days (or number of days until death if this was within 42 days). QALYs gained from 6 weeks to 3 months were calculated in

a similar way. Once total QALYs gained were calculated for all participants, the average QALY gain for participants in each group was calculated. Alternative assumptions regarding the analysis of QALYs were investigated in sensitivity analyses, such as using the date of completion of the 6-week EQ-5D-3L rather than assuming this was at 42 days.

Missing data

We first summarised descriptively the volume of missing data for both resource use and EQ-5D-3L scores, which showed that 2.5% of resource use data were completely missing: 2.4% in the restrictive group and 2.5% in the liberal group. Overall, 10.7% of EQ-5D-3L scores were missing across the three time points (pre-surgery, 6 weeks and 3 months); 10.9% in the restrictive group and 10.5% in the liberal group. Although the level of missing data on resource use sounds small, because there are a large number of resource use variables for the trial, any simple methods to deal with the missing data would work poorly. For instance, using complete case analysis would leave only 61% of participants remaining for analysis. Multiple imputation was used to handle this missing data.

When data were partially missing, for example for linked questions for which only the first part was answered, mean imputation was used to handle such missing data. This occurred when a resource use question was in two parts: if participants were asked to respond yes/no to whether or not they used a particular resource (e.g. if they were readmitted to hospital) and then if yes, to record further details on the volume of resource use (e.g. the number of days they were readmitted, or the number of visits). Further details of mean and multiple imputation are described next.

Mean imputation for partially missing data

When data were partially missing, mean imputation was used. For example, if participants reported a readmission to hospital, but information on the LOS was missing, a mean LOS across all readmissions was calculated and this mean was then imputed if data were missing. Similarly if a participant reported GP visits, but did not record the number of visits, the mean number of visits from other participants was calculated and then imputed for those participants whose data were missing. This approach was also used to complete some of the intubation durations.

There were a number of dates and times recorded on the CRFs for events such as extubation, reintubation and re-extubation and movements between wards. If the exact time of an event was unknown, there was provision on the CRFs to record an approximate time of morning, afternoon or overnight. If only an approximate time was available, we used the same assumptions as were made in the effectiveness analyses, which were based on discussions with the research nurses. For calculations involving the date and time of hospital discharge, a discharge time of 18:00 was assumed (consistent with the effectiveness analyses).

Multiple imputation for missing data

Multiple imputation using a series of chained regression equations was used to impute missing resource use and EQ-5D-3L data. Following recent guidelines,[51] multiple imputation using chained equations was conducted using the mi command in Stata. Multiple imputation uses regression to predict *m*-values for each missing data cell (*m* is often 5 and was here), 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.

Missing resource use data were imputed in two stages. First, the missing data within inpatient resource use were imputed based on the available inpatient resource use data together with independent variables: centre, sex, treatment group, age at operation and cardiac procedure (as four categories) in the regression equations; second, all the post-discharge resource use with missing data were imputed on the same independent variables with the addition of total LOS. All readmission variables, including ICU days, complications and SAEs, were imputed conditional on readmission LOS being greater than zero; that is, only participants who had a readmission could then have complications in the follow-up period. Indicator variables for SAEs included in the

imputation only counted participants for whom we attached a cost to their SAE. Missing EQ-5D-3L data were imputed based on the available EQ-5D-3L scores at each of the three time points together with independent variables: centre, sex, treatment group, age at operation, cardiac procedure and total costs. Finally, Rubin's Rule was used to summarise data across the *m* datasets.[52] This approach accounts for the variability both within and between imputed datasets and takes uncertainty in the estimated mean into account.

Adjustment for baseline utility

Given that 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.[53] Regression adjustment also allows for regression to the mean and increases precision. Therefore, we adjusted our QALYs for baseline EQ-5D-3L. For each of the five imputed datasets, we regressed total QALYs on treatment group and baseline EQ-5D-3L and used the Stata command, *mi estimate*, to combine the five imputed datasets, and used Rubin's Rule to combine the standard errors (SEs) across the five imputations. This provided an estimate of the QALY difference and its SE between the trial groups, adjusted for baseline EQ-5D-3L. 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-3L.

Within-trial statistical analysis of cost-effectiveness results

Most of the cost-effectiveness analyses were conducted in Stata version 12; some of the graphs and unit cost calculations were conducted in Microsoft Excel® 2010 (Microsoft Corporation, Redmond, WA, USA).

Initially, resource use, costs and health-related quality of life were summarised using means, SDs and SEs of means, using both the central limit theorem and bootstrapping. ICERs were 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. Non-parametric bootstrapping of costs and QALYs was then used to quantify the degree of uncertainty around the ICER. Bootstrapping was used to avoid making parametric assumptions.

A thousand bootstrap samples were drawn for each of the five imputed datasets. 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-3L. 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-3L.

These 5000 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. In order that the points could be seen, only 1000 replicates were plotted (200 replicates for each of the five imputations).

For each of the five imputations, the mean and SD of the 1000 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 five imputed datasets. CIs around the cost and QALY differences were then generated based on these SEs rather than SEs based on parametric methods.

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 health-care decision-makers are willing to pay for health gain. All 5000 bootstrap replicates were used to generate the CEAC. The restrictive threshold would be considered as cost-effective if the ICER falls below £20,000; however, the ICERs and CEACs presented would allow decision-makers to assess cost-effectiveness at a willingness-to-pay threshold of their choice.

Discounting

Costs and effects were not discounted as our time horizon was < 12 months.

Sensitivity analysis

One-way sensitivity analysis was used to investigate the impact on the results of the cost and cost-effectiveness analyses when varying key parameters or major cost drivers and also to investigate the impact of uncertainty on the cost-effectiveness results. Factors that were examined in the sensitivity analysis for costing were:

- varying the unit costs of treatment of complications, ward stays, reoperations, expensive drugs, oral versus intravenous drug administration and the source of medication unit costs (BNF vs. eMIT) (see *Appendix 3*, *Sensitivity analyses around unit costs*)
- conducting the costing from the point of randomisation rather than the point of surgery as undertaken in the baseline analysis (further details in *Appendix 3*, *Costs from randomisation*)
- exploring the impact of any high-cost participants (outliers) if the cost data are skewed.

Non-NHS costs were also considered and analyses were conducted to determine whether or not these differed between the trial groups and hence whether or not there was a need to conduct a sensitivity analysis from a wider societal perspective (instead of a NHS and Personal Social Services perceptive).

For the sensitivity analysis on outcomes, we varied the assumptions for calculating QALYs; the alternative strategies examined were:

- not adjusting for baseline utility
- exploring the use of the last observation carried forward until death rather than assuming utility changes linearly until death
- using the date of completion of the 6-week EQ-5D-3L rather than assuming it is completed at exactly 6 weeks
- calculating QALYs from the point of randomisation rather than surgery.

Finally, we carried out a sensitivity analysis examining life-years gained as a secondary outcome measure in the economic evaluation. Previous economic evaluations conducted by the authors have often found that EQ-5D-3L scores are similar across trial groups.[54] Such a finding could reflect reality but could also be a function of the 3-level version of the EQ-5D-3L not being sufficiently sensitivity to changes in quality of life, or that quality-of-life improvements arise before EQ-5D-3L measurements (failing to capture periods of lower quality of life), especially following SAEs.

Subgroup analysis

Subgroup analyses were conducted to investigate whether or not cost-effectiveness results varied between participant subgroups. The pre-specified subgroups used for the effectiveness analyses were used for the cost-effectiveness subgroup analyses:

- operation type (isolated CABG vs. other operation types)
- age at operation (< 75 years vs. ≥ 75 years)
- pre-operative diagnosis of diabetes (none vs. diet, oral medication or insulin controlled)
- pre-operative diagnosis of lung disease (none vs. chronic pulmonary disease or asthma)
- pre-operative renal impairment (eGFR ≤ 60 ml/minute vs. eGFR > 60 ml/minute)
- sex (males vs. females)
- pre-operative ventricular function (good vs. moderate or poor).

The impact of subgroups was evaluated using ordinary least squares regression predicting total costs and QALYs, conditional on treatment group, subgroup and an interaction between treatment group and subgroup (and baseline EQ-5D-3L 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.

Patient and public involvement

At the time of formulating the research question for TITRe2 and deciding to apply for funding, information about progress on the pilot study[26] and the proposed trial was presented to the Research Advisory Group of the Bristol Heart Institute. This group comprised members of the public who are stakeholders in the use of, or delivery of, health care and health-care research, including patients and potential patients, those who commission or deliver health-care services and a representative of the British Heart Foundation. The group agreed that it was important for patients and the NHS to answer the research question and supported our proposal for the trial.

The trial recruited patients who had moderate to high levels of anxiety before surgery because of the life-threatening nature of their condition and the operation, and took place in a particularly acute care setting. Although patients had full capacity when they were approached about the trial, about 90% were randomised and first received the intervention when they were on the ICU or HDU, when they were likely to be artificially ventilated or sedated. In terms of the conduct of the trial, most patient and public involvement (PPI) occurred through the representative on the TSC, Karin Smyth. At the time of her appointment to the TSC, she had recently been a non-executive director of Bristol North Primary Care Trust and a lay/patient representative on the Research Advisory Group.

Information about the trial used when approaching patients to take part was developed with input from patients who had had cardiac surgery previously, both initially and when the information was revised, in order to try to better communicate the possible benefits and risks of withholding or giving extra transfusions. We also consulted a group of past patients when we were considering the option of obtaining follow-up information by postal questionnaire, as well as by telephone. This option was raised when staff in the trials unit were having to spend large amounts of time carrying out telephone follow-ups. We had not budgeted for such a large amount of time and there was a risk that either a backlog of follow-up information would build up or other trial-related tasks would be delayed. We particularly valued the involvement of this group of patients in endorsing the principle that postal follow-up would be an acceptable alternative and in optimising the format of the questionnaire for self-completion by participants, which we believe contributed to the completeness of follow-up information. We are currently involving patients and lay representatives in disseminating information about the results of the trial to participants.

The lay representative of the TSC played an important role towards the end of the trial when there was some concern about emerging findings from the trial based on the data available at the time. Having reassurance from both lay and professional members of the TSC was vital at this time in ensuring successful completion of the trial as planned.

We also would like to draw attention to the reciprocal benefits that PPI can contribute. With her permission, we are reproducing comments that Karin Smyth made spontaneously about her membership of the TSC.

I wanted to put on record my appreciation of being involved in this trial. As I have found in my own work the role of a 'lay person' is a peculiar and ill-defined one. When Gavin [Professor Murphy] asked me to be involved it was as someone who had commissioning and health care management experience but who was not, at that point, working in the NHS and could be a lay person. The science has often been beyond my own understanding but I am grateful for your patience and explanation when that was the case. I was made to feel a full part of the team.

Karin Smyth, reproduced with permission

Contractual and financial arrangements

When applying for funding, we chose to adopt a fee-per-participant payment model in order to reimburse the research costs incurred by participating centres in taking part. These research costs arose primarily from the need to collect data during participants' index admissions but also from the time spent by local research teams helping with collection of follow-up data, for example if a participant was readmitted to a participating centre or a nearby referring hospital after discharge. We preferred this model to one in which each participating centre is given a set amount of funding, for example to employ a part-time research nurse, because it created an incentive for centres to recruit and randomise participants, and contained local research costs.

We developed a spreadsheet to estimate the total locally incurred costs (i.e. for the total target sample size), estimating the amount of a consultant's, research nurse's and clerical person's time per participant needed to identify, approach and consent patients and collect the data required. The spreadsheet took into account the different numbers of patients/participants at each stage of the recruitment process; we projected that 6000 patients would need to be identified, 5000 approached, 3000 consented and registered, and 2000 randomised. Items in the spreadsheet were then classified as research or service support activities. Most but not all of the activities prior to randomisation were considered to represent service support (i.e. approaching and consenting patients, including discussion with a clinician). Therefore, for simplicity, we estimated the fee-per-participant for randomised participants only (including the costs of pre-randomisation tasks within this amount, averaged per randomised participant). The total came to £260 per randomised participant, divided into £100 for service support costs and £160 for local research costs. The latter total included 0.25 hours of consultant time (reviewing and signing SAE forms), 7.75 hours of research nurse time (collecting data, communicating with the participants and usual-care staff and responding to data queries from the coordinating centre) and 2.75 hours of clerical time (primarily entering data into the database).

On the basis of our original assumption that a centre would randomise eight participants, on average, per month, we expected the corresponding income [$8 \times 12 \times (£160 + £100) = £24{,}960$] to generate sufficient research income to pay for approximately 0.6 full time equivalents of a research nurse and the appropriate amounts of consultant and clerical time.

This payment structure was implemented through the contracts (using the model non-commercial agreement) between the Sponsor (University Hospitals of Bristol NHS Foundation Trust) and sites. (A separate contract was in place between the Sponsor and the University of Bristol, which held the grant.) The contract specified that payments would be made in two parts: £120 'Upon receipt of complete and accurate data following participant discharge, including documentary evidence of qualifying or suspected qualifying events for the primary outcome as specified in the protocol and case report form' and an additional £40 'Upon receipt of additional data required as a result of 3-month-follow-up (e.g. response to queries on follow-up or SAEs)'. The trial database kept track of data submitted, payments due and payments already invoiced. A query was run quarterly to generate an itemised activity report for each site detailing the payment due. This report formed the basis for an invoice to the University of Bristol, which held the grant.

Chapter 3 Trial cohort

Screened patients

Screening data were provided for 11,483 patients at 17 UK centres (*Figure 2*). A total of 7918 screened patients were excluded from the study: 3055 were not sent a PIL; 1863 were not approached; 281 were ineligible; and 2719 did not consent. In addition, there were 696 participants who were not sent a PIL and 118 participants who were not approached, as they were already deemed ineligible when they were screened. Similarly, for 10 participants, the reason for non-consent was recorded as ineligibility and reasons are unknown for these participants. The most common reasons for ineligibility were: congenital or acquired platelet, red blood cell or clotting disorder (83 patients); and inability to give full informed consent (62 patients). Similarly, the most prevalent reasons for not consenting were: wanting the standard procedure (1053 patients) and personal reasons (678 patients). Therefore, 3565 participants (31.0% of those screened) consented to take part in the study, of whom 94 were not considered for randomisation (for reasons see *Figure 2*). Of the remaining 3471 participants, 2007 (57.8%) were randomised, 1004 to the restrictive group and 1003 to the liberal group.

The numbers of patients screened, excluded from the study, consented and randomised are given in *Table 6*, demonstrating a large variation in screening rates. The percentage of screened patients consented into the study ranges from 11.1% to 90.0%, suggesting that quality in screening (or the completeness of recording screened patients in the log) was very variable between centres. Two centres (site A, consent rate 34.3%, and site H, consent rate 11.1%) were identified as using the screening log as intended, suggesting centres with higher consent rates were perhaps not screening all non-trial patients and, therefore, some of the variation is likely to have arisen from varying data completeness across centres up to the point of consent.

Furthermore, the percentages of consented patients that were randomised ranged from 36.0% to 92.3% (accepting that the latter percentage is based on a relatively small denominator). These differences are likely to have arisen from differences in clinical practice and case mix of patients between centres, as well as from the different strategies used by sites to target certain kinds of patient who were more likely to be randomised (such targeting was encouraged by the trial management team to maximise the yield of randomised participants among those who consented).

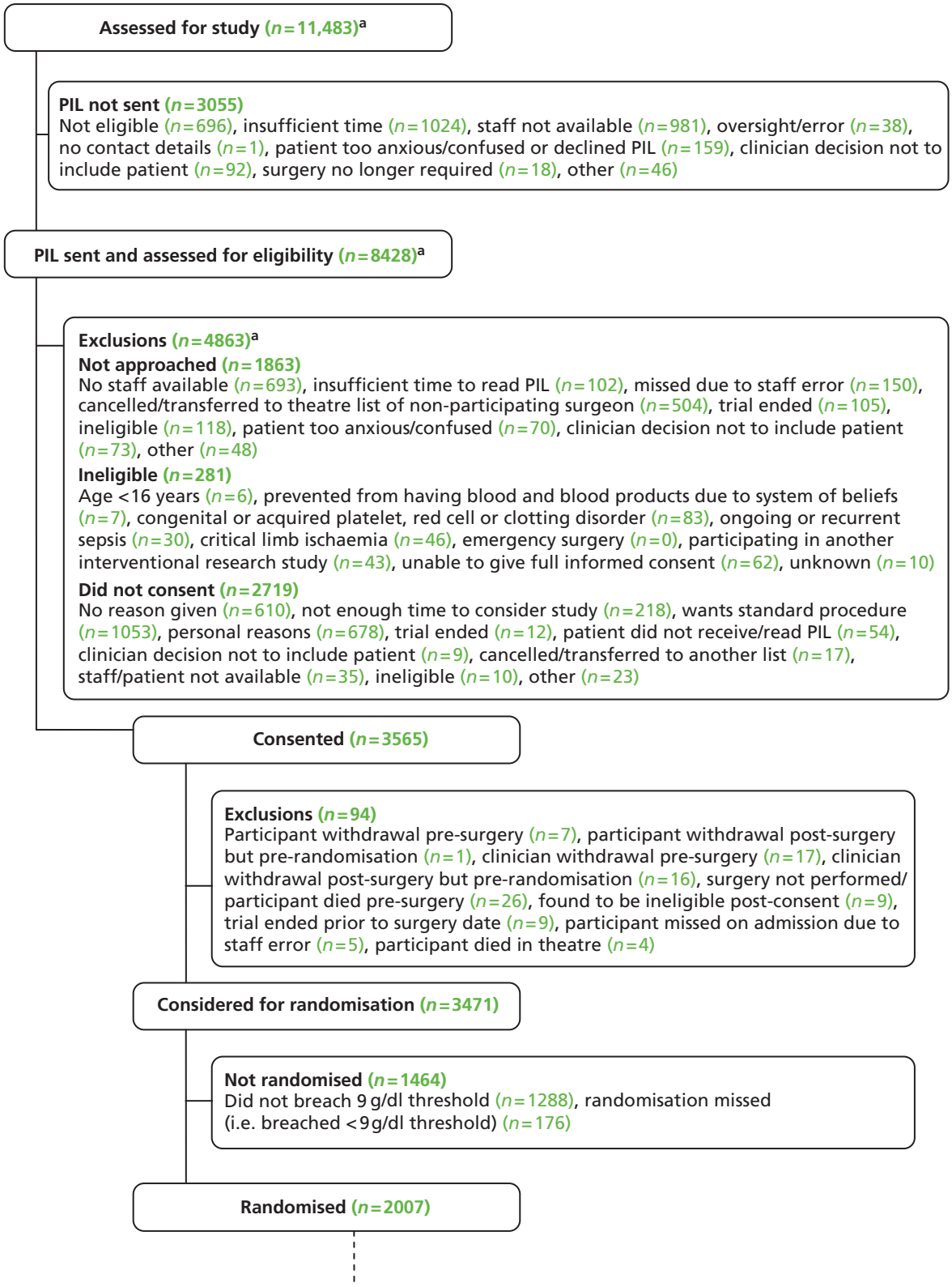


FIGURE 2 Flow of participants.

a, These figures should be interpreted with caution owing to variable data quality between centres. The proportion of screened patients consented into the study varied between centres (range 11–90%).

b, Only withdrawals in which participants were unwilling for data collected to be used or for follow-up to continue were treated as exclusions. Some participants withdrew from treatment but were willing for data collection to continue. (*continued*)

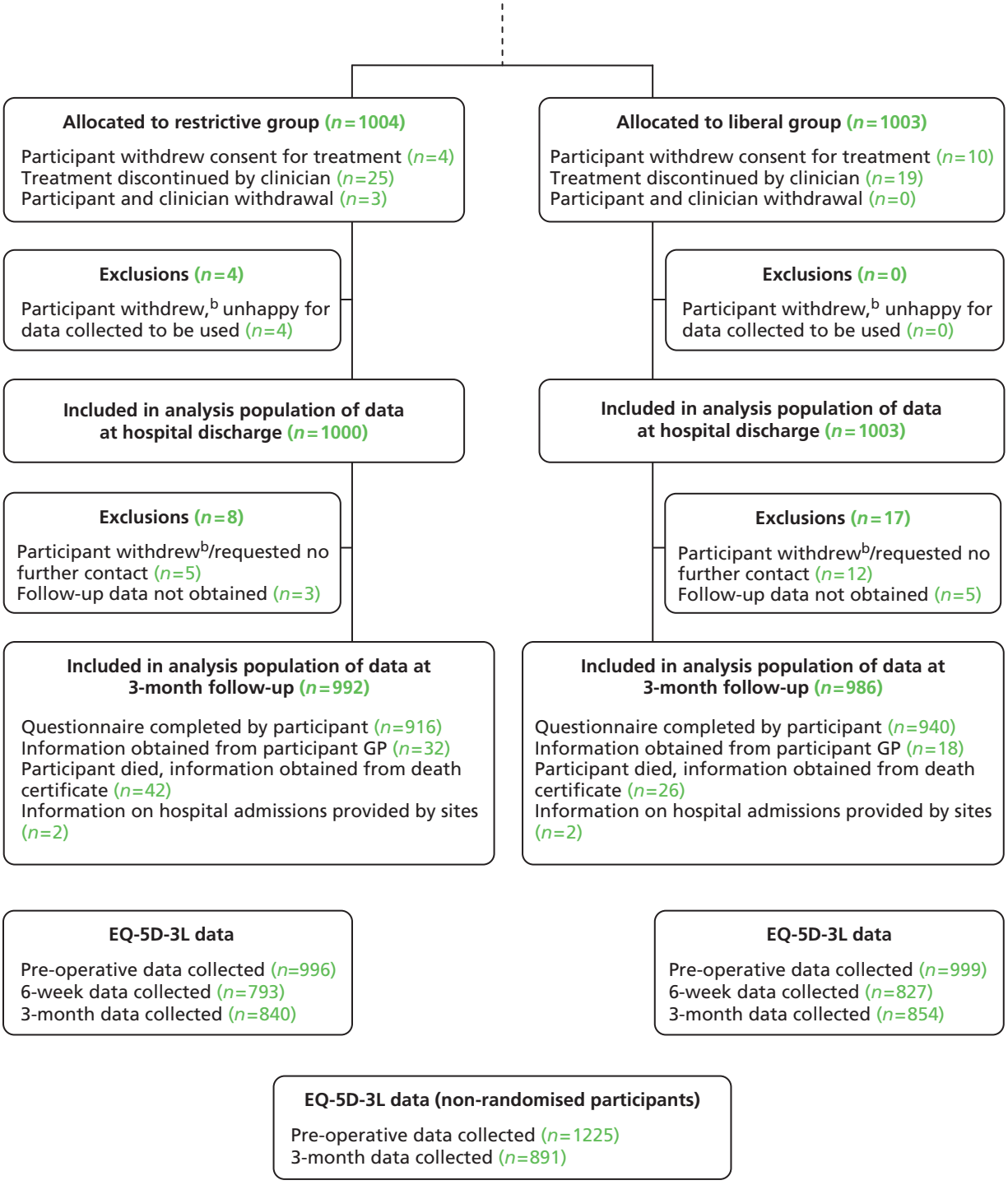


FIGURE 2 Flow of participants.

a, These figures should be interpreted with caution owing to variable data quality between centres. The proportion of screened patients consented into the study varied between centres (range 11–90%).

b, Only withdrawals in which participants were unwilling for data collected to be used or for follow-up to continue were treated as exclusions. Some participants withdrew from treatment but were willing for data collection to continue.

TABLE 6 Screening data by centre

Centre	Number of months recruiting into study	Screened	Excluded from study				Consented (% of screened patients)	Randomised (% of consented patients)
			PIL not sent	Not approached	Ineligible	Did not consent		
Site A	44	1690	50	250	128	683	579 (34.3)	393 (67.9)
Site B	35	819	64	240	6	135	374 (45.7)	135 (36.1)
Site C	40	1077	213	274	1	209	380 (35.3)	142 (37.4)
Site D	9	20	0	1	0	1	18 (90.0)	8 (44.4)
Site E	40	282	34	12	7	91	138 (48.9)	76 (55.1)
Site F	41	902	7	259	40	256	340 (37.7)	224 (65.9)
Site G	27	271	37	54	6	94	80 (29.5)	47 (58.8)
Site H	30	3067	2232	150	24	320	341 (11.1)	179 (52.5)
Site I	35	531	0	130	4	78	319 (60.1)	147 (46.1)
Site J	32	844	243	121	8	222	250 (29.6)	157 (62.8)
Site K	28	284	38	24	4	64	154 (54.2)	134 (87.0)
Site L	21	228	2	2	2	72	150 (65.8)	54 (36.0)
Site M	22	283	1	54	8	123	97 (34.3)	56 (57.7)
Site N	25	774	70	112	35	312	245 (31.7)	183 (74.7)
Site O	14	328	32	163	7	55	71 (21.6)	51 (71.8)
Site P	2	30	11	2	1	3	13 (43.3)	12 (92.3)
Site Q	3	53	21	15	0	1	16 (30.2)	9 (56.3)
Total	44	11483	3055	1863	281	2719	3565 (31.0)	2007 (56.3)

Recruitment

Participants were consented to the study between 13 July 2009 and 14 February 2013, and randomised between 15 July 2009 and 18 February 2013. Follow-up data for the last participant were collected 21 August 2013. The 2007 randomised participants were recruited from 17 centres (see *Table 6*).

Actual cumulative recruitment compared with the original and revised targets are shown in *Figure 3*. At the start of the study, recruitment was predicted as follows: (1) we expected two centres to start recruiting in month one, with a further two centres opening per month thereafter until eight centres were open; (2) we predicted five consented participants per month at centres in their first 2 months of recruitment, 10 consented participants per month at centres in months three and four of recruitment and 19 consented participants per centre per month thereafter; and (3) we also predicted that two-thirds of consented participants would be randomised.

As the trial progressed, it became clear that these estimates were optimistic: (1) it took 1 year to set up the first eight sites to the point of starting recruitment instead of the 4 months we predicted, mainly due to delays with contracts but also due to other site-specific reasons; (2) the predicted numbers of consented participants per centre per month were not achieved at the majority of centres; and (3) the percentage of consented participants who were randomised was substantially lower than the predicted 66% (at the end of trial it was 56%). Extra centres (over the eight predicted) were opened to try to increase recruitment, but the targets were still not achieved.

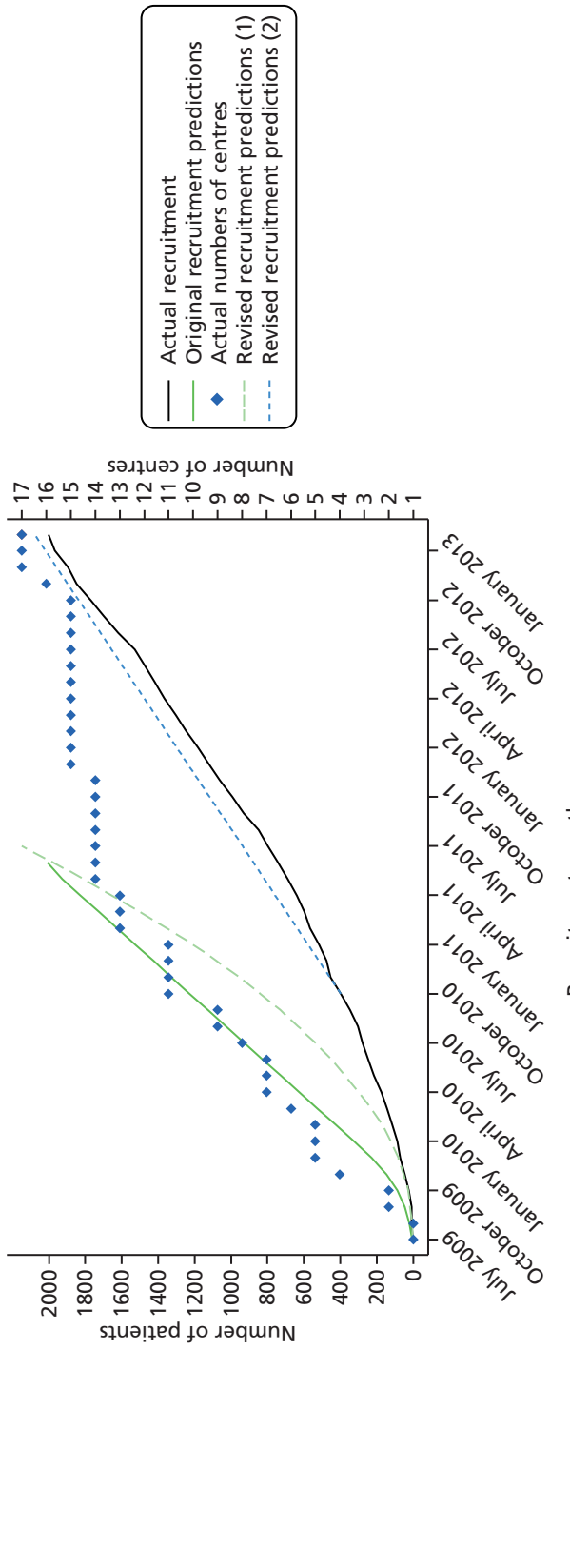


FIGURE 3 Recruitment over time. 'Original recruitment predictions' are as described in the original protocol. 'Revised recruitment predictions (1)' are using the assumptions in the original protocol (five consented participants per month for centres in months one and two of recruitment, 10 consented participants per month for centres in months three and four of recruitment, and 19 consented participants per month thereafter; two-thirds of consented participants would be randomised) applied to the actual numbers of centres recruiting. 'Revised recruitment predictions (2)' are as per the trial extension request and are based on the actual recruitment as of the end of October 2010 plus 60 randomised participants per month thereafter.

Therefore, in November 2010 an extension request was made to the National Institute for Health Research (NIHR). This extension was based on actual cumulative recruitment to the end of October 2010 (399 randomised participants) and predicted that thereafter 60 randomised participants would be recruited each month across all centres. This request was granted and the trial was extended with a revised end of recruitment date of 31 January 2013. For the following 10 months, the new target was not met (a median of 50 participants per month were randomised); however, in September 2011 recruitment took an upward turn and the 60 randomised participants per month target was exceeded for the first time. Subsequently, recruitment remained above target at a median of 63 participants per month for the remainder of the trial. The highest monthly recruitment was achieved in August 2012 when 91 participants were randomised. The last participant was recruited in mid February 2013, just 2 weeks behind target.

Recruited patients

Very few data were collected about patients who did not take part in the study (*Table 7*). On average, patients who did not take part (for whatever reason) were older than participants who consented [median 71 years (IQR 62–77 years) vs. 68 years (IQR 61–75 years)] and were less likely to be male (66.7% vs. 75.4%).

Characteristics of (1) participants who consented but were not randomised and (2) randomised participants are described in *Table 8*. As anticipated (because they were by definition not anaemic), non-randomised participants were generally younger [median 66.5 years (IQR 59.5–73.1 years) vs. 70.3 years (IQR 63.5–76.4 years)], more likely to be male (84.8% vs. 68.5%), with a lower risk of perioperative mortality [median EuroSCORE of 4 (IQR 2–5) vs. 5 (IQR 3–7)] and a higher pre-operative haemoglobin [mean 14.4 g/dl (SD 1.3 g/dl) vs. 13.3 g/dl (SD 1.5 g/dl)]. Non-randomised participants were more likely to be having CABG surgery (54.6% vs. 40.6%) and were less likely to be transfused red blood cells (8.1% vs. 79.4%) or other blood products (FFP 6.6% vs. 29.0%, platelets 10.1% vs. 36.8%, cryoprecipitate 1.6% vs. 10.0%) intra-operatively and/or postoperatively. EQ-5D-3L scores were similar. A higher proportion of non-randomised participants were alive at hospital discharge (raw percentages, not taking differences in the composition of the subpopulations, were 99.3% vs. 97.9%). Haemoglobin levels were considerably higher for non-randomised participants than randomised participants (*Figure 4*), with differences being highest in the first 24 hours postoperatively.

TABLE 7 Characteristics of patients included and excluded in study

Characteristic	Excluded from study				Included in study (*N* = 3565)
	PIL not sent (*N* = 3055)	Not approached (*N* = 1863)	Ineligible (*N* = 281)	Did not consent (*N* = 2719)	
Age (years), median (IQR)	71.0 (62.0–78.0)	70.0 (61.0–76.0)	71.0 (61.0–77.0)	71.0 (63.0–77.0)	68.0 (61.0–75.0)
Males, *n* (%)	2077 (68.0)	1303 (69.9)	170 (60.5)	1730 (63.6)	2687 (75.4)

TABLE 8 Characteristics of randomised and non-randomised participants

Characteristic	Consented not randomised (*N* = 1464)	Randomised (*N* = 2003)
Cardiac history		
EuroSCORE,[a] median (IQR)	4.0 (2.0–5.0)	5.0 (3.0–7.0)
NYHA class, *n*/*N* (%)		
I	420/1426 (29.5)	493/1951 (25.3)
II	683/1426 (47.9)	885/1951 (45.4)
III	301/1426 (21.1)	525/1951 (26.9)
IV	22/1426 (1.5)	48/1951 (2.5)
CCS class, *n*/*N* (%)		
No angina	437/1430 (30.6)	718/1962 (36.6)
I	260/1430 (18.2)	362/1962 (18.5)
II	451/1430 (31.5)	526/1962 (26.8)
III	236/1430 (16.5)	281/1962 (14.3)
IV	46/1430 (3.2)	75/1962 (3.8)
Pacemaker, *n*/*N* (%)		
No	1420/1464 (97.0)	1940/2002 (96.9)
Temporary	10/1464 (0.7)	10/2002 (0.5)
Permanent	34/1464 (2.3)	52/2002 (2.6)
Heart rhythm, *n*/*N* (%)		
AF/flutter	165/1463 (11.3)	250/1998 (12.5)
Heart block	14/1463 (1.0)	43/1998 (2.2)
Sinus	1284/1463 (87.8)	1705/1998 (85.3)
Coronary disease, *n*/*N* (%)		
None	365/1462 (25.0)	620/1991 (31.1)
Single vessel	162/1462 (11.1)	225/1991 (11.3)
Double vessel	213/1462 (14.6)	282/1991 (14.2)
Triple vessel	660/1462 (45.1)	805/1991 (40.4)
Not investigated	62/1462 (4.2)	59/1991 (3.0)
Disease in left main stem (> 50% stenosis), *n*/*N* (%)	224/1450 (15.4)	304/1977 (15.4)

continued

TABLE 8 Characteristics of randomised and non-randomised participants (*continued*)

Characteristic	Consented not randomised (*N* = 1464)	Randomised (*N* = 2003)
Non-cardiac history		
Age (years), median (IQR)	66.5 (59.5–73.1)	70.3 (63.5–76.4)
Males, *n/N* (%)	1241/1464 (84.8)	1373/2003 (68.5)
BMI (kg/m^2),[b] mean (SD)	29.5 (4.8)	28.2 (4.9)
Urgent operative priority, *n/N* (%)	132/1464 (9.0)	245/2003 (12.2)
Diabetic, *n/N* (%)		
No diabetes	1191/1464 (81.4)	1604/2003 (80.1)
Diet controlled	54/1464 (3.7)	69/2003 (3.4)
Insulin	61/1464 (4.2)	98/2003 (4.9)
Oral medication	158/1464 (10.8)	232/2003 (11.6)
Smoker, *n/N* (%)		
Non-smoker	668/1464 (45.6)	928/2002 (46.4)
Ex-smoker (> 1 month)	652/1464 (44.5)	922/2002 (46.1)
Current smoker	144/1464 (9.8)	152/2002 (7.6)
Haemofiltration/dialysis, *n/N* (%)	4/1464 (0.3)	19/2001 (0.9)
CVA/TIA, *n/N* (%)	108/1464 (7.4)	163/2003 (8.1)
Pre-operative tests		
Haemoglobin (g/dl), mean (SD)	14.4 (1.3)	13.3 (1.5)
eGFR[b] (ml/minute/1.73m^2) median (IQR)	85.7 (69.2–108)	73.9 (56.8–93.2)
Medications		
Intravenous nitrates until theatre, *n/N* (%)	12/1463 (0.8)	5/2002 (0.2)
Unfractionated intravenous heparin within 6 hours of surgery, *n/N* (%)	17/1463 (1.2)	19/2002 (0.9)
Low-molecular-weight heparin within 12 hours of surgery, *n/N* (%)	14/1463 (1.0)	23/2002 (1.1)
Inotropes until theatre, *n/N* (%)	7/1463 (0.5)	3/2002 (0.1)
Aspirin within 5 days of surgery, *n/N* (%)	302/1462 (20.7)	561/1999 (28.1)
Clopidogrel within 5 days of surgery, *n/N* (%)	32/1463 (2.2)	78/2000 (3.9)
Operative details		
Cardiac procedure, *n/N* (%)		
CABG only	800/1464 (54.6)	814/2003 (40.6)
Valve only	382/1464 (26.1)	597/2003 (29.8)
CABG and valve	189/1464 (12.9)	393/2003 (19.6)
Other	93/1464 (6.4)	199/2003 (9.9)
Alive at end of surgery, *n/N* (%)	1464/1464 (100)	2003/2003 (100)

TABLE 8 Characteristics of randomised and non-randomised participants (*continued*)

Characteristic	Consented not randomised (*N* = 1464)	Randomised (*N* = 2003)
Transfusions (intra-operative and postoperative)		
Red blood cells, *n/N* (%)	119/1464 (8.1)	1591/2003 (79.4)
FFP, *n/N* (%)	97/1464 (6.6)	581/2003 (29.0)
Platelets, *n/N* (%)	148/1464 (10.1)	738/2003 (36.8)
Cryoprecipitate, *n/N* (%)	23/1464 (1.6)	201/2003 (10.0)
Activated factor VII used, *n/N* (%)	3/1464 (0.2)	12/2003 (0.6)
Beriplex used, *n/N* (%)	52/1464 (3.6)	100/2003 (5.0)
EQ-5D-3L scores		
Pre-operative utility,[c] median (IQR)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
3-month post-operative utility,[d] median (IQR)	0.8 (0.7–1.0)	0.8 (0.7–1.0)
Pre-operative visual analogue score,[e] median (IQR)	75.0 (60.0–85.0)	70.0 (53.0–80.0)
3-month post-operative visual analogue score,[f] median (IQR)	80.0 (70.0–90.0)	80.0 (70.0–90.0)
Mortality		
Alive at hospital discharge, *n/N* (%)	1454/1464 (99.3)	1961/2003 (97.9)

AF, atrial fibrillation; BMI, body mass index; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; NYHA, New York Health Association; TIA, transient ischemic attack.
a Missing for 19 consented not randomised participants and 38 randomised participants.
b Missing for one randomised participant.
c Missing for 243 consented not randomised participants and 20 randomised participants.
d Missing for 585 consented not randomised participants and 331 randomised participants.
e Missing for 247 consented not randomised participants and 19 randomised participants.
f Missing for 576 consented not randomised participants and 318 randomised participants.

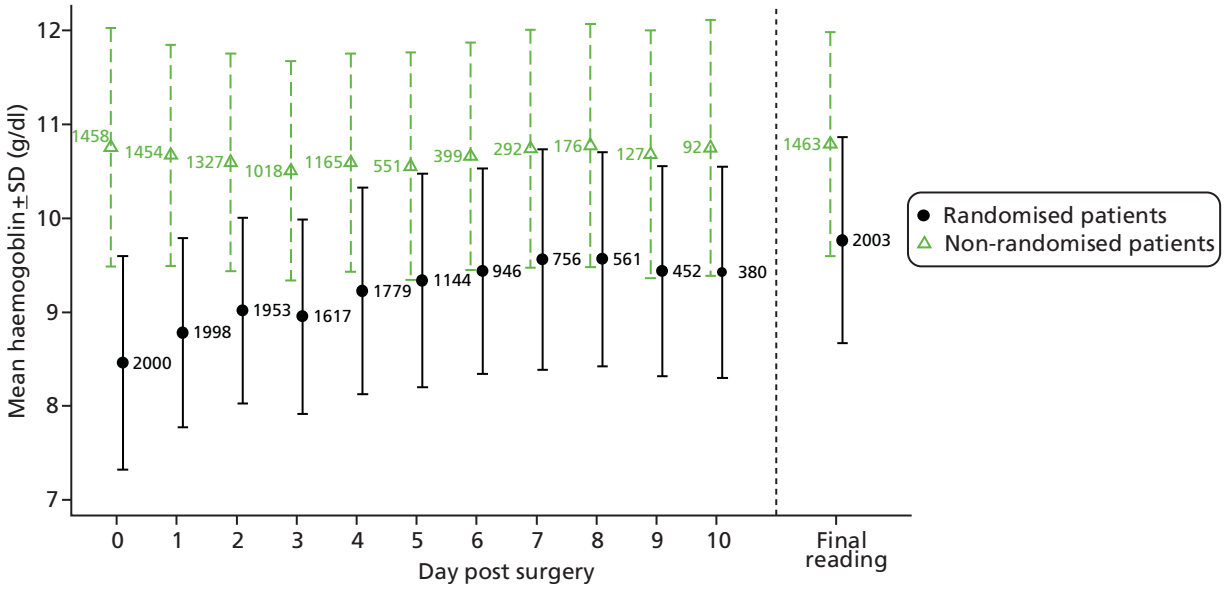


FIGURE 4 Daily mean nadir haemoglobin levels for randomised/non-randomised participants. The numbers alongside the points are the numbers of participants contributing readings for that data point. The *x*-axis has an origin of the day of surgery for both groups.

Withdrawals

Participant withdrawals and clinician discontinuations of treatment are summarised in *Table 9*. Prior to randomisation there were eight participants who withdrew consent, seven of whom did so pre-operatively. There were also 33 pre-randomisation decisions by clinicians to discontinue treatment according to the allocation, 17 of which occurred pre-operatively. The most common reason for discontinuation was the participant's condition (13 participants).

A further 17 participants (seven in the restrictive group and 10 in the liberal group) withdrew consent after randomisation but before hospital discharge, of whom four were unhappy for data collected to be used (all in the restrictive group) and a further three were unhappy for follow-up to continue. The most common reason for

TABLE 9 Participant withdrawals and clinician decisions to discontinue treatment

Pre-randomisation			
Withdrawal/discontinuation of treatment type			**Total consented participants ($n = 3565$)**
Participant withdrawals			***8 (0.2%)***
Timing			
Pre-surgery			7
Post surgery but pre-randomisation			1
Reason			
After discussion with family decided to withdraw			2
Surgery rearranged and participant no longer happy to take part			2
Participant decided to take part in another study			1
No reason given			3
Clinician treatment discontinuations			***33 (0.9%)***
Timing			
Pre-surgery			17
Post surgery but pre-randomisation			16
Reason			
Condition of participant			13
Complex procedure			4
Clinician wants haemoglobin at a specific level			5
Change of planned operation			5
Change of surgeon			6
Post randomisation but pre-hospital discharge			
Withdrawl/discontinuation of treatment type	**Randomised to restrictive threshold ($n = 1004$)**	**Randomised to liberal threshold ($n = 1003$)**	**Total randomised participants ($N = 2007$)**
Participant withdrawals	7 (0.7%)	10 (1.0%)	17 (0.8%)
Participant happy for data already collected to be used	3	10	13
Participant happy to participate in follow-up	2	8	10

TABLE 9 Participant withdrawals and clinician decisions to discontinue treatment (*continued*)

Post randomisation but pre-hospital discharge			
Withdrawl/discontinuation of treatment type	Randomised to restrictive threshold ($n = 1004$)	Randomised to liberal threshold ($n = 1003$)	Total randomised participants ($N = 2007$)
Reason			
Wants normal care	2[a]	0	2
Post-operative problems, does not want further intervention	2	2	4
Unhappy with allocation	0	1	1
Does not want any more transfusions	0	6	6
Blood products given before and after surgery	1[b]	0	1
Ineligibility (discovered post randomisation)	1[c]	0	1
No reason given	1	1	2
Clinician treatment discontinuations	28 (2.8%)	19 (1.9%)	47 (2.3%)
Reason			
Participant too unstable/unwell	16	6	22
Clinician does not want participant to have any more blood	1[b]	7	8
Clinician wants participant to have more blood	1	0	1
Clinician wants to transfuse at higher haemoglobin	6[a]	0	6
Clinician wants to transfuse at lower haemoglobin	1	1	2
Participant already had many breaches of threshold	0	2	2
Reaction to blood	0	1	1
Continued participation would prolong hospital stay	0	1	1
Ineligibility (discovered post randomisation)	1[c]	0	1
Clinical need (no further details given)	1	0	1
No reason given	1	1	2
Post-hospital discharge			
Participant withdrawals	4 (0.4%)	10 (1.0%)	14 (0.7%)
Reason			
Participant too ill/had complications	0	5	5
Participant not contactable as lives abroad	1	1	2
Requests no further questionnaires/contact	1	3	4
No reason given	2	1	3

a One participant withdrew because he/she wanted normal care and the clinician responsible discontinued treatment because he/she wanted to transfuse the participant at a higher haemoglobin than the allocated threshold.
b One participant withdrew because of having already had blood products before and after surgery and the clinician responsible discontinued treatment because he/she did not want the participant to have any further transfusions.
c One participant was withdrawn after randomisation because he/she was found to be ineligible on account of critical limb ischaemia. This comorbidity was not apparent at the time of consent, but was documented after randomisation on the basis of a Doppler blood flow investigation.
A total of 17 participants were included in the analysis dataset at hospital discharge but excluded prior to follow-up (see *Figure 2*); the 14 participants who withdrew post discharge plus three participants who withdrew pre-discharge were unhappy for follow-up to continue but happy for data collected so far to be used.

withdrawal was that the participant did not want any more transfusions (six participants, all in the liberal group). Clinicians decided to discontinue treatment according to the allocation after randomisation for 47 participants (28 in the restrictive group and 19 in the liberal group), the most common reason being that the participant was too unstable/unwell (22 participants, 16 in the restrictive group and six in the liberal group). Making such a decision did not necessarily mean that the clinician had a definitive opinion about the transfusion needs of the participant but, often, simply that the clinician considered the additional uncertainty or constraint created by the randomised treatment allocation to be undesirable when managing some critically ill participants. Three participants both withdrew and had their treatment discontinued (all in the restrictive group). A further 14 participants withdrew after hospital discharge (four in the restrictive group and 10 in the liberal group).

Participant follow-up

Follow-up data at 3 months post randomisation were obtained for 1978 participants (992 in the restrictive group and 986 in the liberal group), 98.7% of the 2003 eligible participants (see *Figure 2*). The questionnaire was completed by 1856 participants and by the research team from information supplied by the participant's GP for 50 participants. Relevant information was extracted from the death certificate for a further 68 participants who died. For the remaining four participants, information on hospital admissions only (which provided the required data to ascertain the primary outcome) was provided by sites. Of the 25 participants with no follow-up data, 17 had withdrawn consent or requested no further contact; the remaining eight were lost to follow-up.

For randomised participants, EQ-5D-3L data were collected for almost all participants (1995/2003) pre-operatively, for 1620/2003 (80.9%) at 6 weeks and 1694/2003 (84.6%) at 3 months post randomisation (see *Figure 2*). Of the 1464 participants considered for randomisation who were not randomised, EQ-5D-3L data were collected for 1225 participants (83.7%) pre-operatively and 891 participants (60.9%) at 3 months post randomisation.

Numbers analysed

The analysis population consisted of 2003 participants, that is the 2007 randomised participants excluding four withdrawn participants who were unhappy for their data to be used. Primary outcome data were available for 1906 participants (95.2%). For most of the secondary outcomes, very few data were missing with the exception of the infectious event component of the primary outcome and the EQ-5D-3L (see *Participant follow-up*). Post-operative complication data up to 3 months after randomisation were complete for 1982 participants (99.0%).

Baseline data and operative characteristics

Baseline characteristics are summarised in *Table 10* and intraoperative characteristics in *Table 11*. The median additive EuroSCORE was 5 (IQR 3–7) and logistic EuroSCORE was 4.0 (IQR 2.2–7.2). The median age was 70.3 years (IQR 63.5–76.4 years) and 68.5% of participants were male. Just fewer than 20% of participants were diabetic and 12.2% required urgent operations (i.e. urgent operative priority). Pre-operative haemoglobin concentrations had a mean value of 13.3 g/dl (SD 1.5 g/dl) and the median eGFR was 73.8 ml/minute/1.73 m^2 (IQR 56.8–93.2 ml/minute/1.73 m^2). In terms of intraoperative characteristics, the median duration of operation was 4.0 hours (IQR 3.3–5.0 hours) and 95.1% of operations were performed using cardiopulmonary bypass (CPB). Most operations were either isolated CABG (40.7%) or valve (30.5%) procedures. Tranexamic acid was used in 80.7% of procedures. All pre-operative and intraoperative characteristics were generally well balanced between the two groups, although the logistic EuroSCORE was slightly higher in the liberal group than the restrictive group [median 4.3 (IQR 2.4–7.5) vs. 3.8 (IQR 2.1–7.0)]. Pre-randomisation red blood cell transfusions are described in *Chapter 4* and EQ-5D-3L scores in *Chapter 5*.

TABLE 10 Participant demography and past history

Characteristic	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)
Cardiac history			
Additive EuroSCORE,[a] median (IQR)	5.0 (3.0–7.0)	5.0 (3.0–7.0)	5.0 (3.0–7.0)
Logistic EuroSCORE,[a] median (IQR)	3.8 (2.1–7.0)	4.3 (2.4–7.5)	4.0 (2.2–7.2)
NYHA class, *n*/*N* (%)			
I	235/997 (24.1)	258/974 (26.5)	493/1951 (25.3)
II	445/997 (45.5)	440/974 (45.2)	885/1951 (45.4)
III	268/997 (27.4)	257/974 (26.4)	525/1951 (26.9)
IV	29/997 (3.0)	19/974 (2.0)	48/1951 (2.5)
CCS class, *n*/*N* (%)			
No angina	365/982 (37.2)	353/980 (36.0)	718/1962 (36.6)
I	169/982 (17.2)	193/980 (19.7)	362/1962 (18.5)
II	273/982 (27.8)	253/980 (25.8)	526/1962 (26.8)
III	139/982 (14.2)	142/980 (14.5)	281/1962 (14.3)
IV	36/982 (3.7)	39/980 (4.0)	75/1962 (3.8)
Pacemaker, *n*/*N* (%)			
No	972/1000 (97.2)	968/1002 (96.6)	1940/2002 (96.9)
Temporary	7/1000 (0.7)	3/1002 (0.3)	10/2002 (0.5)
Permanent	21/1000 (2.1)	31/1002 (3.1)	52/2002 (2.6)
Heart rhythm, *n*/*N* (%)			
AF/flutter	119/997 (11.9)	131/1001 (13.1)	250/1998 (12.5)
Heart block	18/997 (1.8)	25/1001 (2.5)	43/1998 (2.2)
Sinus	860/997 (86.3)	845/1001 (84.4)	1705/1998 (85.3)
Coronary disease, *n*/*N* (%)			
None	310/993 (31.2)	310/998 (31.1)	620/1991 (31.1)
Single vessel	112/993 (11.3)	113/998 (11.3)	225/1991 (11.3)
Double vessel	132/993 (13.3)	150/998 (15.0)	282/1991 (14.2)
Triple vessel	403/993 (40.6)	402/998 (40.3)	805/1991 (40.4)
Not investigated	36/993 (3.6)	23/998 (2.3)	59/1991 (3.0)
Disease in left main stem (> 50% stenosis)	159/987 (16.1)	145/990 (14.6)	304/1977 (15.4)

continued

TABLE 10 Participant demography and past history (*continued*)

Characteristic	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)
Non-cardiac history			
Age (years), median (IQR)	69.9 (63.1–76.0)	70.8 (64.1–76.7)	70.3 (63.5–76.4)
Males, *n/N* (%)	693/1000 (69.3)	680/1003 (67.8)	1373/2003 (68.5)
BMI (kg/m^2),[b] mean (SD)	28.2 (5.0)	28.2 (4.9)	28.2 (4.9)
Urgent operative priority, *n/N* (%)	126/1000 (12.6)	119/1003 (11.9)	245/2003 (12.2)
Diabetic, *n/N* (%)			
No diabetes	802/1000 (80.2)	802/1003 (80.0)	1604/2003 (80.1)
Diet controlled	33/1000 (3.3)	36/1003 (3.6)	69/2003 (3.4)
Insulin	49/1000 (4.9)	49/1003 (4.9)	98/2003 (4.9)
Oral medication	116/1000 (11.6)	116/1003 (11.6)	232/2003 (11.6)
Smoker, *n/N* (%)			
Non-smoker	461/1000 (46.1)	467/1002 (46.6)	928/2002 (46.4)
Ex-smoker (> 1 month)	472/1000 (47.2)	450/1002 (44.9)	922/2002 (46.1)
Current smoker	67/1000 (6.7)	85/1002 (8.5)	152/2002 (7.6)
Haemofiltration/dialysis, *n/N* (%)	7/999 (0.7)	12/1002 (1.2)	19/2001 (0.9)
CVA/TIA, *n/N* (%)	76/1000 (7.6)	87/1003 (8.7)	163/2003 (8.1)
Pre-operative tests			
Haemoglobin (g/dl) mean (SD)	13.3 (1.5)	13.3 (1.5)	13.3 (1.5)
eGFR[c] (ml/minute/1.73m^2) median (IQR)	74.5 (57.2–92.9)	72.8 (56.4–93.2)	73.8 (56.8–93.2)
Medications			
Intravenous nitrates until theatre, *n/N* (%)	1/1000 (0.1)	4/1002 (0.4)	5/2002 (0.2)
Unfractionated intravenous heparin within 6 hours of surgery, *n/N* (%)	10/1000 (1.0)	9/1002 (0.9)	19/2002 (0.9)
Low-molecular-weight heparin within 12 hours of surgery, *n/N* (%)	13/1000 (1.3)	10/1002 (1.0)	23/2002 (1.1)
Inotropes until theatre, *n/N* (%)	2/1000 (0.2)	1/1002 (0.1)	3/2002 (0.1)
Aspirin within 5 days of surgery, *n/N* (%)	277/999 (27.7)	284/1000 (28.4)	561/1999 (28.1)
Clopidogrel within 5 days of surgery, *n/N* (%)	41/1000 (4.1)	37/1000 (3.7)	78/2000 (3.9)

AF, atrial fibrillation; BMI, body mass index; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular event; NYHA, New York Health Association; TIA, transient ischaemic attack.
a Missing for 17 restrictive group participants and 21 liberal group participants.
b Missing for one liberal group participant.
c Missing for two liberal group participants.

TABLE 11 Operative characteristics

Characteristic	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)
Duration of operation[a] (hours) median (IQR)	4.0 (3.3–5.0)	4.0 (3.2–5.0)	4.0 (3.3–5.0)
Lowest haematocrit,[b] mean (SD)	25.5 (4.2)	25.6 (4.4)	25.6 (4.3)
CPB used, *n*/*N* (%)	950/999 (95.1)	953/1003 (5.0)	1903/2002 (5.1)
If yes: total bypass time (minutes), median (IQR)	97.0 (77.0–132)	95.0 (75.0–127)	96.0 (76.0–129)
If yes: cumulative cross-clamp time[c] (minutes), median (IQR)	66.0 (48.0–92.0)	63.0 (46.0–86.0)	65.0 (47.0–90.0)
If yes: myocardial protection, *n*/*N* (%)			
Blood	796/948 (84.0)	809/952 (85.0)	1605/1900 (84.5)
Crystalloid	107/948 (11.3)	110/952 (11.6)	217/1900 (11.4)
Other	30/948 (3.2)	22/952 (2.3)	52/1900 (2.7)
NA	15/948 (1.6)	11/952 (1.2)	26/1900 (1.4)
Operation type			
Cardiac procedure, *n*/*N* (%)			
CABG only	408/1000 (40.8)	408/1003 (40.7)	816/2003 (40.7)
Valve only	307/1000 (30.7)	304/1003 (30.3)	611/2003 (30.5)
CABG + valve	195/1000 (19.5)	203/1003 (20.2)	398/2003 (19.9)
Major aortic procedure	54/1000 (5.4)	62/1003 (6.2)	116/2003 (5.8)
Other procedure	36/1000 (3.6)	26/1003 (2.6)	62/2003 (3.0)
Number of distal coronary anastomoses, *n*/*N* (%)			
0	374/1000 (37.4)	369/1002 (36.8)	743/2002 (37.1)
1	114/1000 (11.4)	124/1002 (12.4)	238/2002 (11.9)
2	165/1000 (16.5)	137/1002 (13.7)	302/2002 (15.1)
3	234/1000 (23.4)	267/1002 (26.6)	501/2002 (25.0)
4	99/1000 (9.9)	92/1002 (9.2)	191/2002 (9.5)
5	14/1000 (1.4)	12/1002 (1.2)	26/2002 (1.3)
6	0/1000 (0.0)	1/1002 (0.1)	1/2002 (0.0)
Aortic valve replaced/repaired, *n*/*N* (%)	431/999 (43.1)	456/1003 (45.5)	887/2002 (44.3)
MV replaced/repaired, *n*/*N* (%)	154/999 (15.4)	143/1003 (14.3)	297/2002 (14.8)
TV replaced/repaired, *n*/*N* (%)	32/999 (3.2)	33/1003 (3.3)	65/2002 (3.2)
Pulmonary valve replaced/repaired, *n*/*N* (%)	7/999 (0.7)	3/1003 (0.3)	10/2002 (0.5)
***Details of other cardiac procedures,* n**			
Ablation for AF	1	0	1
Atrial septal defect closure	1	0	1
Atrial septal defect closure + radiofrequency ablation for AF	1	0	1
AVR + biopsy of lesion of wall of heart	1	0	1

continued

TABLE 11 Operative characteristics (*continued*)

Characteristic	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)
AVR, left atrial appendage occlusion + pulmonary vein isolation	0	1	1
AVR, Cox-Maze procedure + left atrial appendage occlusion	0	1	1
AVR, MVR, ablation for AF + left atrial Cox-Maze procedure	1	0	1
AVR, MVR, TV repair, left atrial appendage removal + radiofrequency ablation for AF	1	0	1
AVR, TV repair +/– MVR, ablation for AF + left atrial appendage occlusion	0	1	1
AVR +/– TV repair + Morrow procedure	0	1	1
CABG + ablation for AF	1	0	1
CABG + aneurysmectomy	3	0	3
CABG, AVR + left atrial appendage occlusion	0	1	1
CABG, AVR, Cox-Maze procedure + left atrial appendage occlusion	1	0	1
CABG + left atrial appendage occlusion	0	1	1
CABG + left ventricular pacing lead	0	1	1
CABG + Cox-Maze procedure	3	0	3
CABG, MV repair + ablation for AF	0	1	1
CABG, MV repair + left ventricular lead placement	1	0	1
CABG, MV repair + Cox-Maze procedure	0	1	1
CABG, MV repair + myomectomy	1	0	1
CABG, MV repair, TV repair + Cox-Maze procedure	0	1	1
CABG, MVR + left ventricular aneurysm	0	1	1
CABG, TV repair + atrial septal defect closure	1	0	1
CABG, valve + Cox-Maze procedure	1	0	1
CABG, valve + replacement of aneurysmal segment	0	1	1
CABG, valve replacement + thymectomy	1	0	1
Excision of atrial myxoma	0	1	1
Left apical aneurysmectomy	0	1	1
MV repair + ablation for AF	2	2	4
MV repair + atrial septal defect closure + tricuspid	0	1	1
MV repair, left atrial appendage occlusion + patent foramen ovale closure	1	0	1
MV repair + Cox-Maze procedure	0	1	1
MV repair, MV ring + pulmonary vein isolation ablation	0	1	1
MV repair + TV repair	2	1	3
MVR + ablation for AF	1	0	1

TABLE 11 Operative characteristics (*continued*)

Characteristic	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	Overall ($N = 2003$)
MVR + artificial chordae	1	0	1
MVR + patent foramen ovale closure	1	0	1
MVR + TV repair	0	1	1
MVR, TV repair + ablation for AF	2	0	2
MVR, TV repair + Cox-Maze procedure	1	0	1
MVR, TV repair + left atrial appendage occlusion	0	1	1
MVR, TV repair + patent foramen ovale closure	0	1	1
MVR, TV repair, patent foramen ovale closure + Cox-Maze procedure	1	1	2
MVR +/– TV repair, patent foramen ovale closure, left atrial appendage ligation +/– radiofrequency ablation for AF	1	0	1
Reimplantation of anomalous right coronary artery	1	0	1
TV repair + atrial septal defect closure	0	1	1
TV repair, Cox-Maze procedure, ablation for AF + excision of LATR	1	0	1
TV repair, MV repair, left atrial appendage occlusion + left sided Cox-Maze procedure	1	0	1
Valve + ablation for AF	0	1	1
Valve + radiofrequency ablation for AF	1	0	1
Graft conduit harvest sites			
Right arm, *n*/*N* (%)	3/1000 (0.3)	3/1003 (0.3)	6/2003 (0.3)
Left arm, *n*/*N* (%)	40/1000 (4.0)	38/1003 (3.8)	78/2003 (3.9)
Right leg, *n*/*N* (%)	212/999 (21.2)	200/1003 (19.9)	412/2002 (20.6)
Left leg, *n*/*N* (%)	416/999 (41.6)	416/1003 (41.5)	832/2002 (41.6)
Left internal mammary artery, *n*/*N* (%)	488/1000 (48.8)	495/1003 (49.4)	983/2003 (49.1)
Right internal mammary artery, *n*/*N* (%)	19/1000 (1.9)	32/1003 (3.2)	51/2003 (2.5)
Other, *n*/*N* (%)	7/1000 (0.7)	10/1003 (1.0)	17/2003 (0.8)
Blood saving techniques			
Tranexamic acid, *n*/*N* (%)	806/999 (80.7)	809/1002 (80.7)	1615/2001 (80.7)
Trasylol, *n*/*N* (%)	39/942 (4.1)	32/952 (3.4)	71/1894 (3.7)
Cell saver, *n*/*N* (%)	481/999 (48.1)	503/1003 (50.1)	984/2002 (49.2)

AF, atrial fibrillation; AVR, aortic valve replacement; MV, mitral valve; MVR, mitral valve replacement; NA, not applicable; TV, tricuspid valve.
a Missing for one restrictive group participant.
b Missing for 280 restrictive group participants and 274 liberal group participants.
c Missing for one restrictive group participant and one liberal group participant.

Post-operative characteristics that were not specified explicitly as primary or secondary outcomes are summarised in *Table 12* and *Figure 5*. The median haemoglobin at randomisation was 8.5 g/dl (IQR 8.1–8.8 g/dl), the median time between end of surgery and randomisation was 4.9 hours (IQR 1.7–17.7 hours) and the median post-randomisation ventilation time was 3.6 hours (IQR 0.0–10.2 hours). The majority of participants (88.2%) were discharged after cardiac surgery to their homes. There did not appear to be any important difference between the two groups, although the total chest tube drainage at 12 hours was slightly higher in the restrictive group than the liberal group [median 500 ml (IQR 325–790 ml) vs. 475 ml (IQR 300–750 ml)].

TABLE 12 Post-operative characteristics

Characteristic	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)
Medications used in theatre/postoperatively			
Hydroxyethyl starch, *n/N* (%)	230/996 (23.1)	233/1002 (23.3)	463/1998 (23.2)
Human albumin solution (Zenalb, Bio Products Laboratory Ltd), *n/N* (%)	79/996 (7.9)	90/1002 (9.0)	169/1998 (8.5)
Gelofusine, *n/N* (%)	839/996 (84.2)	834/1001 (83.3)	1673/1997 (83.8)
Inotropes, *n/N* (%)	620/995 (62.3)	612/1000 (61.2)	1232/1995 (61.8)
Randomisation			
Haemoglobin at randomisation (g/dl), median (IQR)	8.5 (8.1–8.8)	8.5 (8.1–8.8)	8.5 (8.1–8.8)
Time from surgery to randomisation[a] (hours), median (IQR)	5.0 (1.7–17.8)	4.8 (1.7–17.4)	4.9 (1.7–17.7)
Post-operative details			
Total chest tube drainage at 4 hours (ml),[b] median (IQR)	250 (150–425)	240 (150–400)	250 (150–425)
Total chest tube drainage at 12 hours (ml),[b] median (IQR)	500 (325–790)	475 (300–750)	480 (320–760)
Post-operation cell salvage used, *n/N* (%)	55/989 (5.6)	45/989 (4.6)	100/1978 (5.1)
Post-randomisation ventilation time (hours),[c] median (IQR)	3.6 (0.0–11.0)	3.6 (0.0–9.5)	3.6 (0.0–10.2)
Duration of post-randomisation ward stay (hours),[d] median (IQR)	102 (74.1–164)	104 (75.1–152)	103 (75.0–152)
Discharged from cardiac surgery unit to, *n/N* (%)			
Another unit in hospital[e]	9/1000 (0.9)	18/1003 (1.8)	27/2003 (1.3)
Home	882/1000 (88.2)	885/1003 (88.2)	1767/2003 (88.2)
Other hospital	74/1000 (7.4)	74/1003 (7.4)	148/2003 (7.4)
Other	35/1000 (3.5)	26/1003 (2.6)	61/2003 (3.0)

a Missing for 1 restrictive group participant.
b Missing for 2 restrictive group participants and 1 liberal group participant.
c There were 341 restrictive group participants and 351 liberal group participants with a post-randomisation ventilation time of zero. 32 restrictive group participants and 29 liberal group participants had censored observations. 63 restrictive group participants were re-intubated (59 once, 2 twice, 1 three times and 1 four times) and 60 liberal group participants (50 once, 7 twice and 3 three times).
d There were 44 restrictive group participants and 44 liberal group participants with a post-randomisation ward stay of zero. 2 restrictive group participants and 2 liberal group participants had censored observations. 18 restrictive group participants were readmitted to the ward (14 once, 3 twice and 1 three times) and 19 liberal group participants (18 once and 1 three times).
e The median LOS in the other unit in the hospital was 6 days (IQR 3–26 days) in the restrictive group and 14 days (IQR 3–32 days) in the liberal group.

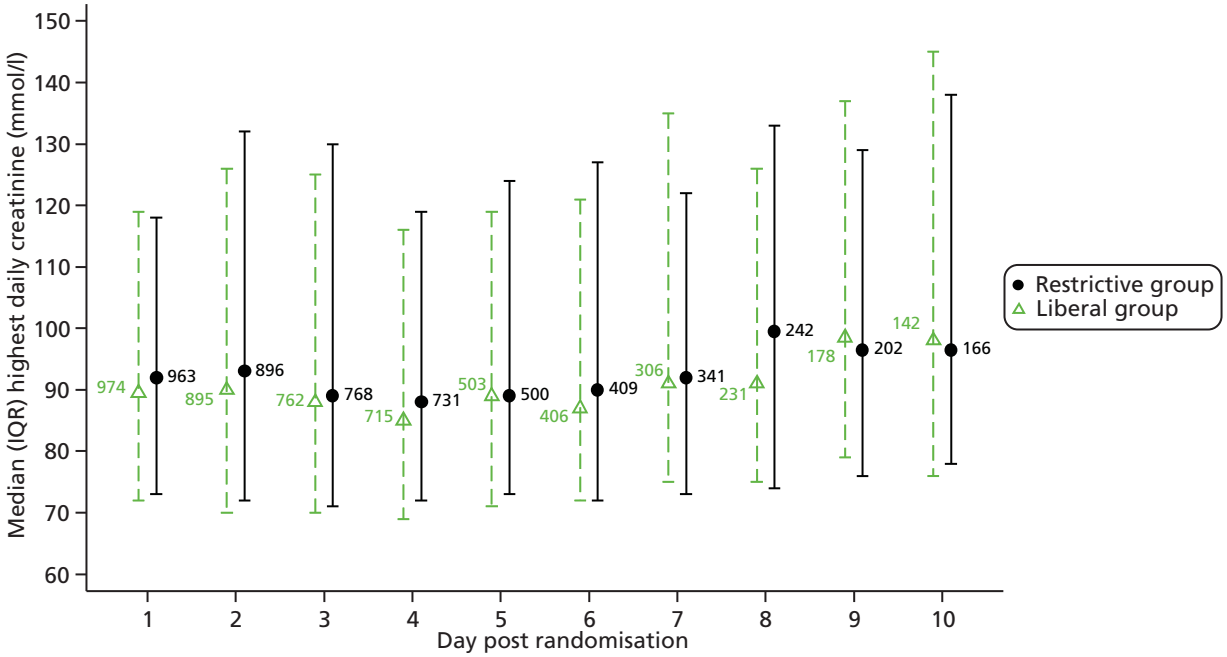


FIGURE 5 Daily highest creatinine levels for randomised/non-randomised participants. The numbers alongside the points are the numbers of participants contributing readings for that data point. The *x*-axis has an origin of the day of randomisation for both groups.

Success of blinding

At discharge, 152 participants of the 1007 questioned thought they knew which group they were allocated to (15.1%), of whom 115 (75.7%) were correct (*Table 13*). At the 3-month follow-up more participants thought they knew which group they were allocated to (459/1669; 27.5%) but proportionately fewer participants (260/459; 56.6%) were correct. More participants thought that being in the liberal group would be better than the restrictive group, although the proportion was higher at discharge (864/1003; 86.1%) than at follow-up (172/278; 61.9%).

TABLE 13 Success of blinding

Described by treatment group			
Aspect of blinding	Randomised to restrictive threshold ($n = 1000$)	Randomised to liberal threshold ($n = 1003$)	Overall ($n = 2003$)
At hospital discharge			
Did the participant think being in one group would be better, if so which[a]			
Restrictive	74	65	139
Liberal	422	442	864
Did not know	1	3	4
Did the participant think they knew which group they were in, if so which[a]			
Restrictive	51	21	72
Liberal	16	64	80
Did not know	430	425	855

continued

TABLE 13 Success of blinding (*continued*)

Described by treatment group			
Aspect of blinding	**Randomised to restrictive threshold (*n* = 1000)**	**Randomised to liberal threshold (*n* = 1003)**	**Overall (*n* = 2003)**
At 3-month follow-up			
Did the participant think being in one group would be better, if so which[b]			
Restrictive	65	41	106
Liberal	86	86	172
Thought one group was better, did not specify which	12	8	20
Did not think one group was any better	553	612	1165
Did the participant think they knew which group they were in, if so which[c]			
Restrictive	158	99	257
Liberal	54	102	156
Thought knew which group, did not specify which	21	25	46
Did not know which group they were in	581	629	1210

Description of data at hospital discharge vs. data at 3-month follow-up					
	At 3-month follow-up				
Hospital discharge	**Restrictive**	**Liberal**	**Thought one group was better, did not specify which**	**Did not think one group was any better**	**Did not answer question**
Did the participant think being in one group would be better, if so which					
Restrictive	16	21	3	77	22
Liberal	38	69	6	547	204
Did not know	0	1	0	1	2
Unavailable to answer questions	52	81	11	540	312
	Restrictive	**Liberal**	**Thought knew which group, did not specify which**	**Did not think one group was any better**	**Did not answer question**
Did the participant think they knew which group they were in, if so which					
Restrictive	31	5	4	25	7
Liberal	10	23	4	41	2
Did not know	102	50	14	576	113
Unavailable to answer questions	114	78	24	568	212

a 503 restrictive group participants and 493 liberal group participants were unavailable to answer questions at hospital discharge.
b 284 restrictive group participants and 256 liberal group participants did not answer question.
c 186 restrictive group participants and 148 liberal group participants did not answer question.

Summary

There is some uncertainty about screening data and there were recruitment challenges throughout the trial. However, a significant upturn in recruitment in late 2011 led to the trial completing recruitment just 2 weeks behind the revised target date. Data completeness is excellent and withdrawals and drop-out rates were few; over 98% of participants were followed up 3 months after randomisation. Baseline characteristics were well balanced between the groups.

Chapter 4 Process outcomes

Haemoglobin levels

Haemoglobin levels at the time of randomisation were similar [median 8.5 g/dl (IQR 8.1–8.8 g/dl)] in both the restrictive and liberal groups (see *Table 12*). After randomisation the groups diverged, daily nadir haemoglobin levels were lower in the restrictive group than the liberal group by approximately 1 g/dl (*Figure 6*). Day three was pre-specified in the SAP to be used as an overall summary measure; at this time the mean haemoglobin was 8.66 g/dl (SD 1.03 g/dl) in the restrictive group and 9.55 g/dl (SD 1.01 g/dl) in the liberal group.

Red blood cell transfusions

Red blood cell transfusions both before and after randomisation are given in *Figure 7* and *Table 14*. Before randomisation, 25.7% of participants were transfused one or more units, with approximately equal numbers of transfused participants in each group. Most of the pre-randomisation red blood cell transfusions were administered intraoperatively and the remaining were given either postoperatively but pre-randomisation or during a reoperation. After randomisation, 53.4% of participants in the restrictive group and 92.2% in the liberal group were transfused one or more units (RR 0.58, 95% CI 0.54 to 0.62; $p < 0.0001$). The median numbers of red blood cell units transfused after randomisation in the restrictive and liberal groups were 1 unit (IQR 0–2 units) and 2 units (IQR 1–3 units), respectively, and 1494 units were transfused in the restrictive group and 2494 units in the liberal group in total. Most red blood cell units were transfused according to the trial protocol; a small number were given either during a reoperation (when the trial protocol was suspended), after treatment according to allocation was discontinued, or in breach of the protocol. During the entire index admission (i.e. pre-randomisation and/or post randomisation), 63.7% of participants in the restrictive group and 94.9% in the liberal group were transfused. The median numbers of units transfused in the index admission was 1 (IQR 0–3) in the restrictive group and 2 (IQR 1–4) in the liberal group.

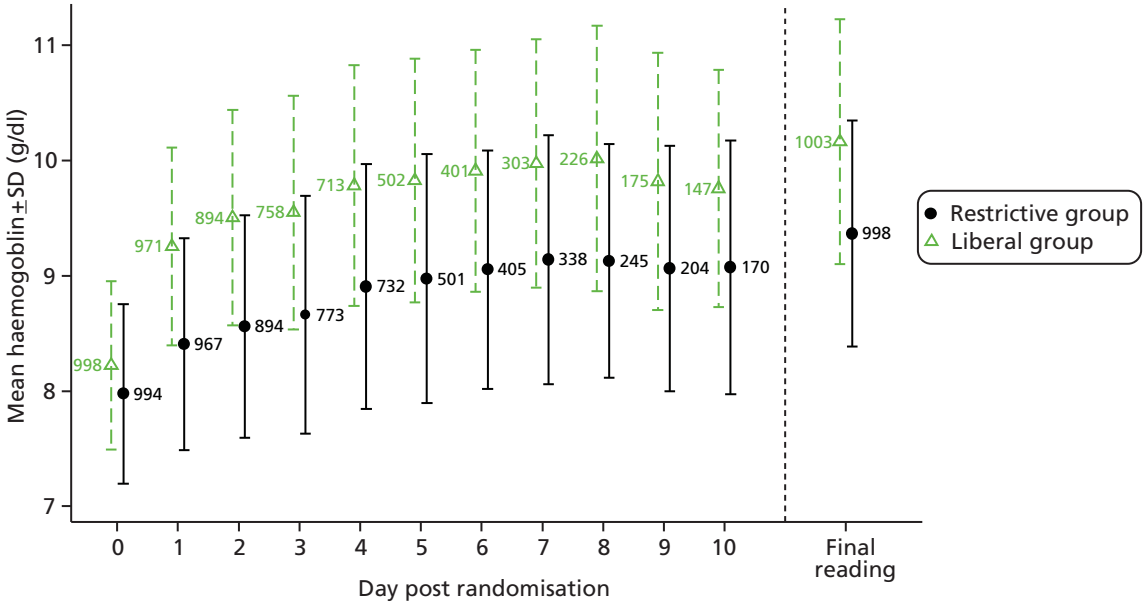


FIGURE 6 Mean daily nadir haemoglobin. The error bars are SDs (calculated independently at each time point).

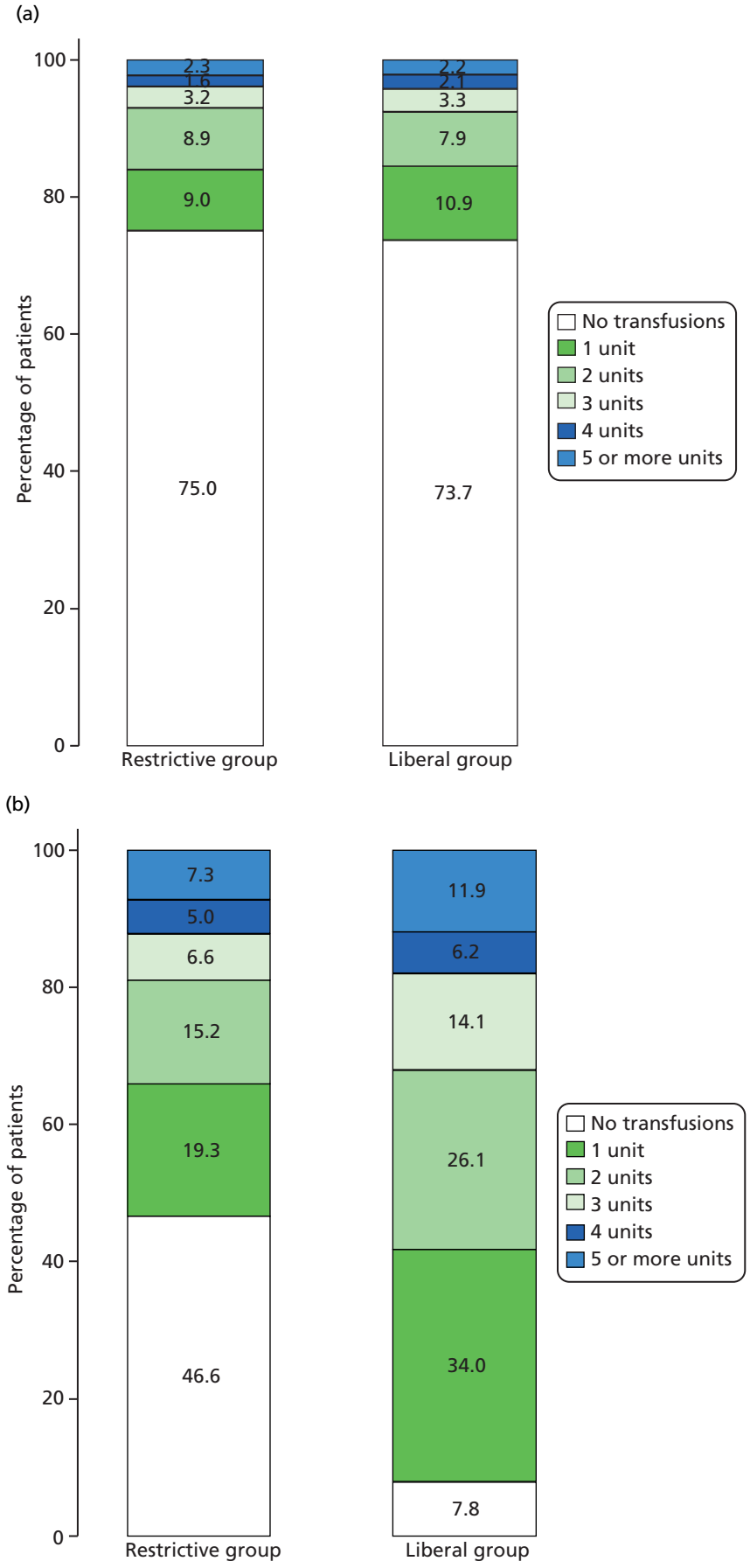


FIGURE 7 Secondary outcome: pre-randomisation and post-randomisation red blood cell transfusions.
(a) Pre-randomisation red blood cell transfusions.
(b) Post-randomisation red blood cell transfusions.

TABLE 14 Red blood cell transfusions

Outcome	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	Overall ($N = 2003$)	RR[a] (95% CI)	*p*-value
Pre-randomisation transfusions					
Total units transfused pre-randomisation, *n*/*N* (%)					
Median (IQR) units	0.0 (0.0–0.5)	0.0 (0.0–1.0)	0.0 (0.0–1.0)		
Not transfused	750/1000 (75.0)	739/1003 (73.7)	1489/2003 (74.3)		
1 unit	90/1000 (9.0)	109/1003 (10.9)	199/2003 (9.9)		
2 units	89/1000 (8.9)	79/1003 (7.9)	168/2003 (8.4)		
3 units	32/1000 (3.2)	33/1003 (3.3)	65/2003 (3.2)		
4 units	16/1000 (1.6)	21/1003 (2.1)	37/2003 (1.8)		
≥ 5 units	23/1000 (2.3)	22/1003 (2.2)	45/2003 (2.2)		
Total units transfused	587	589	1176		
Intraoperative transfusions, *n*/*N* (%)					
Not transfused	816/1000 (81.6)	823/1003 (82.1)	1639/2003 (81.8)		
1 unit	69/1000 (6.9)	69/1003 (6.9)	138/2003 (6.9)		
2 units	71/1000 (7.1)	67/1003 (6.7)	138/2003 (6.9)		
3 units	18/1000 (1.8)	18/1003 (1.8)	36/2003 (1.8)		
4 units	14/1000 (1.4)	18/1003 (1.8)	32/2003 (1.6)		
≥ 5 units	12/1000 (1.2)	8/1003 (0.8)	20/2003 (1.0)		
Post-operative pre-randomisation transfusions, *n*/*N* (%)					
Not transfused	911/1000 (91.1)	894/1003 (89.1)	1805/2003 (90.1)		
1 unit	45/1000 (4.5)	68/1003 (6.8)	113/2003 (5.6)		
2 units	26/1000 (2.6)	22/1003 (2.2)	48/2003 (2.4)		
3 units	10/1000 (1.0)	10/1003 (1.0)	20/2003 (1.0)		
4 units	7/1000 (0.7)	4/1003 (0.4)	11/2003 (0.5)		
≥ 5 units	1/1000 (0.1)	5/1003 (0.5)	6/2003 (0.3)		
Transfusions during a pre-randomisation reoperation, *n*/*N* (%)					
Not transfused	986/1000 (98.6)	992/1003 (98.9)	1978/2003 (98.8)		
1 unit	6/1000 (0.6)	2/1003 (0.2)	8/2003 (0.4)		
2 units	3/1000 (0.3)	5/1003 (0.5)	8/2003 (0.4)		
3 units	3/1000 (0.3)	3/1003 (0.3)	6/2003 (0.3)		
4 units	2/1000 (0.2)	1/1003 (0.1)	3/2003 (0.1)		

continued

TABLE 14 Red blood cell transfusions (*continued*)

Outcome	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)	RR[a] (95% CI)	*p*-value
Post-randomisation transfusions					
Total units transfused post randomisation, *n*/*N* (%)					
Median (IQR) units	1.0 (0.0–2.0)	2.0 (1.0–3.0)	1.0 (0.0–3.0)		
Not transfused	466/1000 (46.6)	78/1003 (7.8)	544/2003 (27.2)	0.58 (0.54 to 0.62)	< 0.0001
1 unit	193/1000 (19.3)	341/1003 (34.0)	534/2003 (26.7)		
2 units	152/1000 (15.2)	262/1003 (26.1)	414/2003 (20.7)		
3 units	66/1000 (6.6)	141/1003 (14.1)	207/2003 (10.3)		
4 units	50/1000 (5.0)	62/1003 (6.2)	112/2003 (5.6)		
≥ 5 units	73/1000 (7.3)	119/1003 (11.9)	192/2003 (9.6)		
Total units transfused	1494	2494	3988		
Transfusions during a post-randomisation reoperation, *n*/*N* (%)					
Not transfused	963/1000 (96.3)	969/1003 (96.6)	1932/2003 (96.5)		
1 unit	15/1000 (1.5)	9/1003 (0.9)	24/2003 (1.2)		
2 units	11/1000 (1.1)	13/1003 (1.3)	24/2003 (1.2)		
3 units	6/1000 (0.6)	4/1003 (0.4)	10/2003 (0.5)		
4 units	1/1000 (0.1)	3/1003 (0.3)	4/2003 (0.2)		
≥ 5 units	4/1000 (0.4)	5/1003 (0.5)	9/2003 (0.4)		
Transfusions after treatment according to protocol discontinued, *n*/*N* (%)					
Not transfused	980/1000 (98.0)	993/1003 (99.0)	1973/2003 (98.5)		
1 unit	4/1000 (0.4)	2/1003 (0.2)	6/2003 (0.3)		
2 units	4/1000 (0.4)	2/1003 (0.2)	6/2003 (0.3)		
3 units	2/1000 (0.2)	0/1003 (0.0)	2/2003 (0.1)		
4 units	2/1000 (0.2)	0/1003 (0.0)	2/2003 (0.1)		
≥ 5 units	8/1000 (0.8)	6/1003 (0.6)	14/2003 (0.7)		

TABLE 14 Red blood cell transfusions (*continued*)

Outcome	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	Overall ($N = 2003$)	RR[a] (95% CI)	*p*-value
Transfusions in breach of protocol, *n*/*N* (%)					
Not transfused	727/1000 (72.7)	896/1003 (89.3)	1623/2003 (81.0)		
1 unit	135/1000 (13.5)	85/1003 (8.5)	220/2003 (11.0)		
2 units	72/1000 (7.2)	10/1003 (1.0)	82/2003 (4.1)		
3 units	34/1000 (3.4)	5/1003 (0.5)	39/2003 (1.9)		
4 units	17/1000 (1.7)	3/1003 (0.3)	20/2003 (1.0)		
≥ 5 units	15/1000 (1.5)	4/1003 (0.4)	19/2003 (0.9)		
Transfusions per protocol, *n*/*N* (%)					
Median (IQR) units	0.0 (0.0–1.0)	2.0 (1.0–3.0)	1.0 (0.0–2.0)		
Not transfused	577/1000 (57.7)	87/1003 (8.7)	664/2003 (33.2)		
1 unit	256/1000 (25.6)	362/1003 (36.1)	618/2003 (30.9)		
2 units	93/1000 (9.3)	265/1003 (26.4)	358/2003 (17.9)		
3 units	46/1000 (4.6)	147/1003 (14.7)	193/2003 (9.6)		
4 units	13/1000 (1.3)	56/1003 (5.6)	69/2003 (3.4)		
≥ 5 units	15/1000 (1.5)	86/1003 (8.6)	101/2003 (5.0)		

a RR from an unadjusted logistic regression model comparing any transfusions with no transfusions (models adjusting for cardiac procedure and/or centre would not converge).
Shading denotes outcomes for which there was no pre-specified plan to estimate the RRs.

Transfusion of blood products other than red blood cells

Platelets were the most common other blood product transfused (36.8% of participants). FFP was transfused in 29.0% of participants, cryoprecipitate in 10.0% and Beriplex and activated factor VII in only 5.0% and 0.6% of participants, respectively (*Figure 8* and *Table 15*). Use of all other products was similar between the two groups over the duration of the index admission.

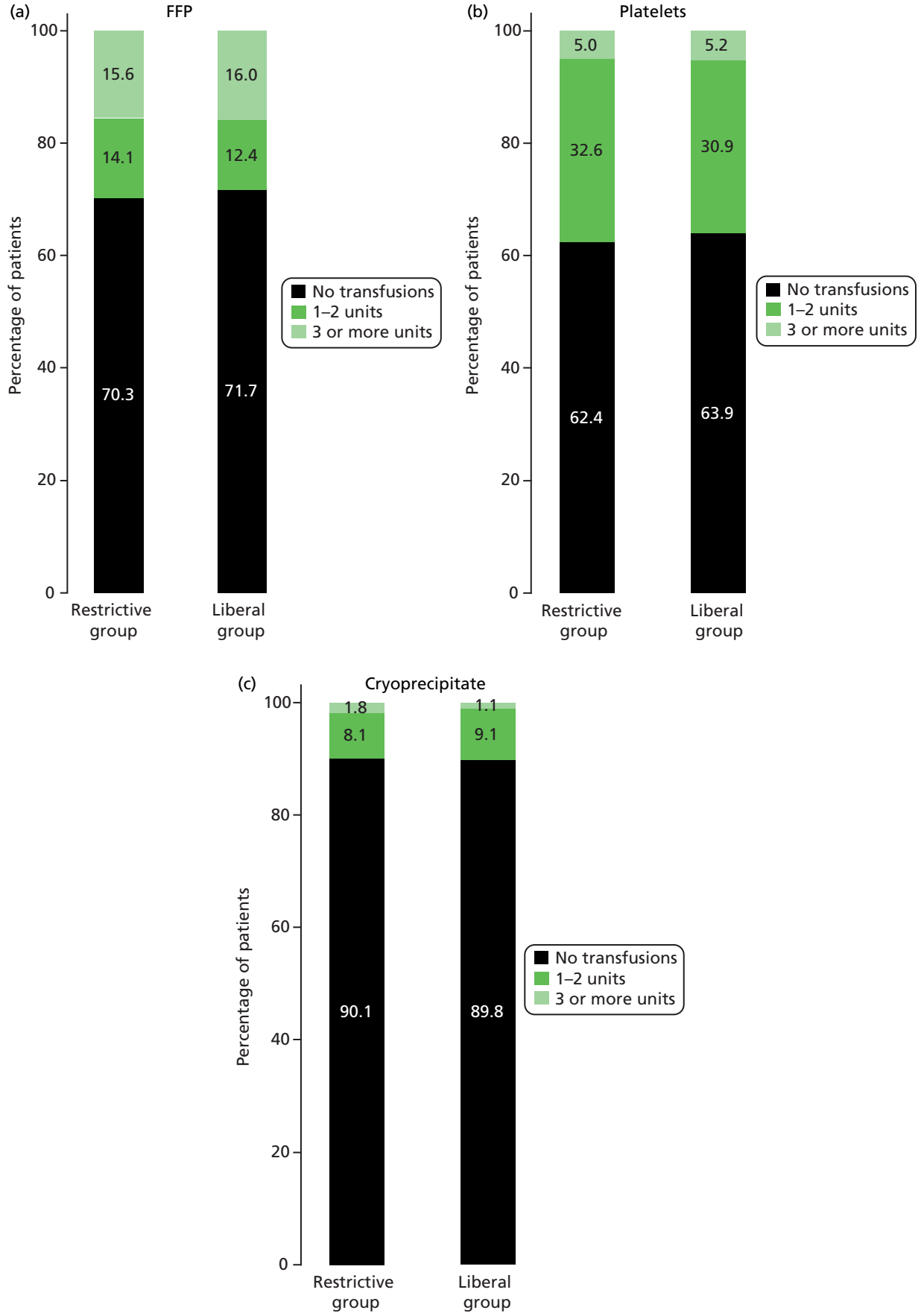


FIGURE 8 Use of (a) FFP, (b) platelets and (c) cryoprecipitate; pre-randomisation and post-randomisation use have been combined.

TABLE 15 Use of blood products other than red blood cells (pre and post randomisation combined)

Outcome	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Overall (*N* = 2003)	Estimate[a] (95% CI)	*p*-value
FFP transfusions, *n*/*N* (%)					
Not transfused	703/1000 (70.3)	719/1003 (71.7)	1422/2003 (71.0)		
1 unit	12/1000 (1.2)	11/1003 (1.1)	23/2003 (1.1)	OR 1.08 (0.88 to 1.33)	0.45
2 units	129/1000 (12.9)	113/1003 (11.3)	242/2003 (12.1)		
3 units	32/1000 (3.2)	30/1003 (3.0)	62/2003 (3.1)		
4 units	82/1000 (8.2)	92/1003 (9.2)	174/2003 (8.7)		
≥ 5 units	42/1000 (4.2)	38/1003 (3.8)	80/2003 (4.0)		
Platelet transfusions, *n*/*N* (%)					
Not transfused	624/1000 (62.4)	641/1003 (63.9)	1265/2003 (63.2)		
1 unit	196/1000 (19.6)	177/1003 (17.6)	373/2003 (18.6)	OR 1.08 (0.89 to 1.31)	0.42
2 units	130/1000 (13.0)	133/1003 (13.3)	263/2003 (13.1)		
3 units	29/1000 (2.9)	25/1003 (2.5)	54/2003 (2.7)		
4 units	11/1000 (1.1)	20/1003 (2.0)	31/2003 (1.5)		
≥ 5 units	10/1000 (1.0)	7/1003 (0.7)	17/2003 (0.8)		
Cryoprecipitate transfusions, *n*/*N* (%)					
Not transfused	901/1000 (90.1)	901/1003 (89.8)	1802/2003 (90.0)		
1 unit	23/1000 (2.3)	22/1003 (2.2)	45/2003 (2.2)	OR 0.99 (0.72 to 1.35)	0.95
2 units	58/1000 (5.8)	69/1003 (6.9)	127/2003 (6.3)		
3 units	6/1000 (0.6)	4/1003 (0.4)	10/2003 (0.5)		
4 units	7/1000 (0.7)	5/1003 (0.5)	12/2003 (0.6)		
≥ 5 units	5/1000 (0.5)	2/1003 (0.2)	7/2003 (0.3)		
Activated factor VII used, yes (%)	7/1000 (0.7)	5/1003 (0.5)	12/2003 (0.6)	RR 1.41 (0.45 to 4.45)	0.56
Beriplex used, yes (%)	52/1000 (5.2)	48/1003 (4.8)	100/2003 (5.0)	OR 1.21 (0.73 to 2.03)	0.46

a Estimates from adjusted logistic regression models (adjusting for cardiac procedure as a fixed effect and centre as a random effect) comparing any blood product with no blood product. For activated factor VII, estimates are from an unadjusted logistic regression model (there were not enough events to deem adjustment appropriate) with a log-link function to enable a RR to be estimated.

Shading denotes outcomes for which there was no pre-specified plan to estimate the ORs or RRs.

Adherence

Non-adherence with the randomisation protocol

There were nine participants consented to the trial who were later found to be ineligible, although none of these participants were randomised (*Table 16*). Of the 1464 non-randomised participants, 176 (12.0%) met the post-consent eligibility criterion (haemoglobin < 9 g/dl) but were not randomised. All of the 2003 randomised participants breached the 9 g/dl threshold. However, randomisation was delayed (i.e. occurred later than 24 hours after the threshold breach occurred) for 65 participants (3.2%) and these instances were classified as non-adherent with respect to the randomisation protocol.

Non-adherence with the allocated transfusion threshold

Non-adherence with the allocated transfusion threshold is described in *Table 17*. There were 1813 deviations from the protocol occurring in 37.6% of participants; 635 deviations in 30.0% of participants in the restrictive group and 1178 deviations in 45.2% of participants in the liberal group. As anticipated,

TABLE 16 Non-adherence with randomisation protocol

Non-adherence type	Consented (*N* = 3565)
Participant was randomised more than 24 hours after meeting post-consent eligibility criteria (haemoglobin < 9 g/dl),[a] *n*/*N* (%)	9/3565 (0.2)
***Considered for randomisation, but not randomised* (n = *1464*)**	
Participant consented and met post-consent eligibility criterion (haemoglobin < 9 g/dl) but was not randomised, *n*/*N* (%)	176/1464 (12.0)
***Randomised* (n = *2003*)**	
Participant did not meet the post-consent eligibility criteria (haemoglobin < 9 g/dl) but was randomised, *n*/*N* (%)	0/2003 (0.0)
Participant was randomised more than 24 hours after meeting post-consent eligibility criteria (haemoglobin < 9 g/dl) but was not randomised,[b] *n*/*N* (%)	65/2003 (3.2)

a None of these participants went on to be randomised. The one patient who was found to be ineligible after randomisation (see *Footnote* c, *Table 9*) was not known to be ineligible at the time of obtaining consent.
b Median time between meeting the criteria and randomisation for these participants was 2 days (IQR 2–3 days, range 1–13 days).

TABLE 17 Non-adherence with the allocated transfusion threshold

	Randomised to restrictive threshold			Randomised to liberal threshold			Overall		
Non-adherence type	Events (*n*)	Participants (*N* = 1000) (*n*/*N*)	%	Events (*n*)	Participants (*N* = 1003) (*n*/*N*)	%	Events (*n*)	Participants (*N* = 2003) (*n*/*N*)	%
Any protocol deviation	635	300/1000	30.0	1178	453/1003	45.2	1813	753/2003	37.6
Any severe protocol deviation	186	97/1000	9.7	116	62/1003	6.2	302	159/2003	7.9
Extra transfusion	573	273/1000	27.3	161	107/1003	10.7	734	380/2003	19.0
Moderate	391	180/1000	18.0	161	107/1003	10.7	552	287/2003	14.3
Severe	182	93/1000	9.3	0	0/1003	0.0	182	93/2003	4.6
Withheld transfusion	62	55/1000	5.5	1017	390/1003	38.9	1079	445/2003	22.2
Mild	34	30/1000	3.0	546	204/1003	20.3	580	234/2003	11.7
Moderate	24	22/1000	2.2	355	167/1003	16.7	379	189/2003	9.4
Severe	4	4/1000	0.4	116	62/1003	6.2	120	66/2003	3.3

extra transfusions (i.e. given outside of protocol) were more common in the restrictive group (573 in 27.3% of participants vs. 161 in 10.7% of participants) and withheld transfusions were more common in the liberal group (1017 in 38.9% of participants vs. 62 in 5.5% of participants). Approximately one-sixth of all deviations were classified as severe; 24.8% of extra transfusions and 11.1% of withheld transfusions. Therefore, severe protocol deviations were more common in the restrictive group than the liberal group (186 in 9.7% of participants vs. 116 in 6.2% of participants).

Characteristics of each instance of non-adherence are reported in *Table 18*. Extra transfusions tended to be given either for the clinical reasons listed on the CRF (36.5%) or for 'other' reasons (42.7%), which were generally clinical reasons not listed as specific options on the CRF. The most common reason for a withheld transfusion was 'oversight/error' (67.2%). Extra transfusions tended to occur earlier than withheld transfusions and were more likely to occur overnight. There were no clear trends in time of year for either type of non-adherence.

Separate logistic regression models were fitted for (1) extra transfusions and (2) withheld transfusions to identify any characteristics (both at an adherence level and participant level) that predicted non-adherence (*Table 19*). The odds of an extra transfusion reduced by 3% with each post-operative day and reduced by 22% at weekends. However, the odds of a withheld transfusion increased by 3% with each post-operative day and increased by 79% at weekends. Both types of non-adherence were much more likely in the ICU than on the ward. Centre recruitment rate was important for predicting both types of non-adherence, which was most common in relatively slow recruiting centres (3–4 participants per month). Participants having more complex operation types (CABG and valve and valve-alone surgery) were more likely to have an extra transfusion, as were participants transfused pre-randomisation. Participants with a longer period of time between operation end and randomisation were more likely to have a withheld transfusion, and the odds of a withheld transfusion decreased by 1% with each year of age.

TABLE 18 Characteristics of instances of non-adherence with transfusion protocol

Characteristic	Extra transfusions			Withheld transfusions		
	Restrictive group (*N* = 573)	Liberal group (*N* = 161)	Overall (*N* = 734)	Restrictive group (*N* = 62)	Liberal group (*N* = 1017)	Overall (*N* = 1079)
Section A[a]						
Reason for non-adherence, *n/N* (%)						
Excessive blood loss	128/558 (22.9)	55/149 (36.9)	183/707 (25.9)	N/A	N/A	N/A
Sepsis	18/558 (3.2)	2/149 (1.3)	20/707 (2.8)	N/A	N/A	N/A
Physiological indicators of oxygen debt	54/558 (9.7)	1/149 (0.7)	55/707 (7.8)	N/A	N/A	N/A
Clinical preference	N/A	N/A	N/A	8/48 (16.7)	167/815 (20.5)	175/863 (20.3)
Oversight/error	98/558 (17.6)	49/149 (32.9)	147/707 (20.8)	26/48 (54.2)	554/815 (68.0)	580/863 (67.2)
Other	260/558 (46.6)	42/149 (28.2)	302/707 (42.7)	14/48 (29.2)	94/815 (11.5)	108/863 (12.5)

continued

TABLE 18 Characteristics of instances of non-adherence with transfusion protocol (*continued*)

Characteristic	Extra transfusions			Withheld transfusions		
	Restrictive group (*N* = 573)	Liberal group (*N* = 161)	Overall (*N* = 734)	Restrictive group (*N* = 62)	Liberal group (*N* = 1017)	Overall (*N* = 1079)
If, clinical reason/other level of clinician making decision, *n*/*N* (%)						
Consultant	203/340 (59.7)	34/71 (47.9)	237/411 (57.7)	5/10 (50.0)	79/174 (45.4)	84/184 (45.7)
Registrar	125/340 (36.8)	32/71 (45.1)	157/411 (38.2)	5/10 (50.0)	70/174 (40.2)	75/184 (40.8)
Junior doctor	9/340 (2.6)	5/71 (7.0)	14/411 (3.4)	0/10 (0.0)	14/174 (8.0)	14/184 (7.6)
Nurse practitioner	3/340 (0.9)	0/71 (0.0)	3/411 (0.7)	0/10 (0.0)	11/174 (6.3)	11/184 (6.0)
Haemoglobin levels at time of non-adherence (g/dl), median (IQR)						
Any non-adherence[b]	7.8 (7.6–8.4)	9.0 (8.2–9.5)[c]	8.0 (7.6–8.8)	7.2 (7.0–7.4)	8.6 (8.3–8.8)	8.6 (8.3–8.8)
Mild	N/A	N/A	N/A	7.1 (7.0–7.4)	8.6 (8.3–8.8)	8.6 (8.1–8.8)
Moderate[d]	7.8 (7.5–8.3)	9.0 (8.2–9.5)[c]	8.1 (7.6–8.9)	7.2 (7.1–7.4)	8.6 (8.4–8.8)	8.6 (8.3–8.8)
Severe[e]	8.0 (7.6–8.5)	N/A	8.0 (7.6–8.5)	7.3 (7.2–7.4)	8.7 (8.5–8.8)	8.7 (8.4–8.8)
Time between operation end and non-adherence (days), median (IQR)						
Any non-adherence	2.0 (0.4–7.0)	0.7 (0.3–4.2)	1.8 (0.3–6.1)	3.0 (1.8–5.4)	3.7 (1.8–8.0)	3.7 (1.8–7.9)
Mild	N/A	N/A	N/A	2.8 (1.5–7.2)	3.0 (1.4–8.6)	3.0 (1.4–8.5)
Moderate	2.7 (0.5–11.2)	0.7 (0.3–4.2)	2.0 (0.4–8.2)	3.7 (2.7–4.6)	4.8 (3.4–9.8)	4.8 (3.2–9.6)
Severe	0.9 (0.3–3.7)	N/A	0.9 (0.3–3.7)	1.9 (1.1–2.8)	3.0 (1.0–4.6)	2.9 (1.0–4.4)
Time of day, *n*/*N* (%)						
Weekday 09:00 to 17:00	153/573 (26.7)	34/161 (21.1)	187/734 (25.5)	13/57 (22.8)	163/923 (17.7)	176/980 (18.0)
Weekday evenings/overnight	262/573 (45.7)	93/161 (57.8)	355/734 (48.4)	18/57 (31.6)	348/923 (37.7)	366/980 (37.3)
Weekend 09:00 to 17:00	65/573 (11.3)	6/161 (3.7)	71/734 (9.7)	8/57 (14.0)	92/923 (10.0)	100/980 (10.2)
Weekend evenings/overnight	93/573 (16.2)	28/161 (17.4)	121/734 (16.5)	18/57 (31.6)	320/923 (34.7)	338/980 (34.5)

TABLE 18 Characteristics of instances of non-adherence with transfusion protocol (*continued*)

Characteristic	Extra transfusions			Withheld transfusions		
	Restrictive group (*N* = 573)	Liberal group (*N* = 161)	Overall (*N* = 734)	Restrictive group (*N* = 62)	Liberal group (*N* = 1017)	Overall (*N* = 1079)
Section B[f]						
Day of week, *n*/*N* (%)						
Sunday	56/1334 (4.2)	10/1333 (0.8)	66/2667 (2.5)	8/1334 (0.6)	166/1333 (12.5)	174/2667 (6.5)
Monday	63/1428 (4.4)	20/1431 (1.4)	83/2859 (2.9)	8/1428 (0.6)	124/1431 (8.7)	132/2859 (4.6)
Tuesday	76/1489 (5.1)	40/1491 (2.7)	116/2980 (3.9)	4/1489 (0.3)	97/1491 (6.5)	101/2980 (3.4)
Wednesday	108/1552 (7.0)	36/1524 (2.4)	144/3076 (4.7)	3/1552 (0.2)	105/1524 (6.9)	108/3076 (3.5)
Thursday	103/1609 (6.4)	19/1586 (1.2)	122/3195 (3.8)	7/1609 (0.4)	138/1586 (8.7)	145/3195 (4.5)
Friday	106/1558 (6.8)	22/1569 (1.4)	128/3127 (4.1)	12/1558 (0.8)	132/1569 (8.4)	144/3127 (4.6)
Saturday	61/1437 (4.2)	14/1440 (1.0)	75/2877 (2.6)	15/1437 (1.0)	161/1440 (11.2)	176/2877 (6.1)
Time of year, *n*/*N* (%)						
February to April	88/2291 (3.8)	42/2368 (1.8)	130/4659 (2.8)	13/2291 (0.6)	204/2368 (8.6)	217/4659 (4.7)
May to July	129/2210 (5.8)	41/2311 (1.8)	170/4521 (3.8)	7/2210 (0.3)	221/2311 (9.6)	228/4521 (5.0)
August to October	227/3031 (7.5)	27/2847 (0.9)	254/5878 (4.3)	18/3031 (0.6)	264/2847 (9.3)	282/5878 (4.8)
November to January	129/2875 (4.5)	51/2848 (1.8)	180/5723 (3.1)	19/2875 (0.7)	234/2848 (8.2)	253/5723 (4.4)
Level of care, *n*/*N* (%)						
ICU	460/4318 (10.7)	137/4184 (3.3)	597/8502 (7.0)	40/4318 (0.9)	708/4184 (16.9)	748/8502 (8.8)
Ward	113/6089 (1.9)	24/6190 (0.4)	137/12279 (1.1)	22/6089 (0.4)	309/6190 (5.0)	331/12,279 (2.7)

N/A, not applicable.
a Denominators in this section are the numbers of relevant non-adherent deviations.
b Missing for 112 extra transfusions in the restrictive group and 22 extra transfusions in the liberal group.
c The lower quartile is < 9 g/dl because, although extra transfusions occurred less often in the liberal group, a substantial proportion of them arose from prescribing 2 units at once without rechecking haemoglobin concentrations.
d Missing for 80 extra transfusions in the restrictive group and 22 extra transfusions in the liberal group.
e Missing for 32 extra transfusions in the restrictive group.
f Denominators in this section are the numbers of patient days in the trial.

TABLE 19 Multiple logistic regression models to identify predictors of non-adherence

Characteristic	Extra transfusions		Withheld transfusions	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Adherence characteristics				
Time from operation end (days)	0.97 (0.95 to 0.98)	$p < 0.001$	1.03 (1.01 to 1.04)	$p < 0.001$
Weekend vs. weekday	0.78 (0.63 to 0.95)	$p = 0.013$	1.79 (1.54 to 2.09)	$p < 0.001$
ICU vs. ward	4.68 (3.76 to 5.83)	$p < 0.001$	3.07 (2.55 to 3.69)	$p < 0.001$
Participant characteristics				
Centre recruitment rate				
≥ 6 participants per month	Reference group	$p < 0.001$	Reference group	$p = 0.022$
4–6 participants per month	1.04 (0.77 to 1.39)		0.84 (0.61 to 1.15)	
3–4 participants per month	2.23 (1.62 to 3.05)		1.39 (0.99 to 1.96)	
< 3 participants per month	1.54 (0.97 to 2.44)		0.71 (0.41 to 1.22)	
Time between operation end and randomisation			1.15 (1.07 to 1.25)	$p < 0.001$
Age (years)			0.99 (0.97 to 1.00)	$p = 0.029$
Cardiac procedure		$p < 0.001$		
CABG only	Reference group			
CABG + valve	1.36 (1.01 to 1.83)			
Valve only	1.75 (1.27 to 2.40)			
Other	1.04 (0.66 to 1.65)			
Transfused pre-randomisation	1.49 (1.15 to 1.93)	$p = 0.003$		

Shading denotes outcomes for which there was no pre-specified plan to estimate the ORs or RRs, or analyses that were not pre-specified.

Adherence by centre is given in *Figure 9*, which demonstrates wide variation between centres with no obvious relationship to total recruitment or average recruitment rates.

Non-adherence was monitored carefully over the course of the trial and various measures were put in place to try and improve non-adherence rates.[33] Some of these measures are described in *Table 20*.

There was no improvement in non-adherence rates over the course of the study despite these measures (*Figure 10*). In the early stages, rates of non-adherence fluctuated somewhat but by the time that half of the participants had been recruited, rates remained fairly constant.

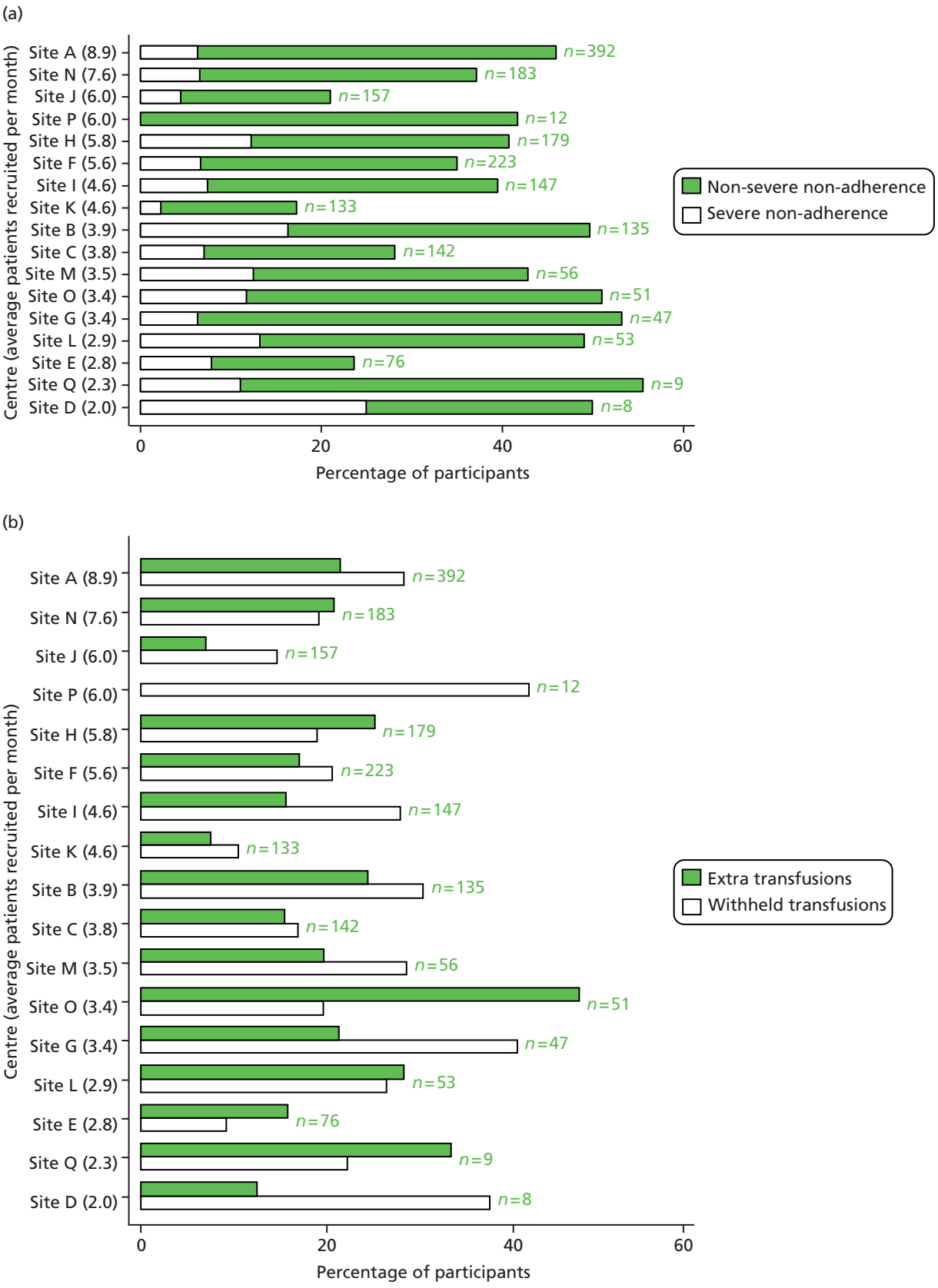


FIGURE 9 Adherence by centre.
(a) Percentage of participants with any severe/non-severe non-adherence by centre.
(b) Percentage of participants having extra and withheld transfusions. Sites are ordered by the average number of participants recruited per month.

TABLE 20 Methods implemented to monitor feedback and/or provide training on adherence

Methods implemented by trial management team across all sites		
For site research teams	**For clinical staff**	**For clinical and site research staff**
Regular newsletters were sent to sites to try to motivate staff to improve adherence and maintain interest in study	Regular teaching slots about the trial for new and existing staff, the timing of which was frequently aimed to coincide with the start of residents' rotations	Colour-coded labels provided for research and clinical staff to add to participants' notes and charts (to clearly identify TITRe2 participants and allocated group)
Mid-study site visits included analysis and discussion of non-adherence with local research teams to try to identify site-specific barriers to adherence and potential solutions	Nurses' manuals at nursing stations containing trial-specific information and summaries of the protocol for the restrictive and liberal groups	Daily haemoglobin transfusion checks by research nurses to monitor adherence with the protocol for randomisation and treatment according to allocated group and to record instances of non-adherence. These checks were usually done Monday to Friday (owing to research nurse working patterns). These checks provided a useful additional avenue of communication if the clinical team had any trial-related queries and provided a physical presence of the trial on the cardiac units
Reports were fed back to sites, both at mid-study visits and thereafter on a quarterly basis, describing site-specific non-adherence over time and non-adherence in relation to other sites	Adherence competitions were trialled but found to be difficult to implement logistically. However, informal prizes were handed out at meetings of study investigators to commend sites that achieved high adherence rates	Trial branded stationery produced to remind staff to check and react to haemoglobin concentrations
Methods for avoiding non-adherence adopted by sites with better adherence were shared at meetings of study investigators. Research nurses were primary contributors at these meetings	Study posters in staff rooms	
Methods implemented by sites themselves		
Careful 'handover' between nursing shifts, highlighting the need to monitor the haemoglobin of a participant carefully and to randomise/transfuse in the event of breaching the allocated threshold (site A)		
Additional plastic wrist band/tag identifying that the patient was taking part in the trial; this band was alongside another band with the participant's identification details, which doctors and nurses had to check when prescribing/administering a red blood cell transfusion (site E)		
Adding coloured covers to the participant's paper medical records highlighting that the patient was taking part in research (site C)		
Out of hours/weekend reminder calls to ICU/ward (for participants known to be at risk of breaching their allocated threshold) to ask whether or not a participant's haemoglobin had been checked		

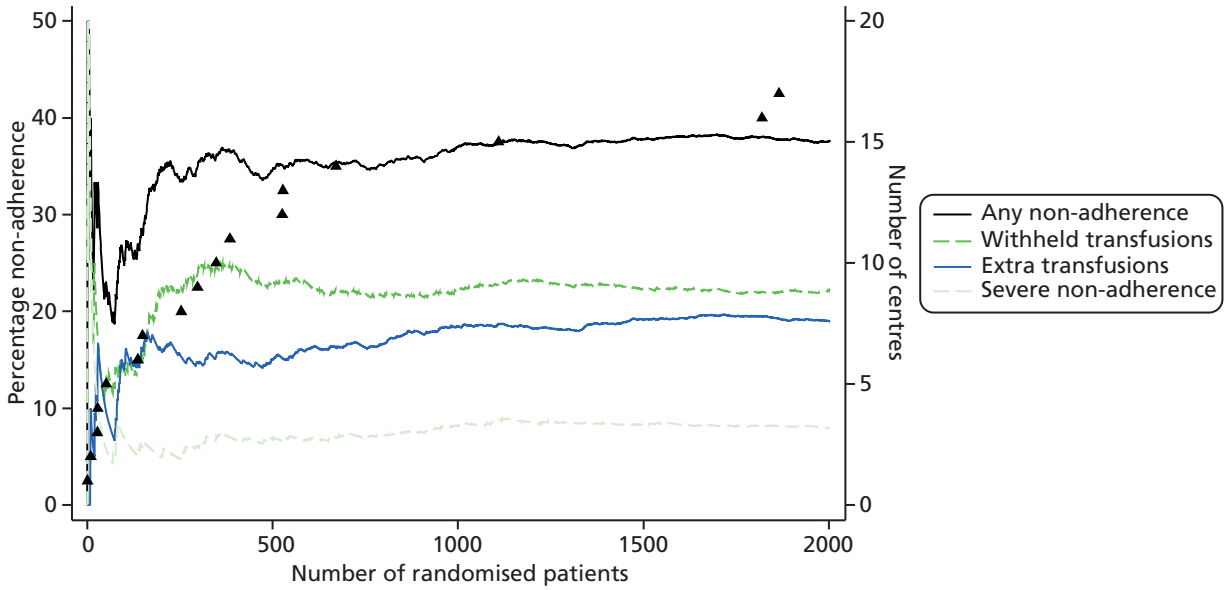


FIGURE 10 Change over time in proportions of non-adherent participants. Lines represent cumulative non-adherence rates; triangles represent the number of centres in the study.

Summary

The proportion of participants with any non-adherence was relatively high (37.6%). However, only 7.9% of participants had non-adherence that was classified as severe and which, by definition, affected overall transfusion rates. This percentage was consistent with the assumptions made when designing the trial. Therefore, we managed to achieve good separation between the groups in terms of both haemoglobin levels (approximately 1 g/dl difference) and transfusion rates (53.4% in the restrictive group vs. 92.2% in the liberal group). Finally, the proportions of participants transfused prior to randomisation, and the proportions given other blood products, were similar in the two groups.

Chapter 5 Primary and secondary outcomes

Primary outcome

Primary analysis

The primary outcome occurred in 35.1% of participants in the restrictive group and 33.0% in the liberal group (*Table 21*). This difference was not statistically significant, OR 1.11 (95% CI 0.91 to 1.34; $p = 0.30$). The most common element of the primary outcome was sepsis (21.6%), followed by AKI (13.2%) and wound infection (5.4%); all other components were relatively rare (< 2%). There were 27.1% participants who experienced the primary outcome before hospital discharge and 10.8% after hospital discharge (some participants experienced qualifying events both in hospital and after discharge). The small excess of primary outcome events in the restrictive group appeared to be mainly driven by AKI events. Most of the AKI events occurred before hospital discharge (96.6%) and AKI events had similar frequencies in each of the three AKI stages (34.4% stage one, 28.6% stage two and 37.1% stage three).

Most participants experiencing the primary outcome encountered their first component event in the first 10 days after randomisation (*Figure 11*). A planned secondary analysis using a Cox proportional hazards model gave HR 1.09 (95% CI 0.93 to 1.27; $p = 0.29$) which is very similar to the OR obtained from logistic regression in *Table 21*.

TABLE 21 Primary outcome

Outcome	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	Estimate (95% CI)	*p*-value
***At any time,*[a] n/N (%)**				
Overall	331/944 (35.1)	317/962 (33.0)	OR 1.11 (0.91 to 1.34)	0.30
Infectious event	238/936 (25.4)	240/954 (25.2)	OR 1.02 (0.83 to 1.26)	0.83
Sepsis[b]	210/982 (21.4)	214/983 (21.8)		
Wound infection	55/921 (6.0)	46/936 (4.9)		
Ischaemic event	156/991 (15.7)	139/991 (14.0)	OR 1.16 (0.90 to 1.49)	0.26
Permanent stroke[c]	15/989 (1.5)	17/985 (1.7)		
MI	3/987 (0.3)	4/981 (0.4)		
Gut infarction[d]	6/987 (0.6)	1/982 (0.1)		
AKI[e]	140/989 (14.2)	122/989 (12.3)		
Stage one	49/989 (5.0)	40/989 (4.0)		
Stage two	39/989 (3.9)	35/989 (3.5)		
Stage three	50/989 (5.1)	46/989 (4.7)		

continued

TABLE 21 Primary outcome (*continued*)

Outcome	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)	Estimate (95% CI)	*p*-value
Pre-discharge*, n/N *(%)				
Overall	282/988 (28.5)	253/984 (25.7)		
Infectious event	184/983 (18.7)	175/983 (17.8)		
Sepsis	178/990 (18.0)	167/993 (16.8)		
Wound infection	17/990 (1.7)	15/990 (1.5)		
Ischaemic event	146/1000 (14.6)	134/1003 (13.4)		
Permanent stroke	11/1000 (1.1)	14/1003 (1.4)		
MI	1/1000 (0.1)	3/1003 (0.3)		
Gut infarction	5/1000 (0.5)	1/1003 (0.1)		
AKI	134/1000 (13.4)	121/1003 (12.1)		
Post discharge*, n/N *(%)				
Overall	104/924 (11.3)	98/938 (10.4)		
Infectious event	94/924 (10.2)	92/937 (9.8)		
Sepsis	49/987 (5.0)	55/981 (5.6)		
Wound infection	55/921 (6.0)	46/936 (4.9)		
Ischaemic event	15/987 (1.5)	6/981 (0.6)		
Permanent stroke	5/987 (0.5)	3/981 (0.3)		
MI	2/987 (0.2)	1/981 (0.1)		
Gut infarction	1/987 (0.1)	0/981 (0.0)		
AKI	7/987 (0.7)	2/981 (0.2)		

a This table does not include any pre-randomisation events. 46 restrictive group participants and 44 liberal group participants experienced an event pre-randomisation: infectious events for 22 restrictive group participants and 24 liberal group participants (all sepsis); ischaemic events for 31 restrictive group participants and 26 liberal group participants (two strokes, one MI and 28 AKI in the restrictive group, and one stroke, three MIs and 23 AKI in the liberal group).
b Sites of sepsis events: respiratory – 134 restrictive group and 128 liberal group, wound – 47 restrictive group and 49 liberal group, blood – 23 restrictive group and 32 liberal group, and other – 49 restrictive group and 53 liberal group.
c Verification methods of strokes: CT scan only – 10 restrictive group and 16 liberal group, MRI only – none, and CT and MRI – two restrictive group and one liberal group.
d Verification methods of gut infarctions: laparotomy only – three restrictive group and three liberal group, post-mortem only – one restrictive group, and laparotomy and post-mortem – two restrictive group.
e AKI stage is the most severe stage reached.

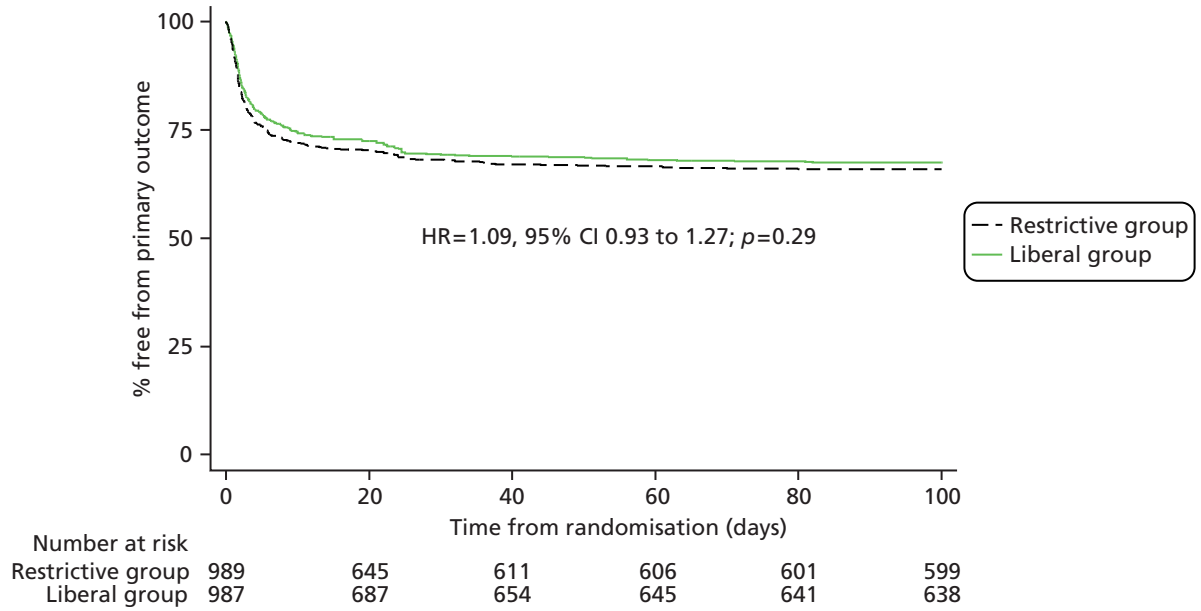


FIGURE 11 Kaplan–Meier estimates of time from randomisation to the primary outcome.
The HR is not adjusted for cardiac procedure (as was planned) because the proportional hazards assumption was violated if this term was included, and the first events occurring were sepsis (169 restrictive group and 171 liberal group), wound infection (21 restrictive group and 26 liberal group), stroke (12 restrictive group and 12 liberal group), MI (one restrictive group and four liberal group), gut infarction (four restrictive group) and AKI (126 in restrictive group and 105 in liberal group).

The combinations of primary outcome components occurring are described in *Table 22*. Four hundred and eighty participants experienced one component, of which sepsis alone was the most common (240/480, 50%); 151 participants experienced two components (of which sepsis and AKI was the most common combination; 72/151, 47.7%) and 17 participants experienced three components (of which sepsis, wound infection and AKI was the most common combination; 11/17, 64.7%). More participants in the restrictive group had AKI alone than the liberal group (7.2% vs. 5.9%), but fewer had AKI and sepsis (3.1% vs. 4.1%).

Sensitivity analyses

Sensitivity analyses were pre-specified in the SAP, but not the study protocol; several of these were planned during data collection in response to knowledge about limitations of the study (e.g. non-adherence) or accruing data (e.g. inconsistency in data characterising renal function) but without any knowledge about how the sensitivity analyses would impact on the findings. The rationale and hypotheses for the sensitivity analyses have been explained previously (see *Chapter 2*, *Sensitivity analyses*).

The effect of non-adherence was assessed by estimating centre-specific treatment effects and ordering sites by rates of severe non-adherence (*Figure 12*). The hypothesis that estimates would tend towards the null with increasing non-adherence was not supported either visually, from the forest plot, or statistically in that a test for heterogeneity suggested no significant differences between sites ($p = 0.65$).

Excluding primary outcome events occurring in the first 24 hours after randomisation did not substantially alter the estimated treatment effect (*Table 23*), which did not support the hypothesis that the effect would tend away from the null. Excluding participants who received transfused red blood cells prior to randomisation caused the treatment effect estimate to increase (OR 1.23, 95% CI 0.97 to 1.54; $p = 0.084$), which was consistent with the hypothesis. Excluding AKI events without the relevant creatinine rise did not alter the treatment effect estimate; however, including additional AKI events not picked up via clinical assessment (anticipated to be milder events) caused the treatment effect estimate to increase (OR 1.20, 95% CI 1.00 to 1.44; $p = 0.045$) and the distribution of AKI events across AKI stages also became more pyramidal, consistent with adding in extra mild events. We had not hypothesised an increase in the

TABLE 22 Combinations of primary outcome events

Number of elements	Sepsis	Wound infection	Stroke	MI	Gut infarction	AKI	Randomised to restrictive threshold ($N = 1000$) *n* (%)	Randomised to liberal threshold ($N = 1003$) *n* (%)
None							613 (61.3)	645 (64.3)
	No	No	No	No	No	No	613 (61.3)	645 (64.3)
One							244 (24.4)	236 (23.5)
	Yes	No	No	No	No	No	120 (12.0)	120 (12.0)
	No	No	No	No	No	Yes	72 (7.2)	59 (5.9)
	No	Yes	No	No	No	No	20 (2.0)	24 (2.4)
	Yes	Missing	No	No	No	No	14 (1.4)	14 (1.4)
	No	No	Yes	No	No	No	6 (0.6)	6 (0.6)
	No	Missing	No	No	No	Yes	2 (0.2)	3 (0.3)
	No	No	No	Yes	No	No	1 (0.1)	3 (0.3)
	Missing	Missing	Yes	Missing	Missing	Missing	1 (0.1)	2 (0.2)
	Missing	No	No	No	No	Yes	3 (0.3)	0 (0.0)
	Yes	Missing	Missing	Missing	Missing	Missing	1 (0.1)	2 (0.2)
	Yes	No	Missing	Missing	Missing	Missing	1 (0.1)	1 (0.1)
	Missing	Missing	Missing	Missing	Missing	Yes	0 (0.0)	1 (0.1)
	Missing	Missing	Yes	No	No	No	0 (0.0)	1 (0.1)
	Missing	No	Yes	Missing	Missing	Missing	1 (0.1)	0 (0.0)
	Missing	No	Yes	No	No	No	1 (0.1)	0 (0.0)
	No	No	No	No	Yes	No	1 (0.1)	0 (0.0)
Two							76 (7.6)	75 (7.5)
	Yes	No	No	No	No	Yes	31 (3.1)	41 (4.1)
	Yes	Yes	No	No	No	No	19 (1.9)	17 (1.7)
	Yes	Missing	No	No	No	Yes	6 (0.6)	4 (0.4)
	No	Yes	No	No	No	Yes	7 (0.7)	2 (0.2)
	Yes	No	Yes	No	No	No	2 (0.2)	4 (0.4)
	Yes	Missing	Missing	Missing	Missing	Yes	2 (0.2)	3 (0.3)
	No	No	Yes	No	No	Yes	3 (0.3)	1 (0.1)
	Yes	No	No	No	Yes	No	2 (0.2)	0 (0.0)
	Missing	Missing	Yes	Missing	Missing	Yes	0 (0.0)	1 (0.1)
	Missing	Yes	No	No	No	Yes	1 (0.1)	0 (0.0)
	No	No	No	No	Yes	Yes	1 (0.1)	0 (0.0)
	No	No	No	Yes	No	Yes	1 (0.1)	0 (0.0)
	Yes	Missing	No	No	Yes	No	1 (0.1)	0 (0.0)
	Yes	Missing	No	Yes	No	No	0 (0.0)	1 (0.1)
	Yes	No	Missing	Missing	Missing	Yes	0 (0.0)	1 (0.1)

TABLE 22 Combinations of primary outcome events (*continued*)

Number of elements	Sepsis	Wound infection	Stroke	MI	Gut infarction	AKI	Randomised to restrictive threshold ($N = 1000$) *n* (%)	Randomised to liberal threshold ($N = 1003$) *n* (%)
Three							11 (1.1)	6 (0.6)
	Yes	Yes	No	No	No	Yes	8 (0.8)	3 (0.3)
	Yes	No	Yes	No	No	Yes	1 (0.1)	1 (0.1)
	Yes	Missing	Missing	Missing	Yes	Yes	0 (0.0)	1 (0.1)
	Yes	No	No	No	Yes	Yes	1 (0.1)	0 (0.0)
	Yes	No	No	Yes	No	Yes	1 (0.1)	0 (0.0)
	Yes	No	Yes	Missing	Missing	Yes	0 (0.0)	1 (0.1)
Missing							56 (5.6)	41 (4.1)
	No	Missing	No	No	No	No	45 (4.5)	26 (2.6)
	Missing	Missing	Missing	Missing	Missing	Missing	5 (0.5)	8 (0.8)
	Missing	No	No	No	No	No	2 (0.2)	6 (0.6)
	Missing	No	Missing	Missing	Missing	Missing	2 (0.2)	1 (0.1)
	Missing	Missing	No	No	No	No	2 (0.2)	0 (0.0)

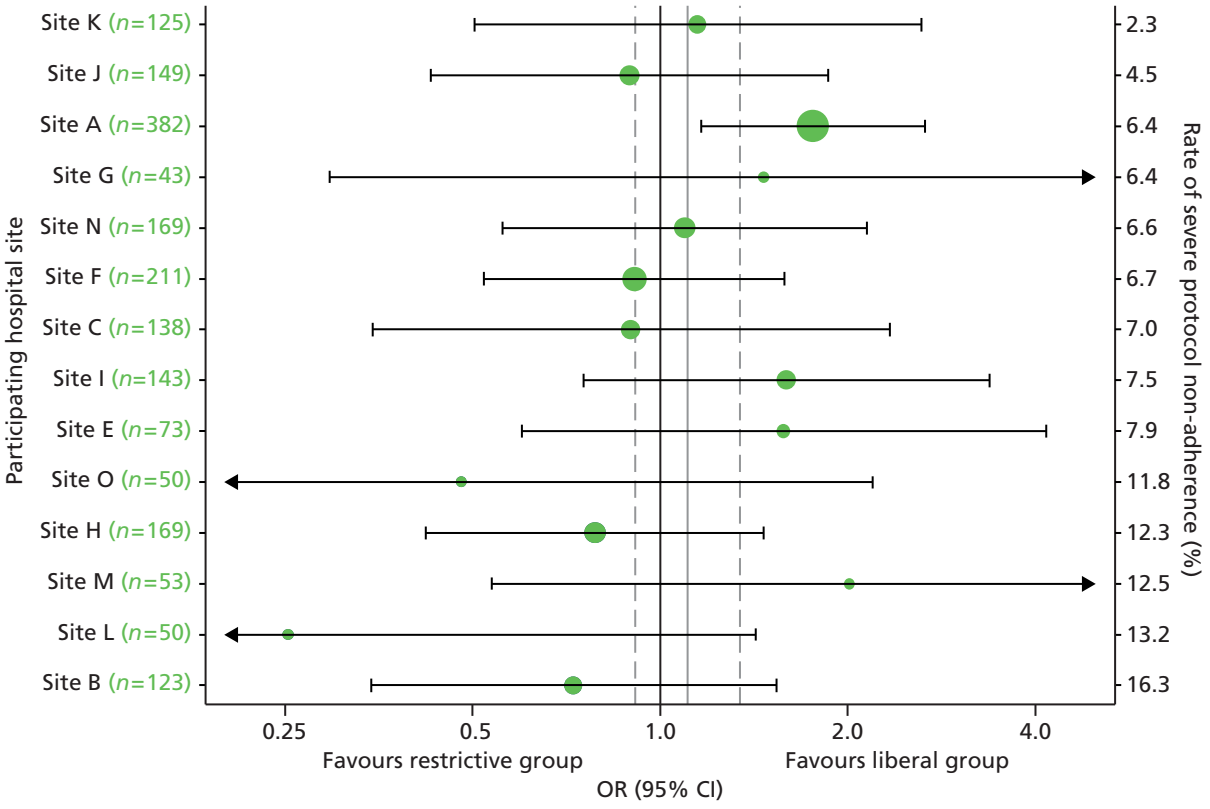


FIGURE 12 Sensitivity analysis: primary outcome OR estimates by site, ranked by severe non-adherence rates. The grey vertical lines represent the overall treatment estimate (solid line) and 95% CI (dashed lines) of the primary outcome for the entire analysis cohort. The sizes of the point estimates reflect the centre sizes. Test for heterogeneity between sites; $p = 0.65$. Estimates have not been calculated for three sites with fewer than 20 participants with complete primary outcome data.

TABLE 23 Sensitivity analyses

Sensitivity analysis	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	OR (95% CI)	*p*-value
Excluding primary outcome events occurring in the first 24 hours after randomisation, *n/N* (%)	293/943 (31.1)	284/956 (29.7)	1.08 (0.88 to 1.31)	0.47
Excluding participants who were transfused red blood cells pre-randomisation, *n/N* (%)	229/707 (32.4)	202/712 (28.4)	1.23 (0.97 to 1.54)	0.084
Excluding AKI events without relevant creatinine rise,[a] *n/N* (%)	328/944 (34.8)	315/962 (32.7)	1.10 (0.91 to 1.34)	0.33
Including additional AKI events identified from routinely collected creatinine data,[b] *n/N* (%)	477/959 (49.7)	440/970 (45.4)	1.20 (1.00 to 1.44)	0.045
Including only 'serious' primary outcome events, *n/N* (%)				
Any serious event	145/985 (14.7)	147/987 (14.9)	0.99 (0.77 to 1.27)	0.94
Sepsis	102/982 (10.4)	110/983 (11.2)		
Stroke	15/989 (1.5)	17/985 (1.7)		
MI	3/987 (0.3)	4/981 (0.4)		
Gut infarction	6/987 (0.6)	1/982 (0.1)		
AKI	50/989 (5.1)	46/989 (4.7)		

a Excluding events that were classified as AKI according to clinical judgement but the recorded creatinine levels did not verify this.
b Including events for which the participant was classified as not having AKI according to clinical judgement, but a creatinine increase in line with AKI criteria was recorded. New AKI event rates are as follows: restrictive group 342/991 (34.5%), liberal group 303/993 (30.5%).

treatment effect for this analysis but it was consistent with the observation that the small difference in the primary outcome frequency arose mainly from AKI events (see *Table 23*) and with the last planned sensitivity analysis, including only serious primary outcome events, which unexpectedly reduced the treatment effect estimate to unity (OR 0.99, 95% CI 0.77 to 1.27; $p = 0.94$).

Finally, the post-hoc analysis of severe in-hospital events (death, severe sepsis, ARDS, tracheostomy, low cardiac output, MI, AKI stage three, gut infarction and/or stroke) showed that this composite outcome occurred in 94/995 (9.5%) participants in the restrictive group and 90/993 (9.1%) in the liberal group (OR 1.05, 95% CI 0.77 to 1.43; $p = 0.75$).

Subgroup analyses

Subgroup analyses pre-specified in the study protocol are summarised in *Figure 13*. The subgroup analysis showing the largest difference between strata contrasted the treatment effect for participants with and without chronic obstructive pulmonary disease or asthma. The analysis suggested that the liberal transfusion strategy might be beneficial for participants with pulmonary comorbidity, although few participants had this comorbidity and the effect is not statistically significant. There was no other evidence of any subgroup effects.

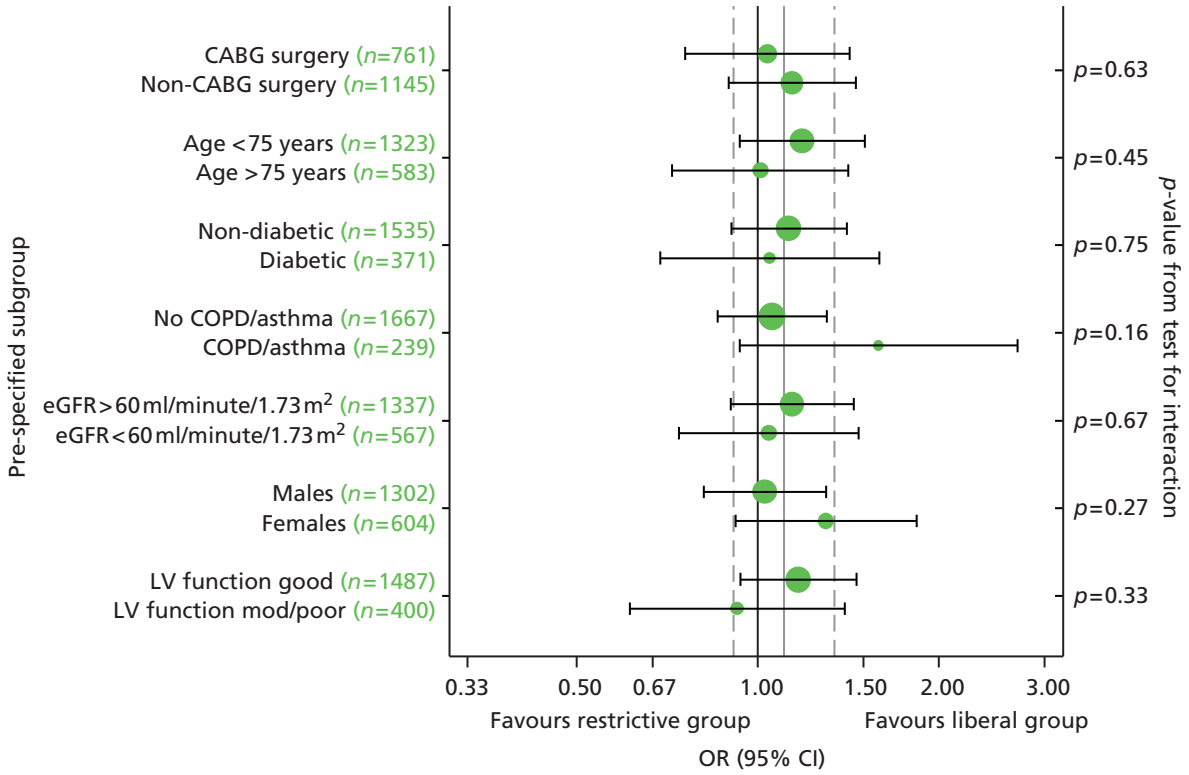


FIGURE 13 Subgroup analyses. The grey vertical lines represent the overall treatment estimate (solid line) and 95% CI (dashed lines) of the primary outcome for the entire analysis cohort. The sizes of the point estimates reflect the sizes of the subgroups.

COPD, chronic obstructive pulmonary disease; LV, left ventricular; mod, moderate.

Secondary outcomes

Primary analyses

Infectious and ischaemic events

Infectious and ischaemic events are summarised in *Table 21*. Infectious events occurred equally often in the two groups, 25.4% in the restrictive group and 25.2% in the liberal group (OR 1.02, 95% CI 0.83 to 1.26; $p = 0.83$). However, as the number of missing data was over 5% (mainly due to missing post-hospital discharge data), a treatment effect was estimated separately for pre-hospital discharge infections only, as specified in the SAP (OR 1.07, 95% CI 0.85 to 1.36; $p = 0.55$). Ischaemic events were slightly more common in the restrictive group (15.7%) than the liberal group (14.0%; OR 1.16, 95% CI 0.90 to 1.40; $p = 0.26$). This small difference appears to arise mainly owing to AKI events – 14.2% in the restrictive group and 12.3% in the liberal group.

Other clinical outcomes

There were significantly more deaths from any cause in the restrictive group (4.2%) than the liberal group (2.6%; HR 1.64, 95% CI 1.00 to 2.67; $p = 0.045$) (*Table 24* and *Figure 14*). Causes of death and other SAEs that preceded death are given in *Table 25*. There are no clear causes of death contributing to the excess in the restrictive group; the common causes were cardiac disorders (21 participants), infections/infestations (13 participants) and general disorders and administration site conditions (10 participants). The primary outcome was experienced before death by 65% of participants. With respect to SAEs preceding death, 55% of the deaths in the restrictive group were preceded by an ischaemic SAE, whereas 58% of the deaths in the liberal group were preceded by an infectious SAE.

TABLE 24 Other clinical outcomes

Outcome	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)	Effect (95% CI)	*p*-value
All-cause mortality, *n/N* (%)	42/1000 (4.2)	26/1003 (2.6)	HR 1.64 (1.00 to 2.67)	0.045
Significant pulmonary morbidity, *n/N* (%)	127/979 (13.0)	116/982 (11.8)	OR 1.11 (0.85 to 1.45)	0.45
Initiation of non-invasive ventilation	88/989 (8.9)	77/984 (7.8)		
Re-intubation/ventilation	50/975 (5.1)	53/973 (5.4)		
Tracheostomy	30/988 (3.0)	32/988 (3.2)		
Duration of ICU/HDU stay (hours),[a] median (IQR)	49.5 (21.9–99.7)	45.9 (20.1–94.8)	HR 0.97 (0.89 to 1.06)	0.53
Duration of hospital stay (days),[b] median (IQR)	7.0 (5.0–10.0)	7.0 (5.0–10.0)	HR 1.00 (0.92 to 1.10)	0.94

a Post-randomisation stay only, which was (1) zero for 63 restrictive group participants and 61 liberal group participants, and (2) censored for 23 restrictive group participants and 15 liberal group participants. In addition, 37 restrictive group participants had more than one ICU/HDU admission (33 had two admissions and four had three admissions) and 32 liberal group participants (31 had two admissions and one had four admissions). A sensitivity analysis investigating the potential effect of informative censoring, assuming all censored patients had the maximum observed (i.e. not censored) duration of ICU/HDU stay, gave an estimated HR 0.94 (95% CI 0.86 to 1.03; $p = 0.20$).

b Post-randomisation stay only, which was (1) zero for four restrictive group participants and two liberal group participants, and (2) censored for 25 restrictive group participants and 17 liberal group participants. A sensitivity analysis investigating the potential effect of informative censoring, assuming all censored patients had the maximum observed (i.e. not censored) duration of hospital stay, gave an estimated HR 0.98 (95% CI 0.90 to 1.07; $p = 0.71$).

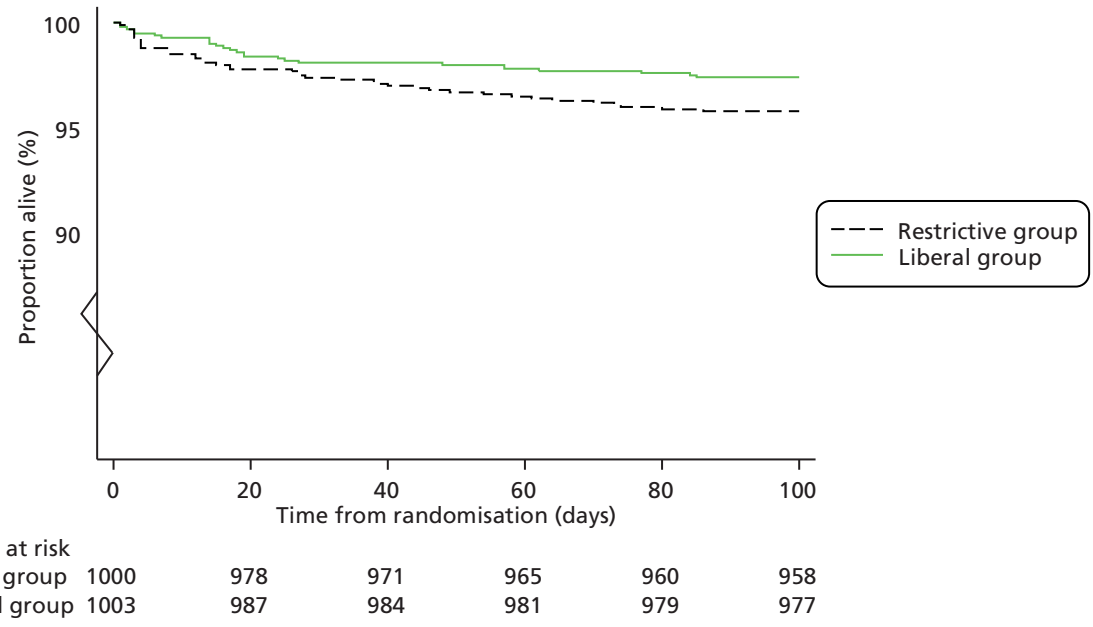


FIGURE 14 Kaplan–Meier estimates of time from randomisation to all-cause mortality.

TABLE 25a Further information on death: causes of death

	Randomised to restrictive threshold		Randomised to liberal threshold	
Causes of death[a]	Events	Participants ($n = 42$)	Events	Participants ($n = 26$)
Blood and lymphatic system disorders	0	0	1	1
Coagulopathy	0	0	1	1
Cardiac disorders	10	10	11	11
Arrhythmia	4	4	1	1
Cardiac arrest	1	1	0	0
Cardiac failure	3	3	1	1
Cardiac failure acute	0	0	2	2
Cardiac failure congestive	1	1	4	4
Left ventricular failure	1	1	1	1
Left ventricular hypertrophy	0	0	1	1
Pericardial haemorrhage	0	0	1	1
GI disorders	6	6	1	1
Duodenal ulcer perforation	1	1	0	0
GI haemorrhage	0	0	1	1
Intestinal infarction	1	1	0	0
Intestinal ischaemia	3	3	0	0
Peritonitis	1	1	0	0
General disorders and administration site conditions	7	7	3	3
Multiorgan failure	7	7	3	3
Hepatobiliary disorders	1	1	0	0
Hepatic necrosis	1	1	0	0
Infections and infestations	8	8	5	5
Bronchopneumonia	1	1	2	2
Empyema	0	0	1	1
Endocarditis	1	1	1	1
Lower respiratory tract infection	1	1	0	0
Pneumonia	3	3	1	1
Sepsis	2	2	0	0
Neoplasms benign, malignant and unspecified	1	1	0	0
Brain cancer metastatic	1	1	0	0
Nervous system disorders	3	3	2	2
Cerebral haemorrhage	1	1	0	0
CVA	1	1	2	2
Haemorrhage intracranial	1	1	0	0
Renal and urinary disorders	1	1	0	0
Renal failure	1	1	0	0
Respiratory, thoracic and mediastinal disorders	4	4	0	0
ARDS	1	1	0	0
Hypoxia	1	1	0	0
Pulmonary oedema	2	2	0	0

continued

TABLE 25a Further information on death: causes of death (*continued*)

Causes of death[a]	Randomised to restrictive threshold		Randomised to liberal threshold	
	Events	Participants ($n = 42$)	Events	Participants ($n = 26$)
Surgical and medical procedures	3	3	3	3
Cardiac operation	3	3	2	2
Ventriculocardiac shunt	0	0	1	1
Vascular disorders	1	1	3	3
Aortic aneurysm rupture	1	1	1	1
Haemorrhage	0	0	2	2

CVA, cerebrovascular accident; GI, gastrointestinal.
a Six participants have two primary causes of death listed: three participants in the restrictive group (participant 1, duodenal ulcer perforation and peritonitis; participant 2, multiorgan failure and sepsis; and participant 3, hypoxia and pulmonary oedema) and three participants in the liberal group (participant 1, endocarditis and ventriculocardiac shunt; participant 2, bronchopneumonia and empyema; and participant 3, bronchopneumonia and coagulopathy).

TABLE 25b Further information on death: SAE preceding death

SAEs preceding death[a]	Randomised to restrictive threshold		Randomised to liberal threshold	
	Events, *n*	Participants ($N = 42$), *n/N* (%)	Events	Participants ($N = 26$), *n/N* (%)
Primary outcome		26/40 (65)		17/26 (65)
Sepsis		11/40 (28)		15/26 (58)
Wound infection		2/42 (5)		0/26 (0)
Permanent stroke		3/42 (7)		0/26 (0)
MI		0/42 (0)		1/26 (4)
Gut infarction		4/42 (10)		0/26 (0)
AKI		16/42 (38)		12/26 (46)
Transient ischaemic attack	0	0/42 (0)	1	1/26 (4)
GI complications	2	2/42 (5)	8	7/26 (27)
Post-operative haemorrhage	1	1/42 (2)	1	1/26 (4)
Cardiac tamponade	0	0/42 (0)	0	0/26 (0)
Pulmonary complications	23	14/41 (34)	29	10/26 (38)
Arrhythmias	15	12/42 (29)	9	7/26 (27)
Re-operation	12	11/42 (26)	4	4/26 (15)
Thromboembolic complications	1	1/42 (2)	0	0/26 (0)
Low cardiac output	6	6/42 (14)	10	6/26 (23)
Wound dehiscence	0	0/42 (0)	6	4/26 (15)
Other (unexpected event)	5	5/42 (12)	1	1/26 (4)
Cardiac arrest	1	1/42	0	0/26
Cardiac failure	3	3/42	0	0/26
Cardiac failure congestive	0	0/42	1	1/26
Compartment syndrome	1	1/42	0	0/26

GI, gastrointestinal.
a Excluding causes of death.

In the restrictive group, 13.0% of participants experienced significant pulmonary morbidity compared with 11.8% participants in the liberal group (OR 1.11, 95% CI 0.85 to 1.45; $p = 0.45$). The median duration of post-randomisation ICU/HDU stay was 49.5 hours (IQR 21.9–99.7 hours) in the restrictive group and 45.9 hours (IQR 20.1–94.8 hours) in the liberal group (see *Table 24*). This difference was not statistically significant (HR 0.97, 95% CI 0.89 to 1.06; $p = 0.53$). Durations of total post-randomisation hospital stay were very similar in both groups [medians and IQRs for both groups were 7 days and IQR 5–10 days (HR 1.00, 95% CI 0.92 to 1.10; $p = 0.94$)].

Quality of life

Crude responses to the five EQ-5D-3L component questions show no clear trends between the treatment groups (*Table 26*), although there was some suggestion of slightly improved scores on the mobility and usual activities domains in the restrictive compared with the liberal group post randomisation. No formal statistical comparisons were performed and the usual activities domain was also slightly imbalanced at baseline. The median utility and visual analogue scale (VAS) scores were similar in the two groups at all three time points (*Table 27*). Modelling the utility score demonstrated that participants in the restrictive group were slightly less likely to experience a score representing imperfect health than the liberal group, although this difference was not statistically significant (OR 0.89, 95% CI 0.71 to 1.12; $p = 0.33$). Scores for those participants with imperfect health were similar in the group groups [geometric mean ratio (GMR) 0.99, 95% CI 0.95 to 1.12; $p = 0.68$). For the VAS, the occurrence model suggested very little difference between the groups in the proportions of participants experiencing imperfect health (OR 1.11, 95% CI 0.57 to 2.15; $p = 0.76$). Of those with imperfect health on the VAS score, the average score was slightly higher (representing better health) for the restrictive group (GMR 0.97, 95% CI 0.92 to 1.02; $p = 0.21$). There was no evidence of a treatment by time interaction for either measure, implying that any difference between groups did not change between 6 weeks and 3 months after randomisation.

Sensitivity analyses

The two sensitivity analyses outlined for the primary outcome that could be applied to the secondary outcome of mortality were performed on a post-hoc basis. The results are shown in *Table 28*. The treatment effects for both analyses, excluding deaths occurring in the first 24 hours after randomisation and excluding participants who had red blood cells transfused before randomisation, were shifted further away from unity, as was hypothesised.

TABLE 26 European Quality of Life-5 Dimensions-3 Level component questions

EQ-5D-3L component	Randomised to restrictive threshold (*N* = 1000)	Randomised to liberal threshold (*N* = 1003)
Mobility*, n/N *(%)		
Pre-operative		
I have no problems walking about	586/995 (58.9)	583/996 (58.5)
I have some problems walking about	400/995 (40.2)	410/996 (41.2)
I am confined to bed	9/995 (0.9)	3/996 (0.3)
6 weeks post randomisation		
I have no problems walking about	524/790 (66.3)	521/823 (63.3)
I have some problems walking about	261/790 (33.0)	299/823 (36.3)
I am confined to bed	5/790 (0.6)	3/823 (0.4)
3 months post randomisation		
I have no problems walking about	572/833 (68.7)	549/850 (64.6)
I have some problems walking about	259/833 (31.1)	300/850 (35.3)
I am confined to bed	2/833 (0.2)	1/850 (0.1)
Self-care*, n/N *(%)		
Pre-operative		
I have no problems with self-care	901/996 (90.5)	923/997 (92.6)
I have some problems with self-care	90/996 (9.0)	71/997 (7.1)
I am unable to wash and dress myself	5/996 (0.5)	3/997 (0.3)
6 weeks post randomisation		
I have no problems with self-care	648/792 (81.8)	664/824 (80.6)
I have some problems with self-care	136/792 (17.2)	152/824 (18.4)
I am unable to wash and dress myself	8/792 (1.0)	8/824 (1.0)
3 months post randomisation		
I have no problems with self-care	722/833 (86.7)	728/849 (85.7)
I have some problems with self-care	108/833 (13.0)	117/849 (13.8)
I am unable to wash and dress myself	3/833 (0.4)	4/849 (0.5)
Usual activities*, n/N *(%)		
Pre-operative		
I have no problems with doing my usual activities	549/995 (55.2)	513/996 (51.5)
I have some problems with doing my usual activities	372/995 (37.4)	418/996 (42.0)
I am unable to perform my usual activities	74/995 (7.4)	65/996 (6.5)
6 weeks post randomisation		
I have no problems with doing my usual activities	263/787 (33.4)	257/822 (31.3)
I have some problems with doing my usual activities	455/787 (57.8)	485/822 (59.0)
I am unable to perform my usual activities	69/787 (8.8)	80/822 (9.7)

TABLE 26 European Quality of Life-5 Dimensions-3 Level component questions (*continued*)

EQ-5D-3L component	Randomised to restrictive threshold ($N = 1000$)	Randomised to liberal threshold ($N = 1003$)
3 months post randomisation		
I have no problems with doing my usual activities	455/835 (54.5)	423/850 (49.8)
I have some problems with doing my usual activities	349/835 (41.8)	394/850 (46.4)
I am unable to perform my usual activities	31/835 (3.7)	33/850 (3.9)
Pain/discomfort*, n/N *(%)		
Pre-operative		
I have no pain or discomfort	609/995 (61.2)	573/995 (57.6)
I have moderate pain or discomfort	356/995 (35.8)	393/995 (39.5)
I have extreme pain or discomfort	30/995 (3.0)	29/995 (2.9)
6 weeks post randomisation		
I have no pain or discomfort	265/791 (33.5)	279/823 (33.9)
I have moderate pain or discomfort	516/791 (65.2)	528/823 (64.2)
I have extreme pain or discomfort	10/791 (1.3)	16/823 (1.9)
3 months post randomisation		
I have no pain or discomfort	418/836 (50.0)	432/850 (50.8)
I have moderate pain or discomfort	400/836 (47.8)	392/850 (46.1)
I have extreme pain or discomfort	18/836 (2.2)	26/850 (3.1)
Anxiety/depression*, n/N *(%)		
Pre-operative		
I am not anxious or depressed	683/994 (68.7)	687/996 (69.0)
I am moderately anxious or depressed	278/994 (28.0)	284/996 (28.5)
I am extremely anxious or depressed	33/994 (3.3)	25/996 (2.5)
6 weeks post randomisation		
I am not anxious or depressed	602/791 (76.1)	592/823 (71.9)
I am moderately anxious or depressed	181/791 (22.9)	215/823 (26.1)
I am extremely anxious or depressed	8/791 (1.0)	16/823 (1.9)
3 months post randomisation		
I am not anxious or depressed	635/836 (76.0)	640/850 (75.3)
I am moderately anxious or depressed	186/836 (22.2)	196/850 (23.1)
I am extremely anxious or depressed	15/836 (1.8)	14/850 (1.6)

TABLE 27 European Quality of Life-5 Dimensions-3 Level composite scores

EQ-5D-3L score	Randomised to restrictive threshold ($n = 1000$) Median (IQR)	Randomised to liberal threshold ($n = 1003$) Median (IQR)	Occurrence model OR[a] (95% CI)	*p*-value	Intensity model GMR[b] (95% CI)	*p*-value	Test for treatment by time interaction[c]
Utility score							
Pre-operative[d]	0.81 (0.69–1.00)	0.81 (0.69–1.00)					
6 weeks post randomisation[e]	0.76 (0.69–0.81)	0.76 (0.64–0.81)					
3 months post randomisation[f]	0.80 (0.69–1.00)	0.80 (0.69–1.00)					
Overall estimate of treatment effect			0.89 (0.71 to 1.12)	0.33	0.99 (0.95 to 1.03)	0.68	0.20
VAS							
Pre-operative[g]	70.0 (55.0–80.0)	70.0 (51.0–80.0)					
6 weeks post randomisation[h]	75.0 (61.0–85.0)	75.0 (60.0–80.0)					
3 months post randomisation[i]	80.0 (70.0–90.0)	80.0 (69.0–90.0)					
Overall estimate of treatment effect			1.11 (0.57 to 2.15)	0.76	0.97 (0.92 to 1.02)	0.21	0.60

a Outcome is less than perfect health (utility < 1, VAS of < 100) vs. perfect health (utility = 1, VAS = 100). Models could not be adjusted for centre.
b Outcome is either 1-(EQ-5D-3L utility) or 100-(EQ-5D-3L VAS), conditional on a non-perfect health score. Models could not be adjusted for centre.
c From occurrence model.
d Missing for nine restrictive group participants and 11 liberal group participants.
e Missing for 217 restrictive group participants and 189 liberal group participants.
f Missing for 172 restrictive group participants and 162 liberal group participants.
g Missing for 10 restrictive group participants and nine liberal group participants.
h Missing for 215 restrictive group participants and 188 liberal group participants.
i Missing for 168 restrictive group participants and 153 liberal group participants.

TABLE 28 Sensitivity analyses for all-cause mortality

Outcome	Randomised to restrictive threshold ($N = 1000$), n/N (%)	Randomised to liberal threshold ($N = 1003$), n/N (%)	HR (95% CI)	p-value
Excluding deaths occurring in the first 24 hours after randomisation	41/999 (4.1)	24/1001 (2.4)	HR 1.73 (1.05 to 2.87)	0.029
Excluding participants transfused red blood cells pre-randomisation	23/750 (3.1)	11/739 (1.5)	HR 2.15 (1.04 to 4.40)	0.032

Adverse events

All expected and unexpected SAEs (excluding the primary outcome and mortality) occurring after randomisation are summarised in *Table 29*. There were 664 events occurring in 35.7% of participants in the restrictive group and 648 events in 34.2% participants in the liberal group. There were slightly more participants with pulmonary complications (12.9% vs. 10.6%) and arrhythmias (15.3% vs. 12.8%) in the restrictive group than the liberal group, and slightly fewer participants with gastrointestinal (GI) complications (3.8% vs. 5.1%). The most common events were arrhythmias (14.0%), pulmonary complications (11.8%) and other (i.e. unexpected) events (9.0%).

A summary measure was created (as a post-hoc analysis) combining the events in *Table 29* with the primary outcome and mortality. This measure could be relevant if the mechanisms hypothesised to justify the superiority hypothesis and to classify SAEs as expected or unexpected were subsequently considered to be unsound. In the restrictive group 523 out of 961 (54.4%) participants experienced this composite, compared with 492 out of 971 (50.7%) in the liberal group.

Detailed examination of the events is undertaken in the following sections.

TABLE 29 Summary of all SAEs

	Randomised to restrictive threshold			Randomised to liberal threshold		
Event type	Events (n)	Participants ($N = 1000$), (n/N)	%	Events (n)	Participants ($N = 1003$), (n/N)	%
Any event	664	354/991	35.7	648	339/991	34.2
Transient ischaemic attack	6	6/987	0.6	3	3/981	0.3
GI complications	40	37/986	3.8	55	50/983	5.1
Post-operation haemorrhage	12	12/987	1.2	18	17/982	1.7
Cardiac tamponade	2	2/987	0.2	2	2/981	0.2
Pulmonary complications	200	127/986	12.9	170	105/988	10.6
Arrhythmias	186	151/989	15.3	152	126/984	12.8
Reoperation	70	63/988	6.4	80	73/983	7.4
Thromboembolic complications	9	9/985	0.9	15	12/981	1.2
Low cardiac output	17	16/988	1.6	20	16/983	1.6
Wound dehiscence	19	16/987	1.6	20	18/981	1.8
Other (unexpected event)[a]	103	88/1000	8.8	113	93/1003	9.3

GI, gastrointestinal.
a It has been assumed that if an unexpected SAE was not reported, then an event was not present.

Expected adverse events

Prior to hospital discharge (*Table 30*) there were 988 expected AEs in the restrictive group occurring in 49.6% of participants, and 938 in 48.4% of participants in the liberal group. Of these, 418 events in the restrictive group (23.2% of participants) and 405 events in the liberal group (21.5% of participants) were classified as serious. The most frequent events were arrhythmias. The numbers of pulmonary complications and arrhythmias were slightly larger in the restrictive group than the liberal group, which is consistent with *Table 29*.

Expected SAEs occurred less frequently after hospital discharge (*Table 31*), when there were 143 SAEs in 11.4% of participants in the restrictive group and 130 SAEs in 10.5% of participants in the liberal group. The most common events were pulmonary complications (5.0%). There were no clear differences between the groups although, again, rates of pulmonary complications and arrhythmias were slightly higher in the restrictive group than the liberal group (5.5% vs. 4.6% and 3.4% vs. 2.4%, respectively).

The classification of SAEs occurring at any time (either before or after discharge) suggests that the small differences in the frequencies of GI complications, pulmonary complications and arrhythmias identified between the groups were not due to any particular SAEs within each category (*Table 32*). Instead, all subcategories of SAEs appear to demonstrate differences between the groups in the same direction, which aggregate to the overall slight differences observed in *Table 29*.

TABLE 30 Expected serious and non-serious AEs before hospital discharge

	Randomised to restrictive threshold				Randomised to liberal threshold			
	Events		Participants ($N = 1000$)		Events		Participants ($N = 1003$)	
Event type	AE	SAE	AE, *n*/*N* (%)	SAE, *n*/*N* (%)	AE	SAE	AE, *n*/*N* (%)	SAE, *n*/*N* (%)
Any event	988	418	496/1000 (49.6)	232/998 (23.2)	938	405	485/1003 (48.4)	216/1003 (21.5)
Transient ischaemic attack	4	2	4/1000 (0.4)	2/1000 (0.2)	2	1	2/1003 (0.2)	1/1003 (0.1)
GI complications	49	20	44/1000 (4.4)	17/999 (1.7)	46	30	40/1003 (4.0)	26/1003 (2.6)
Pancreatitis	2	0	2/1000 (0.2)	0/1000 (0.0)	0	0	0/1003 (0.0)	0/1003 (0.0)
Intestinal obstruction/ perforation	1	0	1/1000 (0.1)	0/1000 (0.0)	5	4	5/1003 (0.5)	4/1003 (0.4)
Other GI complications	46	20	41/999 (4.1)	17/999 (1.7)	41	26	38/1003 (3.8)	24/1003 (2.4)
Post-operation haemorrhage	31	11	31/1000 (3.1)	11/1000 (1.1)	37	16	34/1003 (3.4)	15/1003 (1.5)
Cardiac tamponade	1	1	1/1000 (0.1)	1/1000 (0.1)	1	1	1/1003 (0.1)	1/1003 (0.1)
Pulmonary complications	288	137	177/998 (17.7)	81/998 (8.1)	286	118	169/1003 (16.8)	66/1003 (6.6)
ARDS	5	4	5/999 (0.5)	4/999 (0.4)	3	0	3/1003 (0.3)	0/1003 (0.0)
Reintubation/ ventilation	54	35	50/1000 (5.0)	31/1000 (3.1)	61	31	53/1003 (5.3)	25/1003 (2.5)
Tracheostomy	31	20	30/999 (3.0)	19/999 (1.9)	33	18	32/1003 (3.2)	18/1003 (1.8)
Initiation of mask CPAP	95	29	87/1000 (8.7)	28/1000 (2.8)	88	26	77/1003 (7.7)	23/1003 (2.3)

TABLE 30 Expected serious and non-serious AEs before hospital discharge (*continued*)

	Randomised to restrictive threshold				Randomised to liberal threshold			
	Events		Participants ($N = 1000$)		Events		Participants ($N = 1003$)	
Event type	AE	SAE	AE, *n*/*N* (%)	SAE, *n*/*N* (%)	AE	SAE	AE, *n*/*N* (%)	SAE, *n*/*N* (%)
Pneumothorax requiring drainage	10	6	10/999 (1.0)	6/999 (0.6)	9	3	9/1003 (0.9)	3/1003 (0.3)
Pleural effusion requiring drainage	56	25	54/999 (5.4)	24/999 (2.4)	56	24	49/1003 (4.9)	22/1003 (2.2)
Other pulmonary complications	37	18	36/999 (3.6)	17/999 (1.7)	36	16	33/1003 (3.3)	14/1003 (1.4)
Arrhythmias	489	148	374/1000 (37.4)	121/999 (12.1)	436	127	354/1003 (35.3)	108/1003 (10.8)
Pacing	87	25	84/1000 (8.4)	24/1000 (2.4)	62	14	58/1003 (5.8)	14/1003 (1.4)
SVT/AF requiring treatment	346	96	312/1000 (31.2)	90/1000 (9.0)	329	94	292/1003 (29.1)	83/1003 (8.3)
VF/VT requiring treatment	17	8	13/1000 (1.3)	6/1000 (0.6)	6	2	6/1003 (0.6)	2/1003 (0.2)
Other arrhythmias	39	19	34/999 (3.4)	17/999 (1.7)	39	17	39/1003 (3.9)	17/1003 (1.7)
Reoperation	68	68	62/1000 (6.2)	62/1000 (6.2)	78	78	71/1003 (7.1)	71/1003 (7.1)
Thromboembolic complications	6	5	6/998 (0.6)	5/998 (0.5)	2	1	2/1003 (0.2)	1/1003 (0.1)
Deep-vein thrombosis	0	0	0/1000 (0.0)	0/1000 (0.0)	1	1	1/1003 (0.1)	1/1003 (0.1)
Pulmonary embolus	0	0	0/1000 (0.0)	0/1000 (0.0)	0	0	0/1003 (0.0)	0/1003 (0.0)
Other thromboembolic complications	6	5	6/998 (0.6)	5/998 (0.5)	1	0	1/1003 (0.1)	0/1003 (0.0)
Low cardiac output	32	14	31/1000 (3.1)	13/1000 (1.3)	26	18	22/1003 (2.2)	14/1003 (1.4)
Wound dehiscence	20	12	17/1000 (1.7)	9/1000 (0.9)	24	15	22/1003 (2.2)	13/1003 (1.3)

AF, atrial fibrillation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
SAEs are a subset of AEs.
One participant could experience multiple AEs or SAEs.

TABLE 31 Expected SAEs after hospital discharge

Event type	Randomised to restrictive threshold		Randomised to liberal threshold	
	SAEs, *n*	Participants (*N* = 1000), *n*/*N* (%)	SAEs, *n*	Participants (*N* = 1003), *n*/*N* (%)
Any event	143	113/987 (11.4)	130	103/981 (10.5)
Transient ischaemic attack	4	4/987 (0.4)	2	2/981 (0.2)
GI complications	20	20/987 (2.0)	25	24/981 (2.4)
Pancreatitis	0	0/987 (0.0)	2	2/981 (0.2)
Intestinal obstruction/perforation	0	0/987 (0.0)	0	0/981 (0.0)
Other GI complications	20	20/987 (2.0)	23	23/981 (2.3)
Post-operation haemorrhage	1	1/987 (0.1)	2	2/981 (0.2)
Cardiac tamponade	1	1/987 (0.1)	1	1/981 (0.1)
Pulmonary complications	63	54/987 (5.5)	52	45/981 (4.6)
ARDS	0	0/987 (0.0)	0	0/981 (0.0)
Reintubation/ventilation	0	0/987 (0.0)	0	0/981 (0.0)
Tracheostomy	0	0/987 (0.0)	0	0/981 (0.0)
Initiation of mask CPAP	1	1/987 (0.1)	0	0/981 (0.0)
Pneumothorax requiring drainage	0	0/987 (0.0)	1	1/981 (0.1)
Pleural effusion requiring drainage	34	31/987 (3.1)	32	30/981 (3.1)
Other pulmonary complication	28	26/987 (2.6)	19	17/981 (1.7)
Arrhythmias	38	34/987 (3.4)	25	24/981 (2.4)
Pacing	0	0/987 (0.0)	0	0/981 (0.0)
SVT/AF requiring treatment	27	24/987 (2.4)	22	21/981 (2.1)
VF/VT requiring treatment	0	0/987 (0.0)	0	0/981 (0.0)
Other arrhythmias	11	10/987 (1.0)	3	3/981 (0.3)
Re-operation	2	2/987 (0.2)	2	2/981 (0.2)
Thromboembolic complications	4	4/987 (0.4)	14	11/981 (1.1)
Deep-vein thrombosis	2	2/987 (0.2)	5	4/981 (0.4)
Pulmonary embolus	1	1/987 (0.1)	7	6/981 (0.6)
Other thromboembolic complications	1	1/987 (0.1)	2	2/981 (0.2)
Low cardiac output	3	3/987 (0.3)	2	2/981 (0.2)
Wound dehiscence	7	7/987 (0.7)	5	5/981 (0.5)

AF, atrial fibrillation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 32 Expected SAEs at any time

Event type	Randomised to restrictive threshold		Randomised to liberal threshold	
	SAEs, *n*	Participants (*N* = 1000), *n*/*N* (%)	SAEs, *n*	Participants (*N* = 1003), *n*/*N* (%)
Any event	561	311/990 (31.4)	535	293/991 (29.6)
Transient ischaemic attack	6	6/987 (0.6)	3	3/981 (0.3)
GI complications	40	37/986 (3.8)	55	50/983 (5.1)
Pancreatitis	0	0/987 (0.0)	2	2/981 (0.2)
Intestinal obstruction/perforation	0	0/987 (0.0)	4	4/981 (0.4)
Other GI complications	40	37/986 (3.8)	49	47/983 (4.8)
Post-operation haemorrhage	12	12/987 (1.2)	18	17/982 (1.7)
Cardiac tamponade	2	2/987 (0.2)	2	2/981 (0.2)
Pulmonary complications	200	127/986 (12.9)	170	105/988 (10.6)
ARDS	4	4/986 (0.4)	0	0/981 (0.0)
Reintubation/ventilation	35	31/988 (3.1)	31	25/983 (2.5)
Tracheostomy	20	19/987 (1.9)	18	18/985 (1.8)
Initiation of mask CPAP	30	29/987 (2.9)	26	23/982 (2.3)
Pneumothorax requiring drainage	6	6/986 (0.6)	4	4/981 (0.4)
Pleural effusion requiring drainage	59	52/987 (5.3)	56	52/981 (5.3)
Other pulmonary complication	46	42/986 (4.3)	35	31/983 (3.2)
Arrhythmias	186	151/989 (15.3)	152	126/984 (12.8)
Pacing	25	24/987 (2.4)	14	14/981 (1.4)
SVT/AF requiring treatment	123	110/990 (11.1)	116	102/982 (10.4)
VF/VT requiring treatment	8	6/987 (0.6)	2	2/981 (0.2)
Other arrhythmias	30	27/987 (2.7)	20	20/983 (2.0)
Re-operation	70	63/988 (6.4)	80	73/983 (7.4)
Thromboembolic complications	9	9/985 (0.9)	15	12/981 (1.2)
Deep-vein thrombosis	2	2/987 (0.2)	6	5/981 (0.5)
Pulmonary embolus	1	1/987 (0.1)	7	6/981 (0.6)
Other thromboembolic complications	6	6/985 (0.6)	2	2/981 (0.2)
Low cardiac output	17	16/988 (1.6)	20	16/983 (1.6)
Wound dehiscence	19	16/987 (1.6)	20	18/981 (1.8)

AF, atrial fibrillation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
One participant could experience multiple AEs or SAEs.

Unexpected serious adverse events

There were 103 unexpected SAEs occurring in 8.8% of participants in the restrictive group and 113 events in 9.3% participants in the liberal group (*Table 33*). Classifying events according to the MedDRA dictionary suggests that cardiac disorders were the most frequent unexpected SAEs (3.0% of participants), in particular cardiac failure (30 events) and pericardial effusion (20 events). Other types of event were rare. There were more cases of anaemia in the restrictive group (six cases vs. one case) and more cases of cardiac failure in the liberal group (19 cases vs. 11 cases), although the numbers of both events were low. There were no other trends between the groups.

The characteristics of the SAEs suggest slightly higher proportions in the restrictive group resulted in death or were life-threatening (17% vs. 13% and 36% vs. 29%, respectively, *Table 34*). Similarly, slightly higher proportions were classified as of severe intensity in the restrictive group (55% vs. 50%). In total, 41 SAEs were classified as possibly, probably or definitely related to the intervention: 20 (19%) in the restrictive group and 21 (19%) in the liberal group. Of these, 34 were attributed to a red blood cell transfusion being given (14 in the restrictive group and 20 in the liberal group), and seven to a transfusion being withheld (six in the restrictive group and one in the liberal group). Finally, more participants experiencing a SAE had their treatment according to protocol discontinued (14 participants vs. four participants).

TABLE 33 Unexpected SAEs

Event type	Randomised to restrictive threshold ($N = 1000$)		Randomised to liberal threshold ($N = 1003$)	
	Events (*n*)	Participants, *n* (%)	Events (*n*)	Participants, *n* (%)
Any event	103	88 (8.8)	113	93 (9.3)
Description of events (MedDRA terms)				
Blood and lymphatic system disorders	6	5 (0.5)	2	2 (0.2)
Anaemia	4	4	1	1
Haemolytic anaemia	2	1	0	0
Coagulopathy	0	0	1	1
Cardiac disorders	29	26 (2.6)	41	35 (3.5)
Cardiac arrest	7	7	1	1
Cardiac failure	11	11	19	18
Cardiorespiratory arrest	0	0	2	1
Heart valve incompetence	0	0	1	1
Left ventricular failure	2	2	1	1
Left ventricular hypertrophy	0	0	1	1
MV incompetence	1	1	0	0
Palpitations	0	0	1	1
Pericardial effusion	8	6	12	11
Pericarditis	0	0	1	1
Pericarditis constrictive	0	0	1	1
TV incompetence	0	0	1	1

TABLE 33 Unexpected SAEs (*continued*)

Event type	Randomised to restrictive threshold ($N = 1000$)		Randomised to liberal threshold ($N = 1003$)	
	Events (*n*)	Participants, *n* (%)	Events (*n*)	Participants, *n* (%)
Eye disorders	2	2 (0.2)	0	0 (0.0)
Diplopia	1	1	0	0
Visual impairment	1	1	0	0
General disorders and administration site conditions	12	12 (1.2)	10	10 (1.0)
Adverse drug reaction	0	0	1	1
Chest pain	2	2	2	2
Local swelling	0	0	1	1
Malaise	0	0	1	1
Multiorgan failure	6	6	3	3
Non-cardiac chest pain	1	1	2	2
Oedema peripheral	1	1	0	0
Pain	1	1	0	0
Swelling	1	1	0	0
Hepatobiliary disorders	1	1 (0.1)	2	2 (0.2)
Alcoholic liver disease	0	0	1	1
Hepatic cyst	0	0	1	1
Hepatic necrosis	1	1	0	0
Immune system disorders	1	1 (0.1)	0	0 (0.0)
Anaphylactic reaction	1	1	0	0
Infections and infestations	4	4 (0.4)	7	7 (0.7)
Cellulitis	0	0	1	1
Diverticulitis	1	1	1	1
Empyema	0	0	1	1
Endocarditis	2	2	2	2
Gangrene	0	0	1	1
H1N1 influenza	1	1	0	0
Oral candidiasis	0	0	1	1
Injury, poisoning and procedural complications	6	5 (0.5)	10	9 (0.9)
Arteriovenous fistula site haemorrhage	0	0	1	1
Fall	1	1	3	3
Femoral neck fracture	0	0	2	2
Nerve injury	0	0	1	1
Overdose	0	0	1	1
Rib fracture	1	1	0	0

continued

TABLE 33 Unexpected SAEs (*continued*)

Event type	Randomised to restrictive threshold ($N = 1000$)		Randomised to liberal threshold ($N = 1003$)	
	Events (*n*)	Participants, *n* (%)	Events (*n*)	Participants, *n* (%)
Seroma	1	1	0	0
Toxicity to various agents	2	2	0	0
Transfusion reaction	0	0	1	1
Upper limb fracture	1	1	0	0
Wound	0	0	1	1
Investigations	2	2 (0.2)	3	3 (0.3)
Blood pressure decreased	0	0	1	1
International normalised ratio	2	2	1	1
International normalised ratio increased	0	0	1	1
Metabolism and nutrition disorders	4	4 (0.4)	1	1 (0.1)
Hypernatraemia	1	1	0	0
Hypoglycaemia	1	1	1	1
Hyponatraemia	2	2	0	0
Musculoskeletal and connective tissue disorders	7	7 (0.7)	4	4 (0.4)
Back pain	1	1	1	1
Compartment syndrome	2	2	0	0
Muscular weakness	1	1	0	0
Musculoskeletal chest pain	2	2	3	3
Pain in extremity	1	1	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2	2 (0.2)	1	1 (0.1)
Bladder cancer	0	0	1	1
Brain cancer metastatic	1	1	0	0
Breast cancer	1	1	0	0
Nervous system disorders	9	9 (0.9)	11	10 (1.0)
Amnesia	1	1	0	0
Brain injury	0	0	2	1
Convulsion	3	3	1	1
Dizziness	0	0	1	1
Grand mal convulsion	2	2	1	1
Headache	1	1	1	1
Loss of consciousness	0	0	1	1
Neuralgia	0	0	1	1
Partial seizures	0	0	1	1
Syncope	2	2	2	2

TABLE 33 Unexpected SAEs (*continued*)

Event type	Randomised to restrictive threshold ($N = 1000$)		Randomised to liberal threshold ($N = 1003$)	
	Events (*n*)	Participants, *n* (%)	Events (*n*)	Participants, *n* (%)
Psychiatric disorders	2	2 (0.2)	2	2 (0.2)
Alcohol withdrawal syndrome	1	1	1	1
Confusional state	0	0	1	1
Depression	1	1	0	0
Renal and urinary disorders	4	4 (0.4)	7	7 (0.7)
Haematuria	1	1	1	1
Renal colic	1	1	0	0
Renal vasculitis	0	0	1	1
Urinary retention	2	2	5	5
Respiratory, thoracic and mediastinal disorders	1	1 (0.1)	3	3 (0.3)
Dysphonia	0	0	1	1
Epistaxis	0	0	1	1
Hypoxia	1	1	1	1
Surgical and medical procedures	3	3 (0.3)	6	6 (0.6)
Aortic aneurysm repair	1	1	0	0
Cardiac pacemaker revision	0	0	1	1
Coronary arterial stent insertion	0	0	1	1
Debridement	0	0	1	1
Eye excision	1	1	0	0
Haematoma evacuation	0	0	1	1
Leg amputation	1	1	1	1
Ventriculocardiac shunt	0	0	1	1
Vascular disorders	8	8 (0.8)	3	3 (0.3)
Aortic aneurysm rupture	1	1	1	1
Haematoma	1	1	0	0
Hypotension	2	2	0	0
Orthostatic hypotension	2	2	1	1
Peripheral ischaemia	1	1	0	0
Peripheral vascular disorder	1	1	0	0
Vasculitis	0	0	1	1

MV, mitral valve; TV, tricuspid valve.

TABLE 34 Characteristics of unexpected SAEs

Event type	Restrictive group SAEs (*N* = 103)		Liberal group SAEs (*N* = 113)	
	Events, %		Participants, %	
Timing of event				
Pre-discharge	35	34	46	41
Post discharge	68	66	67	59
Reason event classified as SAE[a]				
Resulted in death	18	17	15	13
Was life-threatening	37	36	33	29
Resulted in persistent or significant disability/incapacity	23	22	31	27
Required hospitalisation	62	60	72	64
Prolonged ongoing hospitalisation	26	25	36	32
Other	5	5	4	4
Maximum intensity				
Mild	12	12	18	16
Moderate	34	33	39	35
Severe	57	55	56	50
Final outcome				
Resolved no sequelae	52	50	61	54
Resolved with sequelae	33	32	34	30
Died	18	17	18	16
Relatedness				
Not related	61	59	70	62
Unlikely to be related	22	21	22	19
Possibly related	14	14	18	16
Probably related	3	3	2	2
Definitely related	3	3	1	1
Related to				
Red blood cell transfusion being given	14	14	20	18
Red blood cell transfusion being withheld	6	6	1	1
Treatment according to protocol permanently discontinued	4	4	14	12

a Some events were classified as SAEs for multiple reasons so the reasons sum to more than 100%.

Meta-analysis

A meta-analysis of mortality for TITRe2 and the five earlier RCTs[24–26,37,38] is shown in *Figure 15*. The combined estimate suggests an increased risk of death in the restrictive group, of borderline statistical significance, RR 1.41 (95% CI 0.98 to 2.04). It should be noted that the restrictive and liberal thresholds varied across these trials (*Table 35*). The trials also varied with respect to whether or not the intervention was applied during the operation. In addition, with the exception of TITRe2, all of the studies randomised all participants prior to their operation; hence, they included in their analyses participants who did not

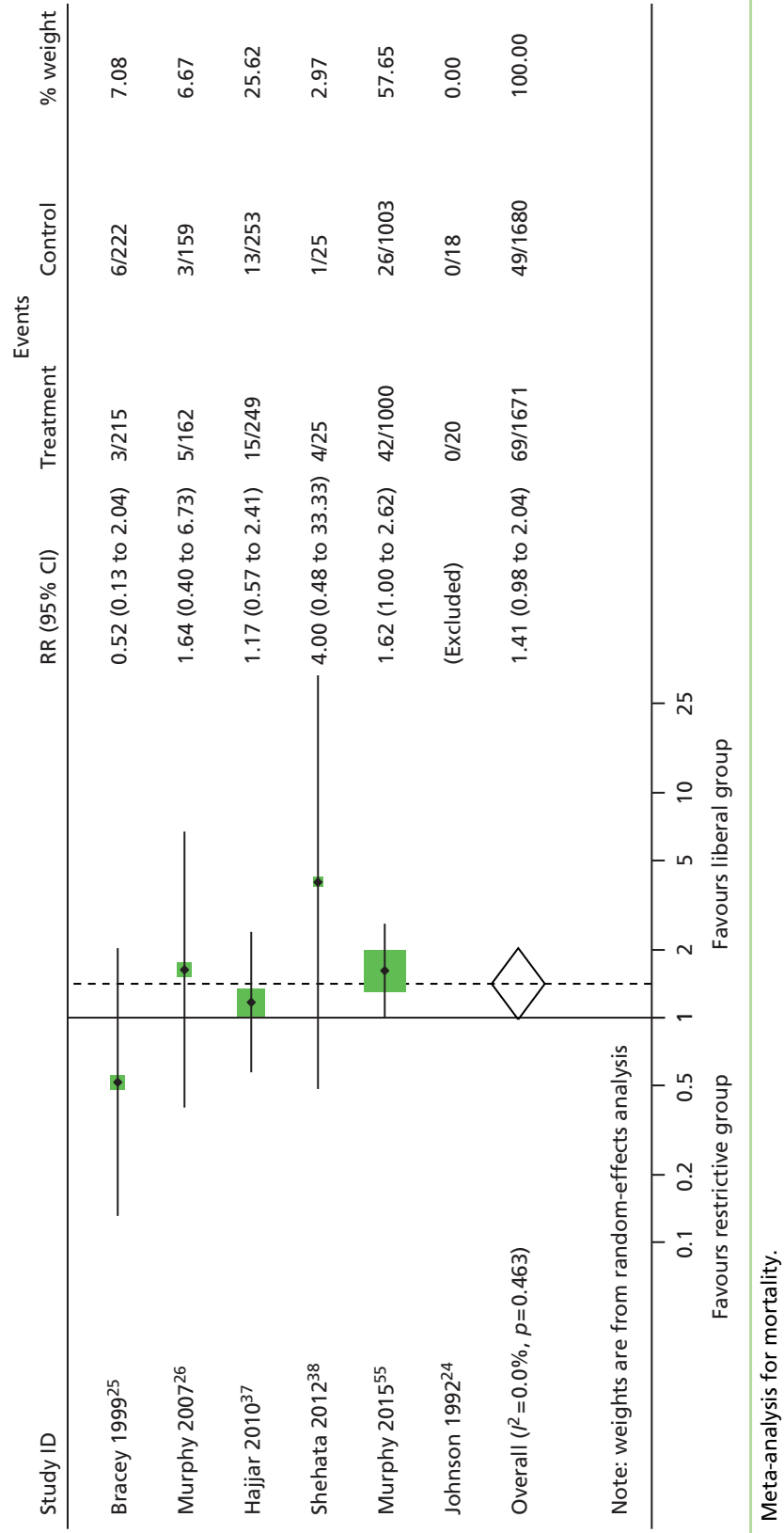


FIGURE 15 Meta-analysis for mortality.

TABLE 35 Transfusion thresholds used in each study

Study	Restrictive group threshold	Liberal group threshold	Intervention period
Johnson 1992[24]	8.3 g/dl	10.7 g/dl	Postoperative only
Bracey 1999[25]	8.0 g/dl	9.0 g/dl	Postoperative only
Murphy 2007[26]	7.0 g/dl	8.0 g/dl	Postoperative only
Hajjar 2010[37]	8.0 g/dl	10.0 g/dl	Intraoperative and postoperative
Shehata 2012[38]	7.0 g/dl intraoperatively during CPB; 7.5 g/dl postoperatively	9.5 g/dl intraoperatively during CPB; 10.0 g/dl postoperatively	Intraoperative and postoperative
Murphy 2015[55]	7.5 g/dl	9.0 g/dl	Postoperative only

breach the liberal threshold and who were almost certainly not transfused. By virtue of randomisation, there should have been similar numbers of participants in each group who did not breach the liberal threshold. Including these participants would be expected to dilute any treatment effect.

Summary

The frequency of the primary outcome was slightly higher in the restrictive group than the liberal group (35.1% vs. 33.0%), mainly owing to ischaemic events and, in particular, AKI. Sensitivity analyses either restricted to participants who were not transfused pre-randomisation or including additional less-severe AKI events augmented this difference. However, restricting the analysis to only the most severe primary outcome events reduced the event frequencies to 14.7% and 14.9% in the restrictive and liberal groups, respectively, and the treatment effect (OR) was reduced to unity. This event frequency was very similar to that assumed at the outset for the sample size justification. There was no evidence of any subgroup effects.

There were significantly more deaths in the restrictive group (4.2%) than the liberal group (2.6%); HR 1.64 (95% CI 1.00 to 2.67). This difference persisted in two post-hoc sensitivity analyses of the mortality outcome. A meta-analysis combining mortality data from five previous RCTs gave a pooled RR 1.41 (95% CI 0.98 to 2.04). There were no statistically significant differences between the groups for any of the other secondary outcomes; however, all estimated treatment differences either favoured the liberal group or were null apart from the EQ-5D-3L utility score. In terms of SAEs, the overall frequency was slightly higher in the restrictive group than the liberal group (35.7% vs. 34.2%).

Chapter 6 Results of the economic evaluation

Quality-adjusted life-years

A summary of the mean EQ-5D-3L scores at each of the time points and the QALYs gained in each group are shown in *Figure 16* and in *Table 36* (compare with medians reported in *Table 27*). These figures differ slightly to those presented earlier because we use means rather than medians, in contrast with the description of effectiveness, and include participants who have died with scores of zero from the date of death. The means are supported by SEs. On average, participants' EQ-5D-3L scores did not fully return to their pre-operative level by 3 months in either treatment group.

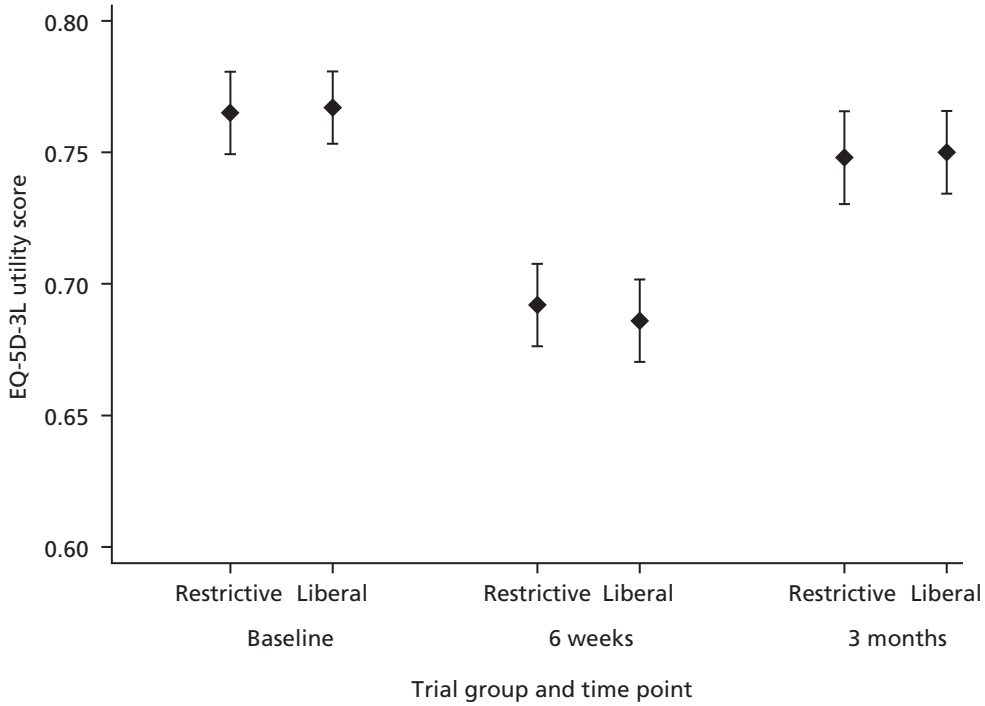


FIGURE 16 Mean EQ-5D-3L utility scores (and 95% CI) at each time point for each treatment group.

TABLE 36 Results for EQ-5D-3L scores and QALYs

Time point	Randomised to restrictive threshold ($n = 1000$), mean (SE)	Randomised to liberal threshold ($n = 1003$), mean (SE)	Restrictive vs. liberal threshold, mean difference (SE)
EQ-5D-3L time point[a]			
Baseline	0.765 (0.008)	0.767 (0.007)	–0.001 (0.011)
6 weeks	0.692 (0.008)	0.686 (0.008)	0.006 (0.011)
3 months	0.748 (0.009)	0.750 (0.008)	–0.002 (0.012)
QALYs to 3 months (adjusted for baseline EQ-5D-3L)	0.1802 (0.0015)	0.1798 (0.0016)	0.0004 (0.0021)

a Deaths included as zero.

As *Table 36* shows, there is very little difference between the groups for EQ-5D-3L scores at any of the three time points and a tiny (non-significant) difference in QALYs between the groups. Indeed, the QALYs to 3 months are 0.18 for both the restrictive and liberal groups, with a mean difference of only 0.0004 (SE 0.0021). This difference of 0.0004 QALYs is approximately 3.5 quality-adjusted hours. Given the significant difference in deaths between the groups (more deaths in the restrictive group), we explored potential reasons why the difference in deaths did not appear to translate into a difference in QALYs. We would have assumed that the participants who died were more ill, which theoretically could have resulted in them reporting lower EQ-5D-3L scores prior to death. We therefore plotted the QALY data for each group: for all participants, for participants excluding deaths and only for deaths. This investigation revealed that it was not merely the participants who died who had low QALYs, but also many other participants. These low EQ-5D-3L scores for surviving participants had the effect of 'diluting' the impact on the means of imputed zero EQ-5D-3L scores for participants who died. Most of the participants who died had total QALYs of 0–0.05. When these participants were excluded, there were a few more participants 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 participants 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. Therefore, we came to the conclusion that the figures in *Table 36* could be showing that there was genuinely no real difference in QALYs between the restrictive and liberal groups, despite the difference in deaths.

Resource use and costs

Table 37 reports information on the main resource use items for the trial groups to 3 months. The table includes information on surgery, blood products, LOS, complications and health-care contacts post discharge. Frequencies are given for binary responses (yes/no) and means and SEs are presented for the number of events or LOS per participant. Red blood cells 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 red blood cells transfused. The average units of red blood cells transfused (compared with medians in *Table 14*) in the restrictive group was 2.08 units (SE 0.09 units) per participant, compared with 3.07 units (SE 0.11 units) units per participant in the liberal group, leading to an average difference of 1.00 unit (SE 0.14 units) per participant. 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.

In terms of unit costs which were attached to the main resource use items, *Table 38* provides some information on the main resource 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 3*, *Unit costs and resource use assumed for complications*.

TABLE 37 Resource use per participant to 3 months from surgery

Resource use component	Randomised to restrictive threshold ($n = 1000$), frequency (%) or mean (SE)	Randomised to liberal threshold ($n = 1003$), frequency (%) or mean (SE)	Restrictive versus liberal threshold, % or mean (SE) difference
Red blood cells, number of units/participant	***2.08 (0.09)***	***3.07 (0.11)***	***–1.00 (0.14)***
Cardiac procedure,* n *(%)			
CABG	408 (41)	408 (41)	0
Valve	307 (31)	304 (30)	1
CABG and valve	195 (20)	203 (20)	0
Other	90 (9)	88 (9)	0
Blood products, number of units/participant			
FFP	1.00 (0.06)	0.95 (0.06)	0.05 (0.08)
Platelets	0.65 (0.03)	0.64 (0.03)	0.01 (0.05)
Cryoprecipitate	0.23 (0.03)	0.21 (0.02)	0.02 (0.04)
Inpatient complications,* n *(%)			
Primary outcome			
Antibiotics for infectious complication	341 (34)	344 (34)	0
Stroke	14 (1)	16 (2)	–1
Suspected MI	3 (0)	7 (1)	–1
Gut infarction	5 (1)	1 (0)	1
AKI: stage 3	60 (6)	51 (5)	1
Other complications,* n *events/participant (%)			
Reoperation	0.09 (0.01)	0.10 (0.01)	–0.01 (0.02)
Reintubation	0.07 (0.01)	0.07 (0.01)	0.00 (0.01)
Tracheostomy	0.03 (0.01)	0.03 (0.01)	0.00 (0.01)
Mask CPAP	0.13 (0.01)	0.12 (0.01)	0.01 (0.02)
Pneumothorax requiring chest drainage	0.01 (0.00)	0.01 (0.00)	0.00 (0.01)
Pleural effusion requiring drainage	0.06 (0.01)	0.06 (0.01)	0.00 (0.01)
Pacing	0.31 (0.02)	0.31 (0.02)	0.00 (0.02)
SVT/AF requiring treatment	0.41 (0.02)	0.39 (0.02)	0.02 (0.03)
VF/VT requiring intervention	0.02 (0.01)	0.01 (0.00)	0.01 (0.01)
Low cardiac output	0.11 (0.01)	0.11 (0.01)	0.00 (0.01)
Inpatient LOS, days/participant			
CICU	1.14 (0.12)	1.12 (0.13)	0.02 (0.18)
HDU	3.09 (0.12)	3.05 (0.12)	0.04 (0.17)
Ward	5.67 (0.15)	5.83 (0.17)	–0.17 (0.23)
Another unit/hospital	1.27 (0.20)	1.36 (0.19)	–0.09 (0.27)

continued

TABLE 37 Resource use per participant to 3 months from surgery (*continued*)

Resource use component	Randomised to restrictive threshold ($n = 1000$), frequency (%) or mean (SE)	Randomised to liberal threshold ($n = 1003$), frequency (%) or mean (SE)	Restrictive versus liberal threshold, % or mean (SE) difference
Blood saving techniques,* n *(%)			
Tranexamic acid	807 (81)	810 (81)	0
Trasylol	41 (4)	35 (3)	1
Intraoperative cell salvage	482 (48)	503 (50)	–2
Post-operative cell salvage	56 (6)	46 (5)	1
Fluids in theatre/CICU/HDU,* n *(%)			
Inotropes	624 (62)	614 (61)	1
Gelofusine® (B. Braun, Melsungen, Germany)	843 (84)	836 (83)	1
HES	231 (23)	233 (23)	0
Readmissions to hospital			
LOS, days/participant	1.38 (0.15)	1.46 (0.16)	–0.08 (0.22)
ED attendances			
Total ED visits, number/participant	0.09 (0.01)	0.08 (0.01)	0.01 (0.01)
Outpatient appointments,* n*/participant (%)			
Cardiac surgery outpatient visits	0.44 (0.02)	0.51 (0.02)	–0.07 (0.03)
Cardiology outpatient visits	0.28 (0.02)	0.26 (0.02)	0.03 (0.03)
Other outpatient visits	0.17 (0.02)	0.17 (0.02)	0.00 (0.03)
Other health-care contacts,* n*/participant (%)			
GP at surgery	1.99 (0.06)	2.07 (0.07)	–0.09 (0.10)
GP at home	0.43 (0.04)	0.37 (0.03)	0.06 (0.06)
Practice nurse	1.56 (0.13)	1.57 (0.14)	–0.01 (0.19)
District nurse	2.47 (0.20)	2.21 (0.23)	0.26 (0.30)

AF, atrial fibrillation; HES, hydroxyethyl starch; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

TABLE 38 Unit costs for key resources

Resource use	Unit cost (£)	Source
Red blood cells (per unit of blood)	123.31	NHSBT Price List 2012/13[45]
Cardiac procedure		
CABG	6714	See *Appendix 3*, *Table 61*
Valve	7336	See *Appendix 3*, *Table 61*
CABG and valve	8054	See *Appendix 3*, *Table 61*
Other	8298	See *Appendix 3*, *Table 61*
Blood products (per unit)		
FFP	27.46	NHSBT Price List 2012/13[45]
Platelets	209.30	NHSBT Price List 2012/13[45]
Cryoprecipitate	189.19	NHSBT Price List 2012/13[45]
Inpatient complications *Primary outcome*		
Antibiotics for infectious complication	See *Appendix 3*, *Table 63*	eMIT, 2014;[46] BNF 66, 2013[47]
Stroke	139	NHS Reference Costs 2012/13[44]
Confirmed by CT scan	62	NHS Reference Costs 2012/13[44]
Confirmed by MRI scan	248	NHS Reference Costs 2012/13[44]
Suspected MI	1868	NHS Reference Costs 2012/13[44]
Gut infarction	62	NHS Reference Costs 2012/13[44]
Confirmed by laparotomy	2693	NHS Reference Costs 2012/13[44]
AKI – stage 3	1438	NHS Reference Costs 2012/13[44]
Other complications		
Reoperation (duration < 3 hours)	6608	NHS Reference Costs 2012/13[44]
Reoperation (duration ≥ 3 hours)	8298	NHS Reference Costs 2012/13[44]
Reintubation	395	NHS Reference Costs 2012/13[44]
Tracheostomy	5354	NHS Reference Costs 2012/13[44]
Mask CPAP	539	NHS Reference Costs 2012/13[44]
Pneumothorax requiring drainage	4218	NHS Reference Costs 2012/13[44]
Pleural effusion requiring drainage	4218	NHS Reference Costs 2012/13[44]
Pacing	3073	NHS Reference Costs 2012/13[44]
SVT/AF requiring treatment	4.79	eMIT, 2014[46]
VF/VT requiring treatment	2007	NHS Reference Costs 2012/13[44]
Low cardiac output	313	NHS Reference Costs 2012/13[44]

continued

TABLE 38 Unit costs for key resources (*continued*)

Resource use	Unit cost (£)	Source
Inpatient LOS		
CICU day	1190	NHS Reference Costs 2012/13[45]
HDU day	619	NHS Reference Costs 2012/13[45]
Ward day	392	NHS Reference Costs 2012/13[45]
Another unit/hospital ICU day	1168	NHS Reference Costs 2012/13[45]
Another unit/hospital ward day	265	NHS Reference Costs 2012/13[45]
Blood saving techniques		
Tranexamic acid	15.50	BNF 66, 2013[48]
Trasylol	316.83	Davies *et al.*[56]
Intra- and post-operative cell salvage	176	Davies *et al.*[56]
Fluids in theatre/CICU/HDU		
Inotropes	57.30	eMIT, 2014[47]
Gelofusine	7.92	Finance Department South Central, 2013, personal communication
HES	40.60	BNF 58, 2009[57]
Readmissions to hospital		
Ward day	265	NHS Reference Costs 2012/13[45]
ICU day	1168	NHS Reference Costs 2012/13[45]
ED attendances		
ED visit (not leading to admission)	101	NHS Reference Costs 2012/13[45]
Outpatient appointments		
Cardiac surgery outpatient visit	299	NHS Reference Costs 2012/13[45]
Cardiology outpatient visit	131	NHS Reference Costs 2012/13[45]
Other outpatient visits	See *Appendix 3*, *Tables 70* and *71*	NHS Reference Costs 2012/13[45]
Other health-care contacts		
GP at surgery	34	Unit Costs of Health and Social Care 2013[49]
GP at home	85	Unit Costs of Health and Social Care 2013[49]
Practice nurse	11.37	Unit Costs of Health and Social Care 2013[49]
District nurse	39	Unit Costs of Health and Social Care 2013[49]

AF, atrial fibrillation; HES, hydroxyethyl starch; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

The combined resource use and unit cost information are presented in *Figure 17* in terms of 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 red blood cells, which is to be expected. Key drivers of total costs were surgery, complications and LOS. A breakdown of total costs is given in *Table 39*. This table is broken down into three cost categories: red blood cells, inpatient episode and post-hospital discharge. A more detailed breakdown of total costs is given in *Table 74* in *Appendix 3*. A separate analysis, which shows that the costs of regular medications were reduced after surgery, is described in *Appendix 3*, *Changes in the use of regular medications between admission to and discharge from the cardiac surgery unit*.

The total cost of care from surgery up to 3 months is £17,945 in the restrictive group and £18,127 in the liberal group, creating a mean difference between the groups of £182 (SE £488). Most of this difference in cost is associated with the higher cost of red blood cells in the liberal group (cost difference of £140). The next main cost difference is in LOS costs, the complications and SAEs, with the liberal group being more expensive than the restrictive group, but only slightly more. In terms of post-discharge costs, the restrictive group costs slightly more than the liberal group for hospital readmissions, with a cost difference of £17 (SE £116) and 'other' medical/social care costs, with a difference of £12 (SE £21). The liberal group costs more than the restrictive group for outpatient appointments with a cost difference of £14 (SE £9).

The differences in costs between the groups are small, although there is substantial uncertainty around the differences in costs as shown in the SEs in the final column in *Table 39*. In terms of the distribution of costs across the trial groups, the histograms presented in *Figures 18* and *19* show that the cost data were skewed for both groups, which is a common finding in health economic evaluations. This skewness was enhanced by the existence of a few very high-cost outliers, especially in the liberal group. There were four participants with costs over £100,000, who were all in the liberal group.

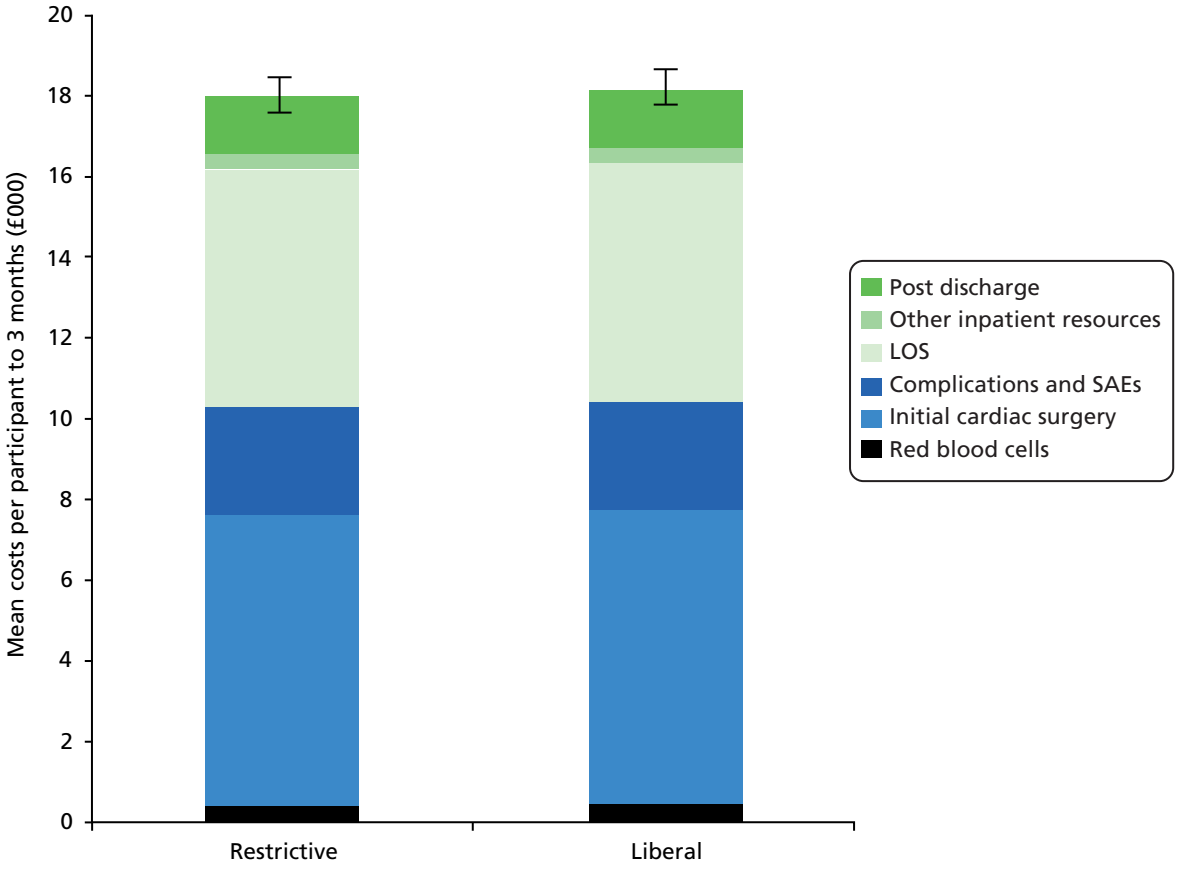


FIGURE 17 Breakdown of total costs for each treatment group. Error bars show SEs around total costs.

TABLE 39 Breakdown of total average cost per participant for both trial groups

Cost component	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
Red blood cells	***287 (13)***	***427 (15)***	***–140 (19)***
Inpatient episode			
Initial cardiac surgery	7309 (18)	7313 (18)	–4 (26)
Other blood products	206 (12)	199 (11)	7 (16)
Complications and SAEs	2684 (137)	2714 (146)	–30 (200)
LOS[a]	5854 (201)	5892 (221)	–38 (299)
Blood saving techniques	159 (9)	152 (8)	7 (12)
Regular medications	26 (2)	29 (2)	–3 (3)
Fluids	55 (1)	55 (1)	0 (2)
Total	**16,293 (309)**	**16,353 (339)**	**–60 (459)**
Post-hospital discharge			
Readmissions	770 (85)	753 (78)	17 (116)
ED visits	16 (2)	12 (2)	4 (3)
Outpatient appointments	202 (6)	216 (7)	–14 (9)
Other medical/social care	378 (14)	366 (16)	12 (21)
Total	**1365 (90)**	**1347 (82)**	**18 (122)**
Total costs	**17,945 (332)**	**18,127 (357)**	**–182 (488)**

a Includes days in another unit/hospital once transferred out of the cardiac unit.
Costs do not always sum to totals owing to rounding.

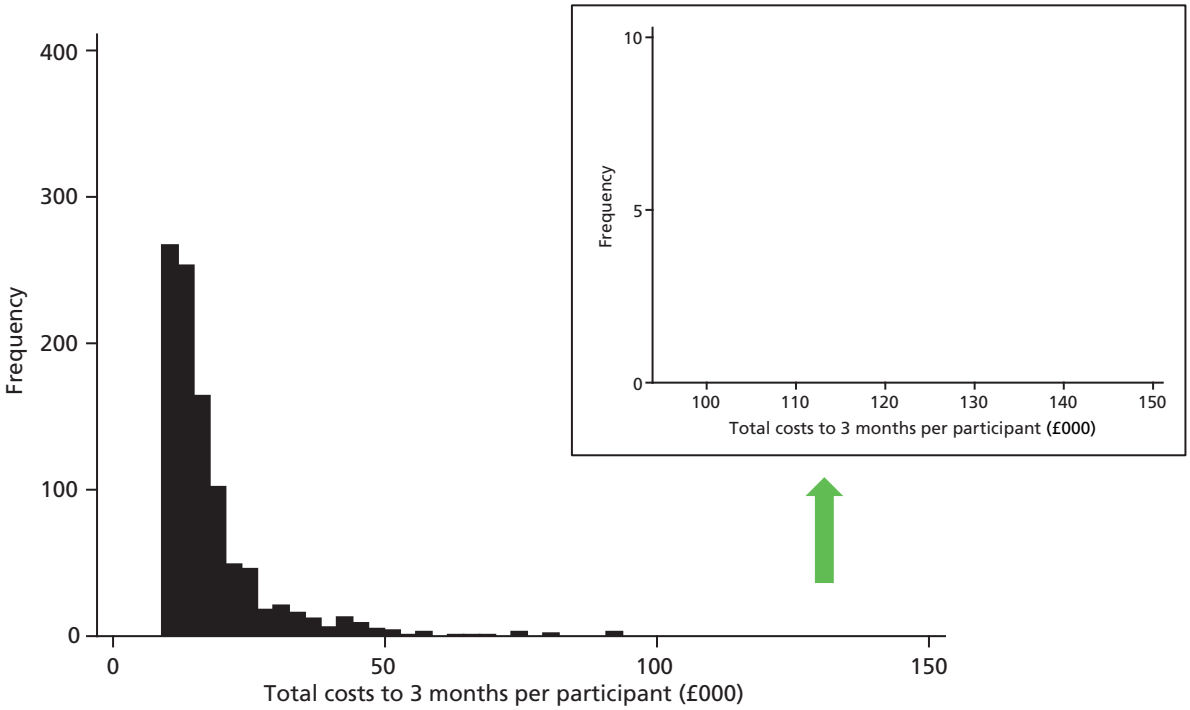


FIGURE 18 Mean total costs (£) per participant in the restrictive group. The inset graph shows that there were outliers in the liberal group but not in the restrictive group.

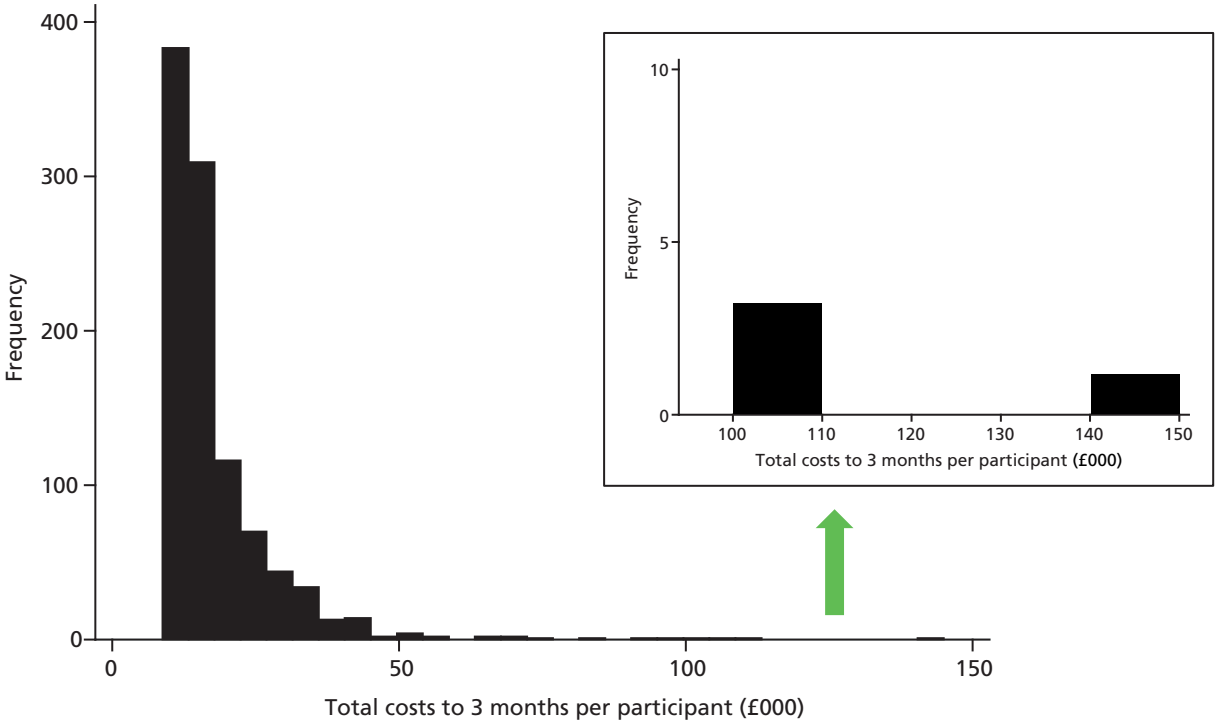


FIGURE 19 Mean total costs (£) per participant in the liberal group. The inset graph shows that there were outliers in the liberal group but not in the restrictive group.

Base-case cost-effectiveness results

The ICER for the restrictive threshold compared with the liberal threshold is shown in *Table 40*. The differences in costs and QALYs between the groups are small and neither difference is statistically significant. The difference between the groups for QALYs is particularly small, that is the denominator for the ICER (the difference in QALYs) is therefore very small. Dividing the difference in costs by a tiny number close to zero, results in a very large ICER (–£428,064). Based on the point estimate, the restrictive threshold is considered cost-effective and 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 20*. The black dot is the point estimate of the cost and QALY difference and is close to the origin. 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 43% probability that the restrictive threshold dominates the liberal threshold, but also a 20% probability of the reverse scenario, that the liberal threshold dominates the restrictive threshold.

The CEAC in *Figure 21* 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, then the probability of restrictive being cost-effective is 65%. 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 0.65–0.66 and the liberal threshold has a probability of being cost-effective of 0.34–0.35. Clearly the restrictive threshold is more likely to be cost-effective, but there is much uncertainty around this. The dashed lines at 0.1 and 0.9 indicate the 80% confidence limits for the probability that a restrictive threshold is cost-effective. As these horizontal lines do not cut the curve at any point, the 80% confidence limits on cost-effectiveness do not exist. Indeed it is not possible to define even 50% confidence limits on cost-effectiveness across willingness-to-pay thresholds from £0 to £100,000.

TABLE 40 Base-case cost-effectiveness results

	Total costs (95% CI)			QALYs (95% CI)				Probability that restrictive is		Probability restrictive is cost-effective at a ceiling ratio of			Probability that restrictive is	
Outcome	Restrictive ($n = 1000$)	Liberal ($n = 1003$)	Difference	Restrictive ($n = 1000$)	Liberal ($n = 1003$)	Difference	ICER (cost/QALY)	Dominant	Dominated	£20,000	£50,000	£100,000	More effective	Less costly
QALYs adjusted for baseline EQ-5D-3L	£17,945 (£17,273 to £18,618)	£18,127 (£17,450 to £18,804)	–£182 (–£1108 to £744)	0.1802 (0.1772 to 0.1832)	0.1798 (0.1766 to 0.1829)	0.0004 (–0.0037 to 0.0045)	Restrictive dominant (–£428,064)	43%	20%	65%	66%	66%	58%	65%

95% CI are based on parametric methods, 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.[58] 1000 bootstrap replicates were generated for each of five imputed datasets, and the mean and SE across the bootstrap replicates for each imputation was calculated. Rubin's Rule was then used to combine the SEs across the five imputed datasets.

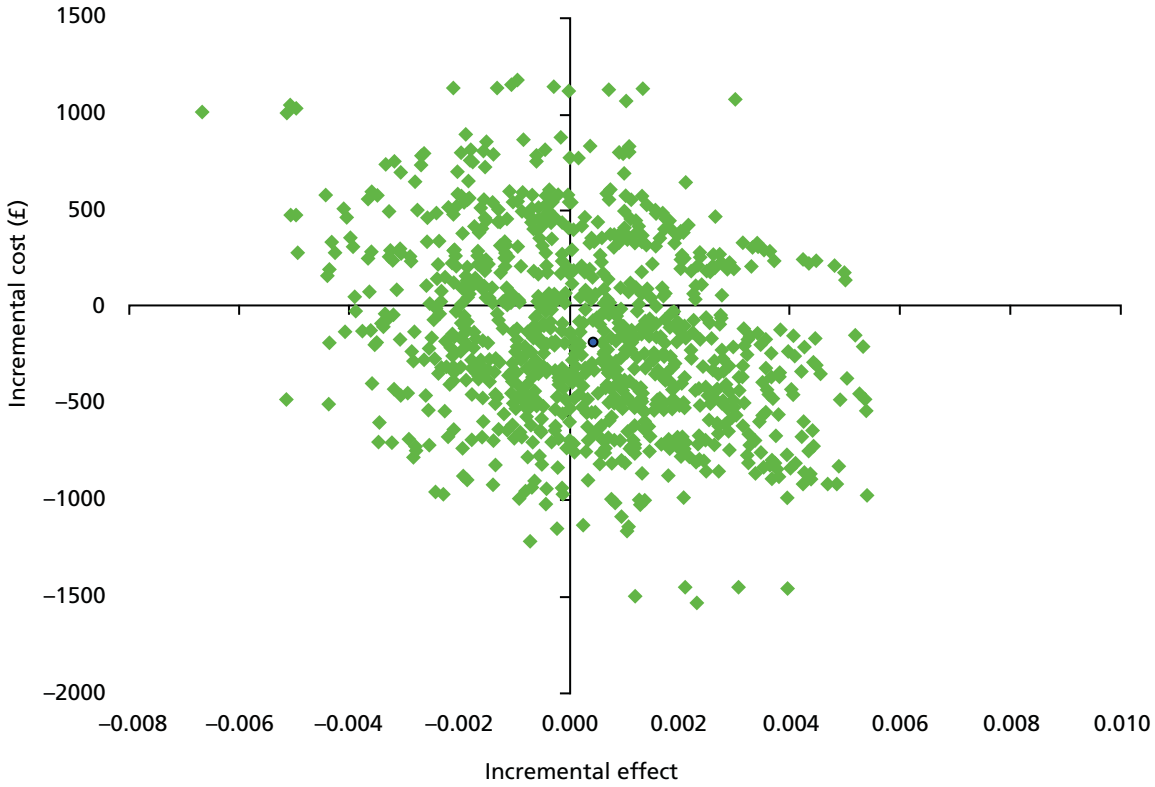


FIGURE 20 Cost-effectiveness plane.

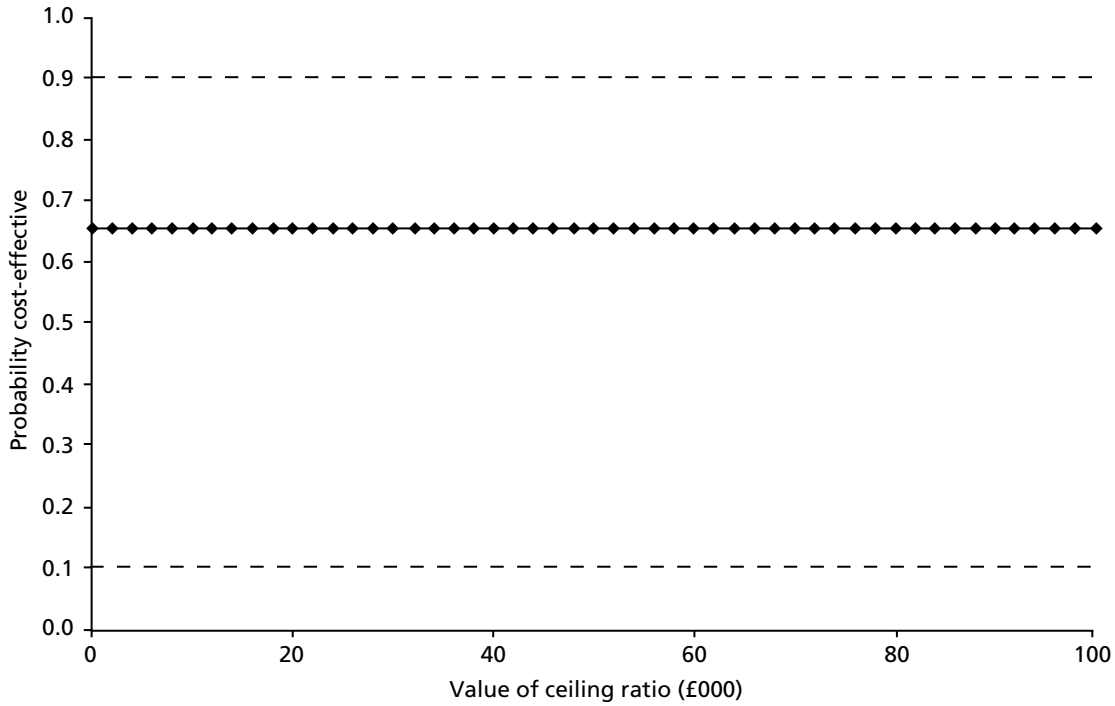


FIGURE 21 Cost-effectiveness acceptability curve.

Sensitivity analyses

Sensitivity analyses for costing were conducted to investigate varying a number of unit costs, moving the time origin from surgery to the time of randomisation and the impact of any high-cost participants. We planned to consider a wider, societal perspective (instead of the NHS and Personal Social Services perceptive taken in the base-case analysis) if non-NHS costs were found to differ between the trial groups. This was not found to be the case (see *Appendix 3*, *Non-NHS costs: did these differ between trial groups?*) and, therefore, this sensitivity analysis was not conducted. In terms of outcomes, alternative assumptions for calculating QALYs were implemented in sensitivity analyses. Finally, we examined life-years gained as a secondary outcome measure. Each of these sensitivity analyses is considered in turn.

Sensitivity analyses around unit costs

The results of the sensitivity analyses around the costs of bed-days, antibiotics, complications and outpatient visits are shown in *Table 79* in *Appendix 3*. Varying the costs 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 –£208 to –£161, bracketing and all very similar to the base-case cost difference of –£182. These findings reinforce how similar resource use is between the groups.

Costing from the point of randomisation

Events that occurred before randomisation were excluded and costs from randomisation to 3 months calculated. Participants were on average randomised 0.8 days after surgery. There is little difference in total costs of care from randomisation to 3 months between the two treatment groups. The total costs from randomisation are £8825 (SE £310) in the restrictive group and £8959 (SE £340) in the liberal group, with a mean difference between the groups of –£134 (SE £460). The costs associated with red blood cells are lower in the restrictive group than the liberal group, as expected. The costs of other inpatient and post-discharge resource use are very similar. Further details on the methods for this analysis and a breakdown of resource use and total costs are provided in *Appendix 3*, *Costs from randomisation*.

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, as all participants go to CICU/HDU after surgery. Red blood cell costs are also reduced because red blood cells are sometimes transfused during surgery.

Sensitivity analyses around cost outliers

The distribution of total costs per participant is positively skewed in both transfusion groups, as seen in *Figures 18* and *19*. It is possible that a few high-cost outliers are exerting influence over the mean costs in each group and the overall findings; therefore, we investigated the existence of outliers and their effects.

There were 12 participants with costs over £80,000, of whom seven were in the liberal group and five were in the restrictive group. Participants with the five highest costs were all in the liberal group. Four participants had costs over £100,000 (£101,173; £107,163; £108,865; and one extreme outlier of £144,985). These participants 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 participants from the analyses. Nevertheless, it is instructive to investigate the impact they are having on cost and cost-effectiveness results, as the imbalance across groups of these outliers could easily have arisen by chance.

Table 41 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 participants were in the liberal group and, therefore, results for the restrictive group are unchanged. If the participant with the highest cost is excluded from the analyses, the difference in costs between the groups reduces from –£182 to –£55. If participants with the four highest costs are excluded, the liberal group becomes less expensive than the restrictive group and the difference in costs between the groups changes from –£182 to +£208. The liberal group also becomes marginally more effective than the restrictive group and the conclusions are reversed, that is, 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 participants are clearly exerting a significant impact on the cost and cost-effectiveness results.

Sensitivity analyses around quality-adjusted life-year calculations

We explored various assumptions for calculating QALYs, including the use of last observation carried forward until death (rather than assuming that utility changes linearly until death) and using the date of the 6-week EQ-5D-3L completion (rather than assuming it was completed exactly at 6 weeks). Details of the alternative strategies explored are given in *Table 42* and the results are provided in *Table 43*. 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 as there were more deaths in this group and a greater number of participants whose QALYs were increased by this sensitivity analysis (unless their EQ-5D-3L score was less than zero at the previous observation). When the exact timing of the 6-week EQ-5D-3L questionnaire was used in the QALY calculations, the mean QALYs gained up to 3 months were slightly higher in the liberal group than in the restrictive group, a reversal of the base-case findings. Participants on average completed the 6-week questionnaire later than planned, at 51 days rather than 42 days.

Life-years

Life-years gained from surgery up to 3 months are shown in *Table 44*. 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 44*. This analysis generated the typical trade-off between the treatment effect and the difference in cost. This trade-off is usually the result of a better effect at a higher cost; here, the reverse was the case with the restrictive threshold gaining fewer life-years but at lower cost than the liberal threshold. The ICER of £66,800 is the incremental saving associated with the loss of 1 life-year by adopting a restrictive rather than a liberal threshold. If a decision-maker's willingness to accept compensation for the loss of 1 life-year was £20,000, then a restrictive threshold would be considered cost-effective.

The cost-effectiveness plane for life-years (*Figure 22*) and the CEAC for life-years (*Figure 23*) show quite interesting differences compared with those for the QALY analysis. In particular, *Figure 22* shows that with life-years, 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 QALYs analysis, the plane had most of its points scattered around the origin showing very little difference. Compared with 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 restrictive is more effective than liberal is just 3% (not statistically significant). There is only a 2% probability that the restrictive threshold dominates the liberal threshold (i.e. is more effective and less costly), but a 34% probability of the reverse scenario – that the liberal threshold dominates the restrictive threshold.

TABLE 41 Sensitivity analyses around the cost outliers

	Randomised to restrictive threshold ($n = 1000$)		Randomised to liberal threshold ($n = 1003$)		Restrictive vs. liberal threshold		
Sensitivity analysis	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (SE)	Mean QALY difference (SE)	ICER
Base case, all participants	£17,945 (£332)	0.1802 (0.0015)	£18,127 (£357)	0.1798 (0.0016)	–£182 (£488)	0.0004 (0.0021)	Restrictive dominant (–£428,064)
Exclude highest cost participant	£17,945 (£332)	0.1802 (0.0015)	£18,001 (£335)	0.1799 (0.0016)	–£55 (£471)	0.0003 (0.0021)	Restrictive dominant (–£210,078)
Exclude four highest cost participants	£17,945 (£332)	0.1802 (0.0015)	£17,737 (£299)	0.1803 (0.0016)	£208 (£447)	–0.0001 (0.0021)	Liberal dominant (–£1,835,715)

TABLE 42 Sensitivity analyses performed around QALYs

Sensitivity analysis	Aspect of methodology	Strategy used in base-case analysis	Alternative strategy for sensitivity analysis
1	QALY calculations: 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	QALY calculations: timing of 6-week EQ-5D-3L	EQ-5D-3L at 6 weeks assumed to be completed at exactly 6 weeks	Use the date of completion of the 6-week EQ-5D-3L
4	QALY calculations: timing	Calculate QALYs gained from time of surgery to 3 months	Calculate QALYs gained from randomisation to 3 months

TABLE 43 Results of sensitivity analyses around QALYs

Sensitivity analysis		Randomised to restrictive threshold ($n = 1000$), QALYs to 3 months, mean (SE)	Randomised to liberal threshold ($n = 1003$), QALYs to 3 months, mean (SE)	Restrictive vs. liberal threshold, QALYs to 3 months mean, difference (SE)
	Base case	0.1802 (0.0015)	0.1798 (0.0016)	0.0004 (0.0021)
1	No adjustment for baseline utility	0.1801 (0.0018)	0.1798 (0.0017)	0.0003 (0.0025)
2	Last observation carried forward until death	0.1807 (0.0015)	0.1800 (0.0016)	0.0007 (0.0021)
3	Exact time between operation and 6-week EQ-5D-3L completion	0.1801 (0.0014)	0.1802 (0.0014)	–0.0002 (0.0020)
4	From randomisation	0.1801 (0.0015)	0.1795 (0.0015)	0.0006 (0.0021)

TABLE 44 Cost-effectiveness results for life-years

	Total costs (95% CI)			Life-years gained (95% CI)				Probability that restrictive is		Probability restrictive is cost-effective at a ceiling ratio of			Probability that restrictive is	
Outcome	Restrictive ($n = 1000$)	Liberal ($n = 1003$)	Difference	Restrictive ($n = 1000$)	Liberal ($n = 1003$)	Difference	ICER (cost/life-year)	Dominant	Dominated	£20,000	£50,000	£100,000	More effective	Less costly
Life-years	£17,945 (£17,273 to £18,618)	£18,127 (£17,450 to £18,804)	–£182 (–£1108 to £744)	0.2428 (0.2404 to 0.2452)	0.2455 (0.2437 to 0.2474)	–0.0027 (–0.0057 to 0.0002)	£66,800	2%	34%	61%	55%	45%	3%	65%

95% CI is based on parametric methods, using a *t*-distribution with degrees of freedom $v = (-1)(1 + r^{-1})^2$, for which r is the ratio of the between-imputation component of the variance and the within-imputation component of the variance.[57] 1000 bootstrap replicates were generated for each of five imputed datasets, and the mean and SE across the bootstrap replicates for each imputation was calculated. Rubin's Rule was then used to combine the SEs across the five imputed datasets. (There was only one dataset for life-years because no data for life-years were missing.)

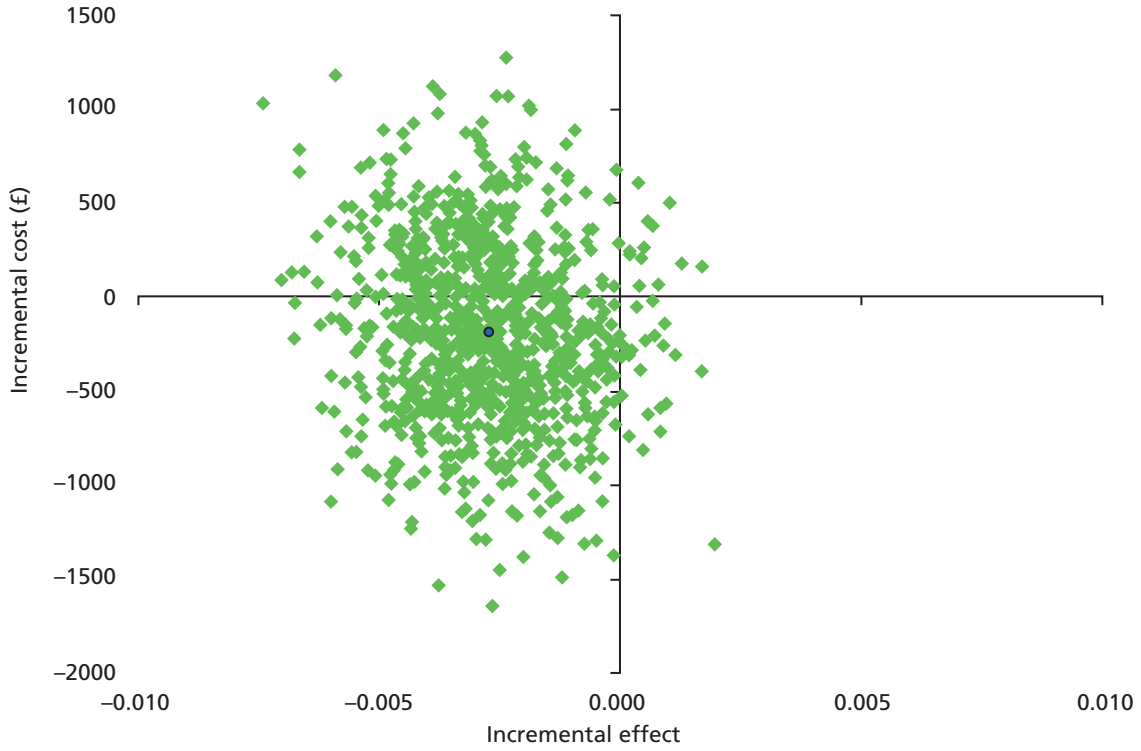


FIGURE 22 Cost-effectiveness plane for life-years.

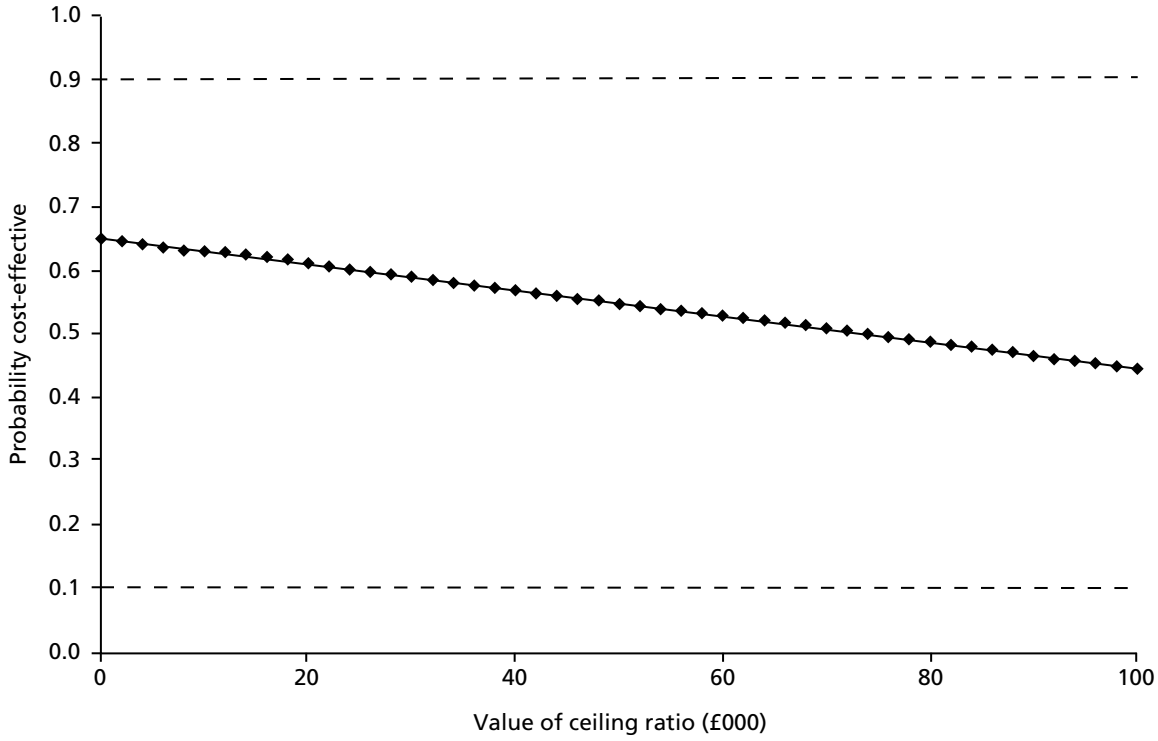


FIGURE 23 Cost-effectiveness acceptability curve for life-years.

The CEAC in *Figure 23* 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 61%. 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.

Subgroup analyses

The results of the seven subgroup analyses conducted to investigate whether or not cost-effectiveness results varied between participant subgroups are presented in *Appendix 3*, *Table 82*. Comparing costs between subgroups as a whole, the findings are generally as expected. Participants in each low-risk stratum before surgery cost less than those in each high-risk stratum, with the exception of sex for which the high-risk stratum (females) cost less than the low-risk stratum (males), and the possible exception of pulmonary disease/asthma, but the numbers at high risk for pulmonary comorbidity were small.

The cost and QALY differences between the treatment groups within the subgroups are all small relative to their SEs. 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, only the interaction term for the subgroup for lung disease for QALYs was found to be significant ($p = 0.003$). Participants in the restrictive group with chronic pulmonary disease or asthma gained a reduced number of QALYs compared with other participants. This effect is consistent with the corresponding subgroup analysis of the primary outcome (see *Chapter 5*, *Subgroup analyses*).

For subgroup analyses 1–4 and 6 (further details in *Appendix 3, Table 82*), the direction of differences between treatment groups does differ between the subgroups. In the 'low-risk' stratum of each subgroup analysis (participants believed to be at lower risk of the primary outcome), the restrictive threshold is both less costly and more effective than the liberal threshold and, therefore, a restrictive threshold is favoured. In the 'high-risk' stratum of each subgroup (participants believed to be at higher risk of the primary outcome), the restrictive threshold is both more costly and less effective than the liberal threshold, so the liberal threshold is favoured. Note that negative ICERs need to be interpreted with caution (an ICER is a ratio of two numbers and, if either of the two is negative, the ICER will be negative). Either the new intervention is less costly and more effective, a desirable finding, or the new intervention is more costly and less effective, an undesirable finding. Both scenarios result in negative ICERs, but have very different meanings. These subgroup analyses should be considered as exploratory and further work would be required to confirm these findings.

Summary

There was very little difference between the groups in either costs or effects, and great uncertainty around the cost-effectiveness results. Mean QALYs to 3 months were 0.18 in both groups and there was a tiny difference between the restrictive and liberal groups (mean difference 0.0004, 95% CI –0.0037 to 0.0045). The total cost of care from surgery up to 3 months was £17,945 in the restrictive group and £18,127 in the liberal group, creating a small mean difference of –£182, 95% CI –£1108 to £744. There were several outliers in the liberal group that exerted a substantial influence on the average costs of participants in that group, altering the results when they were excluded.

The point estimate of cost-effectiveness suggested that the restrictive group was more effective and less costly than the liberal group (i.e. dominant) and, therefore, cost-effective. However given the small differences in costs and effects, there was much uncertainty around this result.

There was evidence of one subgroup effect: participants in the restrictive group with chronic pulmonary disease or asthma gained a reduced number of QALYs compared with other participants ($p = 0.003$).

Chapter 7 Observational analyses

As described in *Chapter 2*, *Observational analyses*, all red blood cells administered and haemoglobin levels recorded after the time of the first event that qualified for the primary outcome or after censoring have been excluded. The classification of all red blood cell transfusions as happening before randomisation, after randomisation but before the primary outcome or censoring and after the primary outcome or censoring is given in *Table 45*. Therefore, for analyses described in this chapter, 1381 participants are classified as having had at least one unit of red blood cells transfused after randomisation and before experiencing the primary outcome or being censored, 484 in the restrictive transfusion threshold stratum (total of 1074 units) and 897 in the liberal transfusion threshold stratum (total of 2030 units).

For the same period (after randomisation and before the time of the primary outcome or censoring), all participants were also classified as having experienced a minimum haemoglobin < 7.5 g/dl versus ≥ 7.5 g/dl. No haemoglobin levels were recorded for two participants between randomisation and the first incidence of the primary outcome or censoring. A total of 595 participants had a minimum haemoglobin level below 7.5 g/dl and 1406 participants had a haemoglobin level ≥ 7.5 g/dl throughout the period.

The analysis population is, therefore, identical to that for the analyses by transfusion threshold stratum reported in *Chapter 5*. However, the two participants with no haemoglobin measurements after randomisation and before experiencing the primary outcome or censoring are excluded from all models that fitted haemoglobin level.

TABLE 45 Timing of red blood cell transfusions by randomisation and occurrence (or censoring) of the primary outcome

Transfusion	Restrictive group		Liberal group	
	Number of transfusions of red blood cells (units)	Number of participants receiving any transfusions (%) ($n = 1000$)	Number of transfusions of red blood cells (units)	Number of participants receiving any transfusions (%) ($n = 1003$)
Pre-randomisation red blood cell transfusions	587	250 (25.0)	589	264 (26.3)
Post-randomisation red blood cell transfusions	1494	534 (53.4)	2494	925 (92.2)
Before the primary outcome or censoring[a,b]	1074	484 (48.4)	2030	897 (89.4)
After the primary outcome or censoring[a]	420	121 (12.1)	464	147 (14.7)

a Participants are classified according to whether (1) one or more red blood cell transfusions occurred before the primary outcome or censoring, or (2) all red blood cell transfusions occurred after the primary outcome or censoring.
b These transfusions comprise those considered in the remainder of this chapter.

Red blood cells and haemoglobin levels

Trial characteristics and outcomes

Pre-operative and intraoperative characteristics and trial outcomes are described by red blood cell transfusion status (after randomisation and before experiencing the primary outcome or censoring) in *Tables 46* and *47*, and by minimum haemoglobin in *Tables 48* and *49*.

Compared with non-transfused participants, transfused participants were on average older [median 70.8 years (IQR 64.2–76.8 years) vs. 69.5 years (IQR 62.6–75.5 years)], had similar additive EuroSCOREs [medians 5 (IQR 3–7)], higher logistic EuroSCOREs [median 4.2 (IQR 2.4–7.5) vs. 3.7 (IQR 2.0–6.6)] and were less likely to be male (67.6% vs. 70.7%). Transfused participants had, on average, lower pre-operative haemoglobin levels [mean 13.2 g/dl (SD 1.5 g/dl) vs. 13.5 g/dl (SD 1.4 g/dl)] and eGFR levels [median 71.7 ml/minute/1.73m^2 (IQR 54.7–91.5 ml/minute/1.73m^2) vs. 77.4 ml/minute/1.73m^2 (IQR 61.3–96.9 ml/minute/1.73m^2)]. Their surgery time was slightly longer [median 4.0 hours (IQR 3.3–5.0 hours) vs. 3.9 hours (IQR 3.3–4.9 hours)] and they were less likely to have had CABG surgery (39.2% vs. 44.1%).

Pre-randomisation red blood cell transfusion frequencies were similar in the two groups (25.6% for transfused and 25.7% for non-transfused). However, the transfusion of other blood products was higher in the participants who also had red blood cells transfused; FFP was transfused in 32.5% of participants who had a red blood cell transfusion vs. 21.2% of participants who did not, platelets in 40.7% and 28.3% of participants and cryoprecipitate in 11.4% and 6.9% of participants, respectively. The minimum haemoglobin reached was lower in the transfused participants [median 7.8 g/dl (IQR 7.2–8.4 g/dl) vs. 8.3 g/dl (IQR 7.8–8.6 g/dl)], but the percentage decline in haemoglobin from the pre-operative level was only very slightly more in the transfused participants [median 41.3% (IQR 35.1–46.7%) vs. 39.3% (IQR 34.7–43.3%)]. In terms of trial outcomes, the primary outcome occurred in 35.3% of transfused participants and 30.9% of non-transfused participants, both mortality (3.7% vs. 2.7%) and significant pulmonary morbidity (14.0% vs. 8.3%) rates were higher for transfused participants, and the duration of ICU/HDU stay was longer [median 59.6 hours (IQR 24.4–109 hours) vs. 32.6 hours (IQR 11.3–76.1 hours)].

TABLE 46 Characteristics of participants by red blood cell transfusion status

Characteristic	Transfused (*N* = 1381)	Not transfused (*N* = 622)
Cardiac history		
Additive EuroSCORE,[a] median (IQR)	5.0 (3.0–7.0)	5.0 (3.0–7.0)
Logistic EuroSCORE,[a] median (IQR)	4.2 (2.4–7.5)	3.7 (2.0–6.6)
NYHA class, *n*/*N* (%)		
I	342/1348 (25.4)	151/603 (25.0)
II	594/1348 (44.1)	291/603 (48.3)
III	382/1348 (28.3)	143/603 (23.7)
IV	30/1348 (2.2)	18/603 (3.0)
CCS class, *n*/*N* (%)		
No angina	477/1354 (35.2)	241/608 (39.6)
I	259/1354 (19.1)	103/608 (16.9)
II	350/1354 (25.8)	176/608 (28.9)
III	208/1354 (15.4)	73/608 (12.0)
IV	60/1354 (4.4)	15/608 (2.5)

TABLE 46 Characteristics of participants by red blood cell transfusion status (*continued*)

Characteristic	Transfused (*N* = 1381)	Not transfused (*N* = 622)
Coronary disease, *n*/*N* (%)		
None	426/1375 (31.0)	194/616 (31.5)
Single vessel	168/1375 (12.2)	57/616 (9.3)
Double vessel	184/1375 (13.4)	98/616 (15.9)
Triple vessel	562/1375 (40.9)	243/616 (39.4)
Not investigated	35/1375 (2.5)	24/616 (3.9)
Disease in left main stem (> 50% stenosis)	204/1364 (15.0)	100/613 (16.3)
Non-cardiac history		
Age (years), median (IQR)	70.8 (64.2–76.8)	69.5 (62.6–75.5)
Males, *n*/*N* (%)	933/1381 (67.6)	440/622 (70.7)
BMI (kg/m^2),[b] mean (SD)	27.9 (4.8)	28.7 (5.1)
Urgent operative priority, *n*/*N* (%)	181/1381 (13.1)	64/622 (10.3)
Diabetic, *n*/*N* (%)	279/1381 (20.2)	120/622 (19.3)
Haemofiltration/dialysis, *n*/*N* (%)	16/1379 (1.2)	3/622 (0.5)
CVA/TIA, *n*/*N* (%)	112/1381 (8.1)	51/622 (8.2)
Pre-operative tests		
Haemoglobin (g/dl), mean (SD)	13.2 (1.5)	13.5 (1.4)
eGFR (ml/minute/1.73m^2),[c] median (IQR)	71.7 (54.7–91.5)	77.4 (61.3–96.9)
Intraoperative characteristics		
Duration of operation (hours),[d] median (IQR)	4.0 (3.3–5.0)	3.9 (3.3–4.9)
CPB used, *n*/*N* (%)	1323/1381 (95.8)	580/621 (93.4)
Cardiac procedure, *n*/*N* (%)		
CABG only	542/1381 (39.2)	274/622 (44.1)
Valve only	428/1381 (31.0)	183/622 (29.4)
CABG + valve	301/1381 (21.8)	97/622 (15.6)
Other	110/1381 (8.0)	68/622 (10.9)
Tranexamic acid, *n*/*N* (%)	1112/1380 (80.6)	503/621 (81.0)
Trasylol, *n*/*N* (%)	48/1315 (3.7)	23/579 (4.0)
Cell saver, *n*/*N* (%)	689/1381 (49.9)	295/621 (47.5)
Blood loss at 4 hours (ml),[e] median (IQR)	275 (170–460)	210 (125–328)
Blood loss at 12 hours (ml),[e] median (IQR)	525 (340–840)	400 (290–600)

BMI, body mass index; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; NYHA, New York Health Association; TIA, transient ischaemic attack.
a Missing for 24 transfused participants and 14 non-transfused participants.
b Missing for one transfused participant.
c Missing for two transfused participants.
d Missing for one non-transfused participant.
e Missing for one transfused participant and two non-transfused participants.

TABLE 47 Outcomes of participants by red blood cell transfusion status

Outcome Intra- and post-operative use of other blood products	Transfused (*N* = 1381)	Not transfused (*N* = 622)
Pre-randomisation red blood cell transfusion, *n/N* (%)	354/1381 (25.6)	160/622 (25.7)
FFP transfusions, *n/N* (%)	449/1381 (32.5)	132/622 (21.2)
Platelet transfusions, *n/N* (%)	562/1381 (40.7)	176/622 (28.3)
Cryoprecipitate transfusions, *n/N* (%)	158/1381 (11.4)	43/622 (6.9)
Activated factor VII used, *n/N* (%)	7/1381 (0.5)	5/622 (0.8)
Beriplex used, *n/N* (%)	65/1381 (4.7)	35/622 (5.6)
Minimum haemoglobin (g/dl),[a] median (IQR)	7.8 (7.2–8.4)	8.3 (7.8–8.6)
Percentage decline in haemoglobin,[a] median (IQR)	41.3 (35.1–46.7)	39.3 (34.7–43.3)
Primary outcome, n/N (%)		
Overall primary outcome	474/1342 (35.3)	174/564 (30.9)
Infectious event	351/1327 (26.5)	127/563 (22.6)
Sepsis	311/1360 (22.9)	113/605 (18.7)
Wound infection	72/1297 (5.6)	29/560 (5.2)
Ischaemic event	213/1371 (15.5)	82/611 (13.4)
Permanent stroke	25/1363 (1.8)	7/611 (1.1)
Suspected MI	6/1357 (0.4)	1/611 (0.2)
Gut infarction	4/1358 (0.3)	3/611 (0.5)
AKI	188/1367 (13.8)	74/611 (12.1)
Other trial outcomes		
All-cause mortality, *n/N* (%)	51/1381 (3.7)	17/622 (2.7)
Significant pulmonary morbidity, *n/N* (%)	192/1367 (14.0)	51/614 (8.3)
Duration of ICU/HDU stay (hours), median (IQR)	59.6 (24.4–109)	32.6 (11.3–76.1)
Duration of post-randomisation hospital stay (days), median (IQR)	7.0 (5.0–11.0)	6.0 (4.0–9.0)

a Missing for two non-transfused participants.

TABLE 48 Characteristics of participants by minimum haemoglobin level

Characteristic	Minimum haemoglobin < 7.5 g/dl (*N* = 595)	Minimum haemoglobin ≥ 7.5 g/dl (*N* = 1406)
Cardiac history		
Additive EuroSCORE,[a] median (IQR)	5.0 (4.0–7.0)	5.0 (3.0–7.0)
Logistic EuroSCORE,[a] median (IQR)	4.2 (2.4–7.2)	4.0 (2.2–7.2)
NYHA class, *n*/*N* (%)		
I	133/580 (22.9)	360/1370 (26.3)
II	259/580 (44.7)	625/1370 (45.6)
III	170/580 (29.3)	355/1370 (25.9)
IV	18/580 (3.1)	30/1370 (2.2)
CCS class, *n*/*N* (%)		
No angina	185/583 (31.7)	533/1378 (38.7)
I	102/583 (17.5)	260/1378 (18.9)
II	168/583 (28.8)	358/1378 (26.0)
III	98/583 (16.8)	182/1378 (13.2)
IV	30/583 (5.1)	45/1378 (3.3)
Coronary disease, *n*/*N* (%)		
None	178/593 (30.0)	442/1396 (31.7)
Single vessel	64/593 (10.8)	161/1396 (11.5)
Double vessel	86/593 (14.5)	196/1396 (14.0)
Triple vessel	256/593 (43.2)	547/1396 (39.2)
Not investigated	9/593 (1.5)	50/1396 (3.6)
Disease in left main stem (> 50% stenosis), *n*/*N* (%)	97/590 (16.4)	206/1385 (14.9)
Non-cardiac history		
Age (years), median (IQR)	70.8 (64.2–76.7)	70.0 (63.3–76.2)
Males, *n*/*N* (%)	391/595 (65.7)	980/1406 (69.7)
BMI (kg/m^2),[b] mean (SD)	27.6 (4.9)	28.4 (4.9)
Urgent operative priority, *n*/*N* (%)	86/595 (14.5)	158/1406 (11.2)
Diabetic, *n*/*N* (%)	126/595 (21.2)	273/1406 (19.4)
Haemofiltration/dialysis, *n*/*N* (%)	7/595 (1.2)	12/1404 (0.9)
CVA/TIA, *n*/*N* (%)	44/595 (7.4)	119/1406 (8.5)

continued

TABLE 48 Characteristics of participants by minimum haemoglobin level (*continued*)

Characteristic	Minimum haemoglobin < 7.5 g/dl (*N* = 595)	Minimum haemoglobin ≥ 7.5 g/dl (*N* = 1406)
Pre-operative tests		
Haemoglobin (g/dl), mean (SD)	13.0 (1.5)	13.4 (1.4)
eGFR (ml/minute/1.73m^2),[c] median (IQR)	69.3 (52.5–86.7)	75.8 (58.5–95.4)
Intraoperative characteristics		
Duration of operation (hours),[b] median (IQR)	4.2 (3.4–5.2)	4.0 (3.3–5.0)
CPB used, *n/N* (%)	567/595 (95.3)	1334/1405 (94.9)
Cardiac procedure, *n/N* (%)		
CABG only	239/595 (40.2)	575/1406 (40.9)
Valve only	171/595 (28.7)	440/1406 (31.3)
CABG + valve	132/595 (22.2)	266/1406 (18.9)
Other	53/595 (8.9)	125/1406 (8.9)
Tranexamic acid, *n/N* (%)	474/595 (79.7)	1139/1404 (81.1)
Aprotinin (Trasylol, The Nordic group), *n/N* (%)	24/561 (4.3)	47/1331 (3.5)
Cell saver, *n/N* (%)	292/595 (49.1)	691/1405 (49.2)
Blood loss at 4 hours (ml),[d] median (IQR)	328 (200–525)	225 (140–350)
Blood loss at 12 hours (ml),[d] median (IQR)	630 (380–1000)	450 (300–700)

BMI, body mass index; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; NYHA, New York Health Association; TIA, transient ischaemic attack.

a Missing for 32 participants in the minimum haemoglobin < 7.5g/dl group and six in minimum haemoglobin ≥ 7.5g/dl group.

b Missing for one participant, in the minimum haemoglobin < 7.5g/dl group.

c Missing for two participants, in the minimum haemoglobin < 7.5g/dl group.

d Missing for two participants, in the minimum haemoglobin < 7.5g/dl group.

Two participants with no haemoglobin levels recorded before first occurrence of the primary outcome are excluded from this table.

TABLE 49 Outcomes of participants by minimum haemoglobin level

Outcome	Minimum haemoglobin < 7.5 g/dl (*N* = 595)	Minimum haemoglobin ≥ 7.5 g/dl (*N* = 1406)
Intra- and post-operative use of blood products		
Pre-randomisation red blood cell transfusion, *n/N* (%)	181/595 (30.4)	333/1406 (23.7)
Post-randomisation (pre-primary outcome) red blood cell transfusions, *n/N* (%)	555/595 (93.3)	826/1406 (58.7)
FFP transfusions, *n/N* (%)	243/595 (40.8)	337/1406 (24.0)
Platelet transfusions, *n/N* (%)	288/595 (48.4)	449/1406 (31.9)
Cryoprecipitate transfusions, *n/N* (%)	82/595 (13.8)	119/1406 (8.5)
Activated factor VII used, *n/N* (%)	1/595 (0.2)	11/1406 (0.8)
Beriplex used, *n/N* (%)	20/595 (3.4)	80/1406 (5.7)
Percentage decline in haemoglobin, median (IQR)	46.7 (42.4–50.7)	38.4 (33.3–42.8)
Primary outcome,* n/N *(%)		
Overall primary outcome	237/574 (41.3)	411/1330 (30.9)
Infectious event	161/566 (28.4)	317/1322 (24.0)
Sepsis	141/583 (24.2)	283/1380 (20.5)
Wound infection	39/560 (7.0)	62/1295 (4.8)
Ischaemic event	128/593 (21.6)	167/1387 (12.0)
Permanent stroke	14/591 (2.4)	18/1381 (1.3)
Suspected MI	1/588 (0.2)	6/1378 (0.4)
Gut infarction	3/588 (0.5)	4/1379 (0.3)
AKI	114/590 (19.3)	148/1386 (10.7)
Other trial outcomes		
All-cause mortality, *n/N* (%)	38/595 (6.4)	30/1406 (2.1)
Significant pulmonary morbidity, *n/N* (%)	111/590 (18.8)	132/1389 (9.5)
Duration of ICU/HDU stay (hours), median (IQR)	71.7 (42.3–131)	42.1 (17.4–87.6)
Duration of post-randomisation hospital stay (days), median (IQR)	8.0 (6.0–13.0)	6.0 (5.0–9.0)

Two patients with no haemoglobin levels recorded before first occurrence of the primary outcome are excluded from this table.

Compared with participants with a haemoglobin ≥ 7.5 g/dl, participants with a haemoglobin < 7.5 g/dl were of a similar age and had a similar median additive EuroSCOREs but slightly higher median logistic EuroSCOREs [median 4.2 (IQR 2.4–7.2) vs. 4.0 (IQR 2.2–7.2)] and were less likely to be male (65.7% vs. 69.7%). Participants with a post-randomisation haemoglobin < 7.5 g/dl had slightly lower pre-operative haemoglobin levels [mean 13.0 g/dl (SD 1.5 g/dl) vs. 13.4 g/dl (SD 1.4 g/dl)] and eGFR levels [median 69.3 ml/minute/1.73 m^2 (IQR 52.5–86.7 ml/minute/1.73 m^2) vs. 75.8 ml/minute/1.73 m^2 (IQR 58.5–95.4 ml/minute/1.73 m^2)].

Participants with a haemoglobin < 7.5 g/dl were more likely to have had a pre-randomisation red blood cell transfusion (30.4% vs. 23.7%), post-randomisation red blood cell transfusion (93.3% vs. 58.7%), FFP transfusion (40.8% vs. 24.0%), platelet transfusion (48.4% vs. 31.9%) and cryoprecipitate transfusion (13.8% vs. 8.5%). In terms of trial outcomes, the primary outcome occurred in 41.3% of participants with a haemoglobin < 7.5 g/dl and 30.9% of participants whose post-randomisation haemoglobin remained ≥ 7.5 g/dl. Both mortality (6.4% vs. 2.1%) and significant pulmonary morbidity (18.8% vs. 9.5%) were more frequent in participants with a haemoglobin < 7.5 g/dl and the duration of ICU/HDU stay was longer [median 71.7 hours (IQR 42.3–131 hours) vs. 42.1 hours (IQR 17.4–87.6 hours)].

Unadjusted relationship between red blood cells, haemoglobin and outcome

The outcome used for these analyses was the primary outcome and/or death, which occurred in 671 out of 1908 (35.2%) participants. In the population as a whole, the risk of this outcome increased with increasing number of transfused units (*Table 50*). For haemoglobin, the risk of outcome decreases as haemoglobin increases.

Haemoglobin levels, transfusion status and outcome are described in *Table 51* and *Figure 24*, both for all participants and stratified by transfusion threshold stratum.

TABLE 50 Univariate relationships between red blood cell transfusion status and minimum haemoglobin level, and primary outcome/death

Transfusions/haemoglobin levels	Number of participants	Primary outcome/death, *n* (%)	Unadjusted OR (95% CI)	*p*-value
Post-randomisation (pre-primary outcome) red blood cell transfusions				
None	565	176 (31.2)	Reference group	0.0200
One	577	198 (34.3)	1.15 (0.90 to 1.48)	
Two	396	150 (37.9)	1.35 (1.03 to 1.77)	
Three to four	260	96 (36.9)	1.29 (0.95 to 1.76)	
Five or more	110	51 (46.4)	1.91 (1.26 to 2.89)	
Post-randomisation (pre-primary outcome) minimum haemoglobin				
Hb < 7 g/dl	216	99 (45.8)	1.91 (1.38 to 2.65)	< 0.0001
7 g/dl < Hb ≤ 7.5 g/dl	358	154 (43.0)	1.71 (1.29 to 2.26)	
7.5 g/dl < Hb ≤ 8 g/dl	363	119 (32.8)	1.10 (0.83 to 1.47)	
8 g/dl < Hb ≤ 8.5 g/dl	447	139 (31.1)	1.02 (0.78 to 1.34)	
Hb ≥ 8.5 g/dl	522	160 (30.7)	Reference group	

Hb, haemoglobin.

TABLE 51 Relationship between red blood cell transfusion status, minimum haemoglobin level and primary outcome/death

	Transfused participants		Non-transfused participants		All participants	
	Primary outcome/death		Primary outcome/death		Primary outcome/death	
Haemoglobin levels	*N*	*n* (%)	*N*	*n* (%)	*N*	*n* (%)
All participants						
Hb < 7 g/dl	205	89 (43.4)	11	10 (90.9)	216	99 (45.8)
7 g/dl < Hb ≤ 7.5 g/dl	335	140 (41.8)	23	14 (60.9)	358	154 (43.0)
7.5 g/dl < Hb ≤ 8 g/dl	213	76 (35.7)	150	43 (28.7)	363	119 (32.8)
8 g/dl < Hb ≤ 8.5 g/dl	273	82 (30.0)	174	57 (32.8)	447	139 (31.1)
Hb ≥ 8.5 g/dl	317	108 (34.1)	205	52 (25.4)	522	160 (30.7)
Total	1343	495 (36.9)	563	176 (31.3)	1906	671 (35.2)
Liberal group						
Hb < 7 g/dl	62	29 (46.8)	6	5 (83.3)	68	34 (50.0)
7 g/dl < Hb ≤ 7.5 g/dl	100	43 (43.0)	2	0 (0.0)	102	43 (42.2)
7.5 g/dl < Hb ≤ 8 g/dl	149	48 (32.2)	2	1 (50.0)	151	49 (32.5)
8 g/dl < Hb ≤ 8.5 g/dl	252	74 (29.4)	24	7 (29.2)	276	81 (29.3)
Hb ≥ 8.5 g/dl	314	106 (33.8)	51	11 (21.6)	365	117 (32.1)
Total	877	300 (34.2)	85	24 (28.2)	962	324 (33.7)
Restrictive group						
Hb < 7 g/dl	143	60 (42.0)	5	5 (100.0)	148	65 (43.9)
7 g/dl < Hb ≤ 7.5 g/dl	235	97 (41.3)	21	14 (66.7)	256	111 (43.4)
7.5 g/dl < Hb ≤ 8 g/dl	64	28 (43.8)	148	42 (28.4)	212	70 (33.0)
8 g/dl < Hb ≤ 8.5 g/dl	21	8 (38.1)	150	50 (33.3)	171	58 (33.9)
Hb ≥ 8.5 g/dl	3	2 (66.7)	154	41 (26.6)	157	43 (27.4)
Total	466	195 (41.9)	478	152 (31.8)	944	347 (36.8)

Hb, haemoglobin.
Percentages are row percentages, e.g. 89/205 = 43.4%.

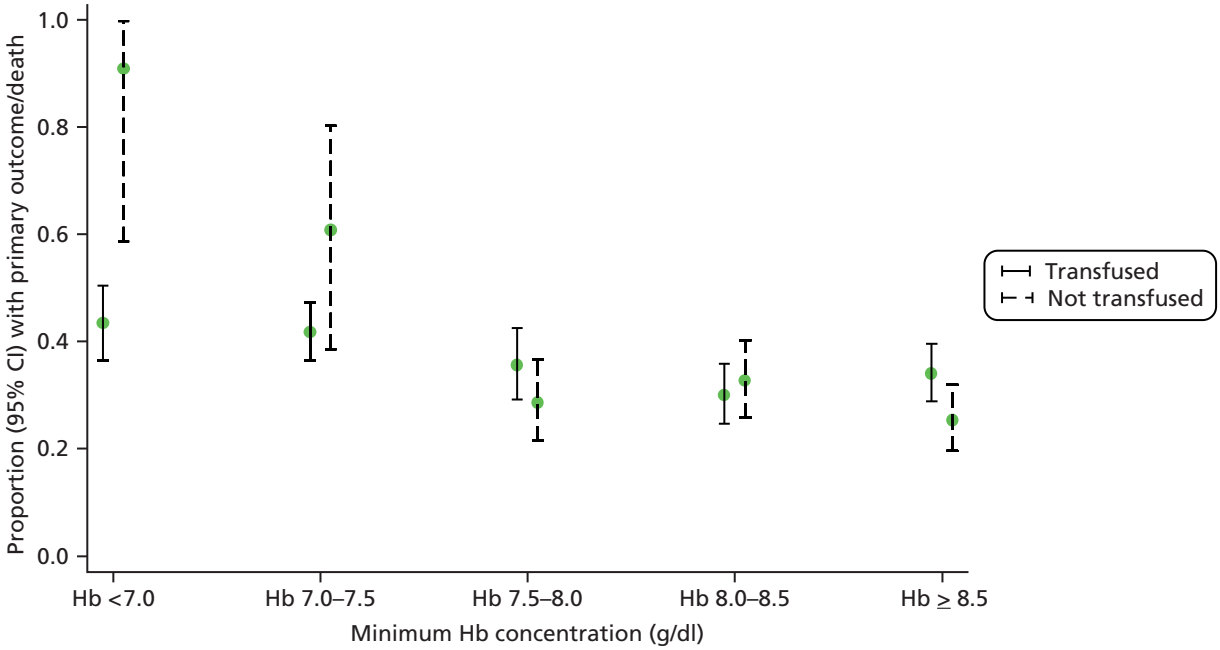


FIGURE 24 Relationship between red blood cell transfusion status, minimum haemoglobin concentration and primary outcome/death.
Hb, haemoglobin.

A number of observations can be made from *Table 51* and *Figure 24*.

- At haemoglobin levels below 7.5 g/dl it is difficult to assess the role of transfusion because almost all such participants (540/574; 94.1%) were transfused; however, there is some evidence of a reduced risk of outcome with transfusion. The overall risk at haemoglobin ≤ 7.5 g/dl was 229/540, 42.4% (95% CI 38.2% to 46.7%) for transfused participants and 24/34, 70.6% (95% CI 52.5% to 84.9%) for non-transfused participants. At haemoglobin levels > 7.5 g/dl there was generally a slightly increased risk of outcome associated with transfusion (with the exception of the 8.0 –8.5 g/dl group), although CIs overlap (see *Figure 24*).
- The reduced risk of outcome with increasing haemoglobin for the entire population is observed separately within transfused and non-transfused participants.
- Examining the difference in risk of the outcome in transfused and non-transfused groups in the liberal threshold stratum only is not very informative because most participants in this stratum were transfused. Within the group of transfused participants there is a general trend for the risk of outcome to decrease with increasing haemoglobin. The overall proportion of non-transfused participants experiencing the outcome in the liberal threshold stratum (28.2%) is slightly lower than the overall proportion across both transfusion threshold strata (31.3%), although this is likely to be at least partially attributable to the fact that non-transfused participants in the liberal stratum (arising mainly owing to non-adherence with the study protocol) are likely to have been healthier participants.
- For participants in the restrictive threshold stratum, there is again a general trend within both transfused and non-transfused participants for the risk of the outcome to decrease with increasing haemoglobin. Similarly, the risk of the outcome appears to reduce among participants transfused at haemoglobin ≤ 7.5 g/dl (although numbers of non-transfused participants are small) and to increase among participants transfused at haemoglobin > 7.5 g/dl (again, arising mainly owing to non-adherence with the study protocol). Outcome event rates for non-transfused participants in the restrictive threshold stratum are similar to the rates for both strata combined, but somewhat higher for transfused participants (except at low haemoglobin levels).

Conventionally adjusted statistical models

As described in *Chapter 2*, *Observational analyses*, separate models have been fitted with (1) red blood cell transfusion after randomisation and before the primary outcome or censoring and (2) haemoglobin < 8 g/dl after randomisation and before the pre-primary outcome or censoring as explanatory variables, adjusting for confounders. Models for post-randomisation red blood cells are described in *Table 52*. Three models are fitted with red blood cells as a categorical variable, an ordinal variable (i.e. fitting the five-level variable as a continuous variable) and a binary variable (i.e. any vs. no red blood cell transfusions).

From *Table 52*, the best fitting model in terms of deviance is the ordinal model and all models fit well in terms of residual and leverage plots and goodness-of-fit tests. All three models suggest a clear dose–response relationship of increased odds of outcome associated with increasing numbers of red blood cell transfusions; for example, the ordinal model suggests increased odds of outcome of 12% (95% CI 3% to 21%) associated with an increase of one level in the post-randomisation red blood cells variable. The odds of outcome were also significantly increased by transfusion of pre-randomisation red blood cells (OR 1.64, 95% CI 1.31 to 2.05).

The ordinal model from *Table 52* was refitted separately within each transfusion threshold stratum (*Table 53*). Associations are similar to those identified in *Table 52*, although there is some evidence of a slightly stronger relationship between pre-randomisation red blood cells and outcome in the liberal threshold stratum and, conversely, between cardiac procedure and outcome in the restrictive threshold stratum.

Models for post-randomisation haemoglobin levels are described in *Table 54*. Two models are fitted with haemoglobin level as a continuous or binary variable (< 7.5 g/dl vs. ≥ 7.5 g/dl).

TABLE 52 Conventionally adjusted models of the effect of red blood cell transfusions on the primary outcome/death

Explanatory variables	Model 1: categorical red blood cells		Model 2: ordinal red blood cells		Model 3: binary red blood cells	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Post-randomisation red blood cell units (before primary outcome)						
0	Reference group	0.0900	1.12 (1.03 to 1.21)	0.0089	Reference group	0.0280
1	1.17 (0.90 to 1.51)				1.28 (1.03 to 1.60)	
2	1.36 (1.02 to 1.81)					
3–4	1.27 (0.92 to 1.76)					
≥ 5	1.70 (1.09 to 2.63)					
Pre-randomisation red blood cells	1.64 (1.31 to 2.05)	< 0.0001	1.64 (1.31 to 2.05)	< 0.0001	1.67 (1.33 to 2.08)	< 0.0001
Logistic EuroSCORE	1.27 (1.10 to 1.46)	0.0008	1.27 (1.10 to 1.46)	0.0008	1.28 (1.11 to 1.47)	0.0005
Cardiac procedure						
CABG	Reference group	0.0230	Reference group	0.0200	Reference group	0.0170
Valve	0.88 (0.67 to 1.14)		0.88 (0.67 to 1.14)		0.88 (0.67 to 1.14)	
CABG + valve	1.35 (1.01 to 1.79)		1.35 (1.02 to 1.80)		1.36 (1.02 to 1.82)	
Other	1.00 (0.68 to 1.46)		1.00 (0.68 to 1.46)		1.01 (0.69 to 1.49)	

The deviances of the models are: model 1 (categorical red blood cells): 2325.4; model 2 (ordinal red blood cells): 2326.6, change in deviance from model 1 = 1.15 (3 degrees of freedom), *p*-value 0.76; model 3 (binary red blood cells): 2328.6, change in deviance from model 1 = 3.21 (3 degrees of freedom), *p*-value 0.36.

TABLE 53 Conventionally adjusted models of the effect of red blood cell transfusions on the primary outcome/death, by transfusion threshold stratum

	Restrictive threshold stratum		Liberal threshold stratum	
Explanatory variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Post-randomisation (pre-primary outcome) red blood cells – ordinal variable	1.19 (1.06 to 1.35)	0.0042	1.13 (0.99 to 1.28)	0.072
Any pre-randomisation red blood cells	1.39 (1.01 to 1.93)	0.046	1.89 (1.38 to 2.59)	0.0001
Logistic EuroSCORE	1.24 (1.02 to 1.52)	0.035	1.32 (1.09 to 1.60)	0.0047
Cardiac procedure				
CABG	Reference group	0.047	Reference group	0.380
Valve	0.92 (0.64 to 1.33)		0.84 (0.57 to 1.22)	
CABG + valve	1.59 (1.06 to 2.41)		1.18 (0.79 to 1.77)	
Other	1.05 (0.62 to 1.79)		0.98 (0.56 to 1.70)	

TABLE 54a Conventionally adjusted models of the effect of minimum haemoglobin level on the primary outcome/death: continuous minimum haemoglobin level

Explanatory variables	OR (95% CI)	*p*-value
Post-randomisation (pre-primary outcome) haemoglobin[a]		
CABG participants	0.92 (0.75 to 1.14)	< 0.0001[b]
Valve participants	0.62 (0.48 to 0.79)	
CABG + valve participants	0.51 (0.38 to 0.68)	
Other participants	0.68 (0.44 to 1.04)	
Pre-operative haemoglobin	0.91 (0.85 to 0.98)	0.0094
Logistic EuroSCORE	1.34 (1.16 to 1.54)	< 0.0001
Females	0.77 (0.61 to 0.97)	0.0250
CABG, at haemoglobin = 8 g/dl	Reference group	0.0600[c]
Valve, at haemoglobin = 8 g/dl	0.84 (0.64 to 1.10)	
CABG + valve, at haemoglobin = 8 g/dl	1.26 (0.93 to 1.69)	
Other, at haemoglobin = 8 g/dl	1.04 (0.70 to 1.55)	

One outlier has been excluded from all models.
The deviances of the models are: model a (continuous haemoglobin): 2298.1; model b (binary haemoglobin): 2303.8.
a This relationship is described graphically in *Figure 25*.
b *p*-value from a test of haemoglobin + haemoglobin by operation type.
c *p*-value from a test of operation type (with haemoglobin centred at 8 g/dl).

TABLE 54b Conventionally adjusted models of the effect of minimum haemoglobin level on the primary outcome/death: binary minimum haemoglobin level

Explanatory variables	OR (95% CI)	*p*-value
Post-randomisation haemoglobin ≥ 7.5g/dl (vs. < 7.5g/dl)		
CABG participants	0.89 (0.63 to 1.26)	< 0.0001[a]
Valve participants	0.51 (0.35 to 0.75)	
CABG + valve participants	0.37 (0.23 to 0.58)	
Other participants	0.47 (0.23 to 0.93)	
Pre-operative haemoglobin (continuous)	0.90 (0.84 to 0.97)	0.0044
Logistic EuroSCORE	1.33 (1.16 to 1.54)	0.0001
Females	0.78 (0.62 to 0.99)	0.0380
CABG, at haemoglobin ≥ 7.5 g/dl	Reference group	0.2200[b]
Valve, at haemoglobin ≥ 7.5 g/dl	0.76 (0.55 to 1.04)	
CABG + valve, at haemoglobin ≥ 7.5 g/dl	1.04 (0.73 to 1.47)	
Other, at haemoglobin ≥ 7.5 g/dl	0.89 (0.56 to 1.42)	
CABG, at haemoglobin ≥ 7.5 g/dl	Reference group	0.0018[c]
Valve, at haemoglobin ≥ 7.5 g/dl	1.33 (0.86 to 2.05)	
CABG + valve, at haemoglobin ≥ 7.5 g/dl	2.52 (1.57 to 4.06)	
Other, at haemoglobin ≥ 7.5 g/dl	1.70 (0.89 to 3.25)	

One outlier has been excluded from all models.
The deviances of the models are: model a (continuous haemoglobin): 2298.1; model b (binary haemoglobin): 2303.8.
a *p*-value from a test of haemoglobin ≥ 7.5 + haemoglobin ≥ 7.5 by operation type.
b *p*-value from a test of operation type + haemoglobin ≥ 7.5 by operation type.
c *p*-value from a test of operation type.

All models fit well in terms of residual and leverage plots and goodness-of-fit tests. For both models, an interaction between post-randomisation haemoglobin and cardiac procedure was statistically significant and, therefore, interpretation of the relationship between haemoglobin and outcome is complex. The effect of haemoglobin for each cardiac procedure is given in *Table 54*, along with the effect of the different cardiac procedures (compared with CABG surgery) at an approximately median haemoglobin value of 8 g/dl (see *Table 54a*). To visualise this relationship, marginal plots of the haemoglobin effect for different cardiac procedures (from the continuous model) averaged across the other covariates are given in *Figure 25*.

There is evidence of a haemoglobin effect for the non-CABG surgery participants – an increase in haemoglobin of 1 g/dl reduces the odds of outcome (valve surgery: OR 0.62, 95% CI 0.48 to 0.79; CABG and valve surgery: OR 0.51, 95% CI 0.38 to 0.68; other procedures: OR 0.68, 95% CI 0.44 to 1.04), see *Table 54* and *Figure 25*. For CABG participants, there is little evidence of any haemoglobin effect (OR 0.92, 95% CI 0.75 to 1.14). Similarly, the binary model suggests reduced odds of outcome associated with haemoglobin ≥ 7.5 g/dl for non-CABG participants (valve surgery: OR 0.51, 95% CI 0.35 to 0.75; CABG and valve surgery: OR 0.37, 95% CI 0.23 to 0.58; other procedures: OR 0.47, 95% CI 0.23 to 0.93) but little evidence of any effect for CABG participants (OR 0.89, 95% CI 0.63 to 1.26).

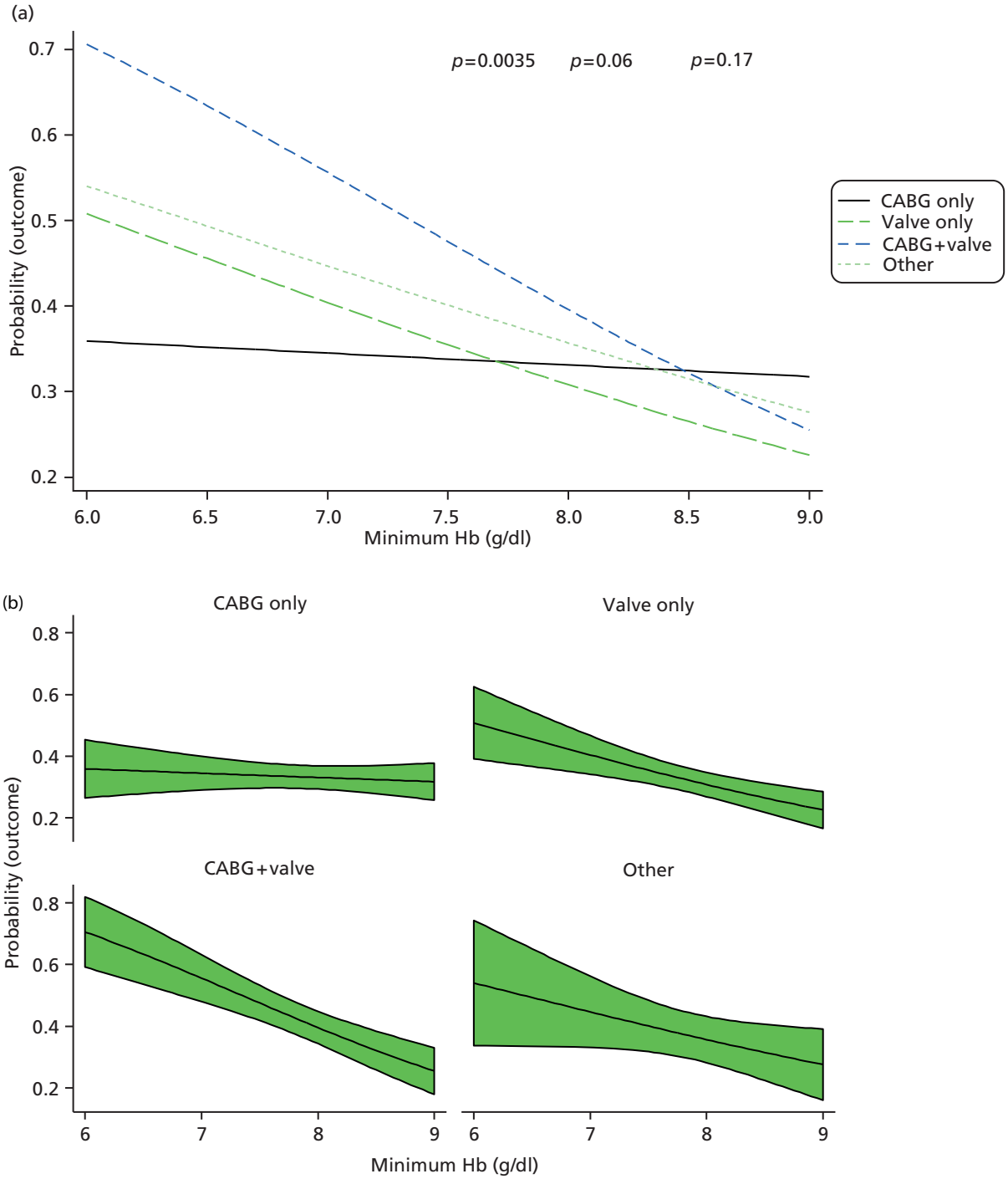


FIGURE 25 Marginal plots of the effect of minimum haemoglobin on primary outcome/death for each cardiac procedure type.
(a) Without CIs, *p*-values represent the operation type effect at three different haemoglobin levels.
(b) With CIs.
Hb, haemoglobin.

The effect of cardiac procedure is estimated at various haemoglobin levels in both models. In the continuous model, cardiac procedure was found to have greater effect at lower haemoglobin levels (see *Figure 25*). Similarly, in the binary model the effect of cardiac procedure is greater for haemoglobin < 7.5 g/dl participants than haemoglobin ≥ 7.5 g/dl participants. In both the continuous and binary models, a reduced odds of outcome was found with increased pre-operative haemoglobin (continuous model OR 0.91, 95% CI 0.85 to 0.98), and increased odds of outcome associated with both increased logistic EuroSCORE (continuous model OR 1.34, 95% CI 1.16 to 1.54) and sex (continuous model OR 0.77, 95% CI 0.61 to 0.97).

The continuous model from *Table 54* was refitted separately within each transfusion threshold stratum (*Table 55*).

The effect of post-randomisation haemoglobin was remarkably similar in the two transfusion threshold strata; the equivalent marginal plots are given in *Figure 26*. Pre-operative haemoglobin had a greater effect on the odds of outcome in the restrictive threshold stratum and EuroSCORE had a greater effect in the liberal threshold stratum.

TABLE 55 Conventionally adjusted models of the effect of minimum haemoglobin level on the primary outcome/death, by transfusion threshold stratum

	Restrictive group		Liberal group	
Explanatory variables	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Post-randomisation haemoglobin				
CABG participants	0.91 (0.67 to 1.23)	0.0029	0.94 (0.68 to 1.29)	0.0024
Valve participants	0.63 (0.43 to 0.93)		0.59 (0.41 to 0.85)	
CABG + valve participants	0.52 (0.34 to 0.79)		0.54 (0.35 to 0.84)	
Other participants	0.67 (0.37 to 1.22)		0.69 (0.36 to 1.32)	
Pre-operative haemoglobin	0.84 (0.76 to 0.94)	0.0013	0.98 (0.89 to 1.09)	0.72
Logistic EuroSCORE	1.23 (1.00 to 1.51)	0.049	1.47 (1.21 to 1.80)	0.0001
Females	0.82 (0.59 to 1.13)	0.22	0.72 (0.52 to 1.01)	0.054
CABG, at haemoglobin = 8 g/dl	Reference group	0.16	Reference group	0.59
Valve, at haemoglobin = 8 g/dl	0.83 (0.55 to 1.26)		0.87 (0.59 to 1.28)	
CABG + valve, at haemoglobin = 8 g/dl	1.44 (0.90 to 2.30)		1.16 (0.77 to 1.74)	
Other, at haemoglobin = 8 g/dl	1.09 (0.61 to 1.97)		1.02 (0.58 to 1.79)	

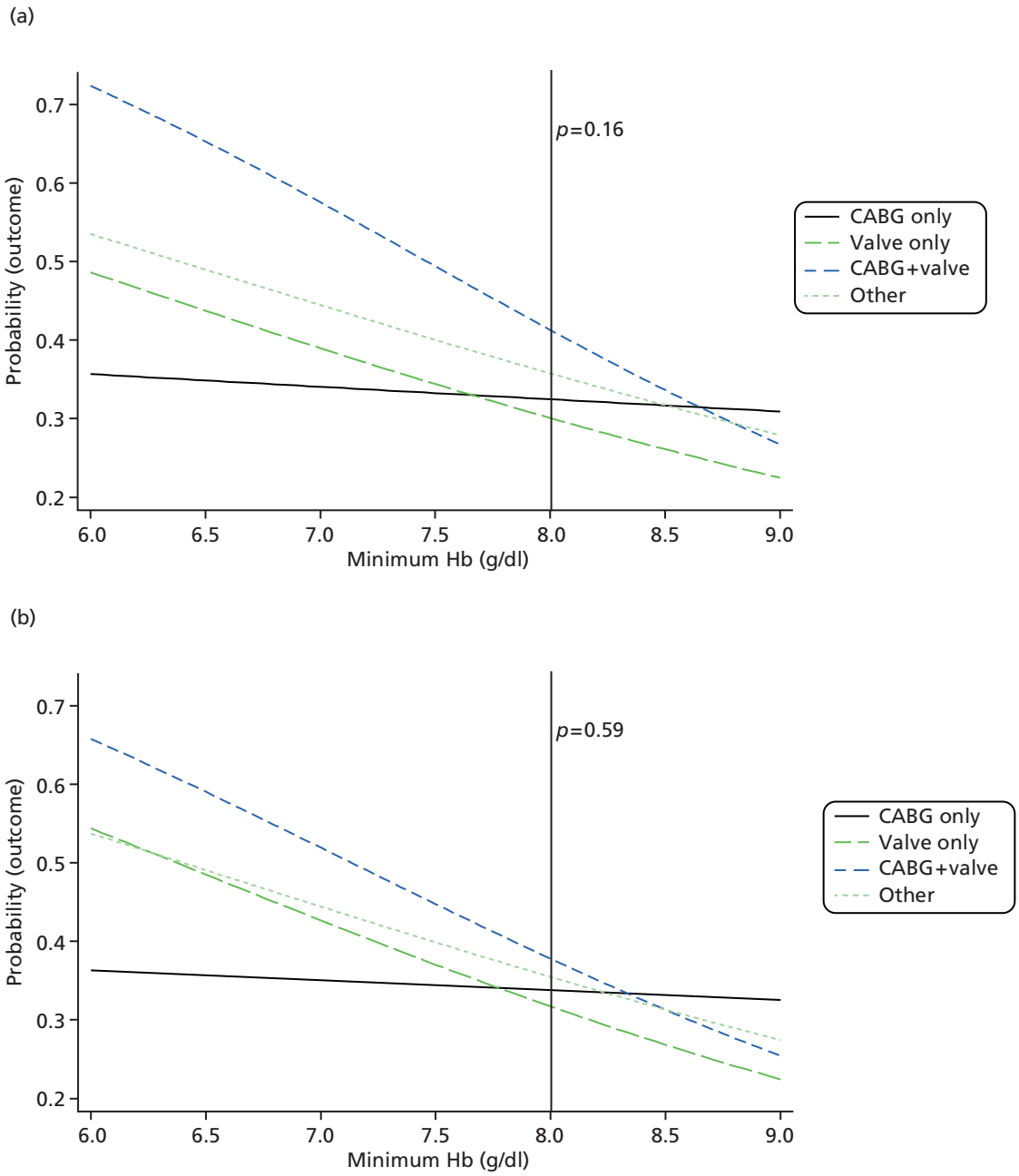


FIGURE 26 Marginal plots of the effect of minimum haemoglobin on primary outcome/death for each cardiac procedure type, by transfusion threshold stratum. *p*-values represent tests of the operation type effect at a haemoglobin level of 8.0 g/dl in each transfusion threshold stratum.
(a) Restrictive group.
(b) Liberal group.
Hb, haemoglobin.

Instrumental variable analysis

The assumptions of IV analysis[59] and why we believe that the assumptions are met in our analyses are described below.

- The instrument (randomised allocation) is associated with the exposure (post-randomisation red blood cell units ***or*** post-randomisation haemoglobin); if a regression of the instrument on the exposure is performed, a *F*-statistic of > 10 is typically used as a cut-off criterion, with values ≤ 10 indicating a weak instrument. There is evidence of a strong relationship between each of the exposure variables and randomised allocation (*Table 56*). Furthermore, *F*-statistics from the relevant univariate regression models are as follows: (1) a log-linear model regressing randomised allocation on the ordinal transfusion variable gave a RR of 0.53, 95% CI 0.49 to 0.58; *F*-statistic 238.8; and (2) a linear regression of randomised allocation on post-randomisation haemoglobin gave a mean difference between groups of –0.44, 95% CI –0.50 to –0.38; *F*-statistic 181.5.
- The instrument is independent of confounders between exposure and outcome. We consider this assumption to be met by virtue of the instrument being randomised allocation; there is no evidence of an association between randomised allocation and any variables (other than haemoglobin and red blood cell transfusions).
- The instrument is independent of the outcome, given the exposure and confounders between the exposure and the outcome. Again we consider this assumption to be met as the instrument is randomised allocation.

Results from IV models are given in *Table 57*. In terms of post-randomisation red blood cells, both models show no statistically significant effect of transfusion. If anything, effect estimates indicate reductions in risk of outcome with transfusion (RR 0.89, 95% CI 0.75 to 1.06, for the ordinal red blood cell transfusion model and RR 0.78, 95% CI 0.53 to 1.14, for the binary predictor, i.e. any vs. no red blood cell transfusion). It is interesting to compare these estimates with the main trial ITT estimate between the randomised groups

TABLE 56 Univariate relationships between (1) red blood cell transfusions and (2) minimum haemoglobin level, and transfusion threshold stratum

Transfusions/haemoglobin levels	Restrictive group ($n = 1000$)	Liberal group ($n = 1003$)
Post-randomisation (pre-primary outcome) red blood cell transfusions, *n* (%)		
None	516 (51.6)	106 (10.6)
One	211 (21.1)	379 (37.8)
Two	142 (14.2)	268 (26.7)
Three to four	94 (9.4)	176 (17.6)
Five or more	37 (3.7)	74 (7.4)
Post-randomisation (pre-primary outcome) minimum haemoglobin, *n* (%)		
Hb < 7 g/dl	153 (15.3)	71 (7.1)
7 < Hb ≤ 7.5 g/dl	267 (26.8)	104 (10.4)
7.5 < Hb ≤ 8 g/dl	226 (22.7)	157 (15.7)
8 < Hb ≤ 8.5 g/dl	186 (18.6)	289 (28.8)
Hb ≥ 8.5 g/dl	166 (16.6)	382 (38.1)

Hb, haemoglobin.

TABLE 57 Estimates of the effect of red blood cell transfusion/minimum haemoglobin effect on primary outcome/death from four IV models

Instrument used	RR (95% CI)	*p*-value
Model 1: post-randomisation red blood cells as an ordinal variable	0.89 (0.75 to 1.06)	0.19
Model 2: post-randomisation red blood cells as a binary variable (any transfusion vs. none)	0.78 (0.53 to 1.14)	0.20
Model 3: post-randomisation haemoglobin as a continuous variable	0.83 (0.64 to 1.08)	0.17
Model 4: post-randomisation haemoglobin as a binary variable (haemoglobin ≥ 7.5 g/dl vs. < 7.5 g/dl)	0.71 (0.43 to 1.19)	0.19

(inverted, i.e. comparing liberal 'transfused' to restrictive 'not transfused' participants), OR 0.90 (95% CI 0.74 to 1.10; $p = 0.30$). The estimates are remarkably similar despite the fact that they are estimating different effects (ITT estimate of effect of transfusion threshold on primary outcome only in the context of non-adherence in the trial compared with the effect of red blood cell transfusion on primary outcome or death on participants who were actually transfused, adjusted for confounding, in the IV analysis).

For post-randomisation haemoglobin, both models show no statistically significant effect with effect estimates indicating reductions in risk of outcome with increasing haemoglobin (RR 0.83, 95% CI 0.64 to 1.08, for the model with haemoglobin fitted as a continuous variable, and RR 0.71, 95% CI 0.43 to 1.19, for the model with haemoglobin fitted as a binary variable comparing haemoglobin levels ≥ 7.5g/dl with < 7.5g/dl). As anticipated, the CIs around effect estimates are relatively wide in all of the IV models.

Next steps

The main limitation of the analyses covered in this section is their restriction to investigating either the effect of red blood cell transfusion or the effect of haemoglobin level. They do not address the combined effects of these factors, preventing us from answering questions such as 'at what haemoglobin threshold does the receipt of transfusion become beneficial?'. This question is not straightforward to answer because red blood cell transfusion is inevitably associated with haemoglobin level and the lowest haemoglobin level experienced by a patient does not necessarily precede transfusion.

An extension to these analyses that may address this issue is to perform analyses restricted to groups of participants that breach a certain haemoglobin threshold (e.g. 7.5 g/dl or 8 g/dl) and then compare outcomes for participants transfused and not transfused at a haemoglobin below that level. Such an analysis could be performed at a small number of different haemoglobin thresholds to estimate the effect of transfusion at different thresholds of haemoglobin.

Age of blood

Descriptive analyses

The age of each red blood cell unit transfused was unable to be retrieved for a relatively large proportion of units. Of the 3104 units transfused post-randomisation but prior to the time of the primary outcome occurring or censoring, the age was unobtainable for 945 units (30.4%). In terms of participants, of the 1381 participants transfused one or more unit, 581 (42.1%) had one or more unit with unknown age. The volume of blood transfused was a strong predictor of missing age of blood for one or more of the units transfused (*Table 58*).

For the purposes of initial descriptive analyses, participants have been grouped into four categories:

(a) Transfused one or more unit older than 21 days ($n = 527$).
(b) Transfused, but received no units older than 21 days ($n = 402$).
(c) Transfused, but unknown if any units were received older than 21 days ($n = 452$). [Note: this number is lower than the number of participants quoted above as having one or more unit with unknown age ($n = 581$) because any participants transfused multiple units with one or more unit older than 21 days will be classified in group (a) above, regardless of any other units with unknown age.]
(d) Not transfused any red blood cells ($n = 622$).

Characteristics and outcomes of participants according to these categories are given in *Tables 59* and *60*.

The three groups of transfused participants (older blood, younger blood and unknown) were of similar ages, but compared with those only transfused younger blood, participants transfused older blood were less likely to be male (71.6% vs. 66.4%), had higher average logistic EuroSCORE [median 4.3 (IQR 2.4–8.0) vs. 3.6 (IQR 2.2–6.6)] and were less likely to have had CABG surgery (37.4% vs. 44.5%). It should be noted that some of these apparent associations are likely to have arisen from confounding; for example, female participants may have been more likely to be given older blood because they were more likely to have multiple red blood cell units transfused, increasing the risk of having an older unit transfused.

Rates of pre-randomisation red blood cell transfusion were lower in the group with unknown age of blood (22.8%) than the other three groups (older blood 27.1%, younger blood 26.9% and no blood 25.7%). The number of post-randomisation red blood cells transfused was, on average, higher in those transfused older blood (66.2% transfused two or more units) and unknown age (61.7% transfused two or more units) than those transfused only younger blood (40.5% transfused two or more units). In addition, participants transfused older blood were more likely to have been given non-red blood cell blood products

TABLE 58 Missing age of blood according to number of red blood cell units transfused

Transfusions	Number of participants	One or more units with missing age, *n* (%)
Post-randomisation (pre-primary outcome) red blood cell transfusions		
None	621	0 (0.0)
One	591	174 (29.4)
Two	409	170 (41.6)
Three to four	271	151 (55.7)
Five or more	111	86 (77.5)

TABLE 59 Characteristics of participants by age of red blood cells transfused

Characteristic	Transfused one or more unit older than 21 days (*N* = 527)	Transfused, but received no units older than 21 days (*N* = 402)	Transfused, but unknown if any units were received older than 21 days (*N* = 452)	Not transfused any red blood cells (*N* = 622)
Cardiac history				
Additive EuroSCORE,[a] median (IQR)	5.0 (4.0–7.0)	5.0 (3.0–7.0)	6.0 (4.0–7.0)	5.0 (3.0–7.0)
Logistic EuroSCORE,[a] median (IQR)	4.3 (2.4–8.0)	3.6 (2.2–6.6)	4.5 (2.6–7.5)	3.7 (2.0–6.6)
NYHA class, *n*/*N* (%)				
I	138/505 (27.3)	104/393 (26.5)	100/450 (22.2)	151/603 (25.0)
II	208/505 (41.2)	187/393 (47.6)	199/450 (44.2)	291/603 (48.3)
III	143/505 (28.3)	97/393 (24.7)	142/450 (31.6)	143/603 (23.7)
IV	16/505 (3.2)	5/393 (1.3)	9/450 (2.0)	18/603 (3.0)
CCS class, *n*/*N* (%)	191/510 (37.5)	139/395 (35.2)	147/449 (32.7)	241/608 (39.6)
No angina, *n*/*N* (%)				
I	103/510 (20.2)	72/395 (18.2)	84/449 (18.7)	103/608 (16.9)
II	121/510 (23.7)	108/395 (27.3)	121/449 (26.9)	176/608 (28.9)
III	73/510 (14.3)	52/395 (13.2)	83/449 (18.5)	73/608 (12.0)
IV	22/510 (4.3)	24/395 (6.1)	14/449 (3.1)	15/608 (2.5)
Coronary disease, *n*/*N* (%)				
None	172/525 (32.8)	110/400 (27.5)	144/450 (32.0)	194/616 (31.5)
Single vessel	66/525 (12.6)	46/400 (11.5)	56/450 (12.4)	57/616 (9.3)
Double vessel	66/525 (12.6)	55/400 (13.8)	63/450 (14.0)	98/616 (15.9)
Triple vessel	211/525 (40.2)	179/400 (44.8)	172/450 (38.2)	243/616 (39.4)
Not investigated	10/525 (1.9)	10/400 (2.5)	15/450 (3.3)	24/616 (3.9)
Disease in left main stem (> 50% stenosis), *n*/*N* (%)	78/520 (15.0)	66/398 (16.6)	60/446 (13.5)	100/613 (16.3)

TABLE 59 Characteristics of participants by age of red blood cells transfused (*continued*)

Characteristic	Transfused one or more unit older than 21 days (*N* = 527)	Transfused, but received no units older than 21 days (*N* = 402)	Transfused, but unknown if any units were received older than 21 days (*N* = 452)	Not transfused any red blood cells (*N* = 622)
Non-cardiac history				
Age (years), median (IQR)	70.7 (64.3–76.6)	70.5 (64.0–77.0)	70.9 (63.8–76.7)	69.5 (62.6–75.5)
Males, *n/N* (%)	350/527 (66.4)	288/402 (71.6)	295/452 (65.3)	440/622 (70.7)
BMI (kg/m^2),[b] mean (SD)	28.0 (5.0)	27.9 (4.8)	27.8 (4.7)	28.7 (5.1)
Urgent operative priority, *n/N* (%)	81/527 (15.4)	53/402 (13.2)	47/452 (10.4)	64/622 (10.3)
Diabetic, *n/N* (%)	104/527 (19.7)	86/402 (21.4)	89/452 (19.7)	120/622 (19.3)
Haemofiltration/dialysis, *n/N* (%)	8/526 (1.5)	4/402 (1.0)	4/451 (0.9)	3/622 (0.5)
CVA/TIA, *n/N* (%)	47/527 (8.9)	30/402 (7.5)	35/452 (7.7)	51/622 (8.2)
Pre-operative tests				
Haemoglobin (g/dl), mean (SD)	13.1 (1.5)	13.3 (1.5)	13.2 (1.5)	13.5 (1.4)
eGFR (ml/minute/1.73m^2),[c] median (IQR)	71.2 (54.4–91.9)	72.1 (55.7–90.4)	72.5 (54.7–91.6)	77.4 (61.3–96.9)
Intra-operative characteristics				
Duration of operation (hours),[d] median (IQR)	4.0 (3.2–5.2)	4.1 (3.4–5.0)	4.0 (3.5–5.0)	3.9 (3.3–4.9)
CPB used, *n/N* (%)	511/527 (97.0)	385/402 (95.8)	427/452 94.5)	580/621 (93.4)
Cardiac procedure, *n/N* (%)				
CABG only	197/527 (37.4)	179/402 (44.5)	166/452 (36.7)	274/622 (44.1)
Valve only	170/527 (32.3)	116/402 (28.9)	142/452 (31.4)	183/622 (29.4)
CABG + valve	111/527 (21.1)	82/402 (20.4)	108/452 (23.9)	97/622 (15.6)
Other	49/527 (9.3)	25/402 (6.2)	36/452 (8.0)	68/622 (10.9)
Tranexamic acid, *n/N* (%)	448/527 (85.0)	334/401 (83.3)	330/452 (73.0)	503/621 (81.0)
Trasylol, *n/N* (%)	17/515 (3.3)	15/398 (3.8)	16/402 (4.0)	23/579 (4.0)
Cell saver, *n/N* (%)	272/527 (51.6)	210/402 (52.2)	207/452 (45.8)	295/621 (47.5)
Blood loss at 4 hours (ml),[e] median (IQR)	274 (160–450)	260 (150–425)	290 (180–500)	210 (125–328)
Blood loss at 12 hours (ml),[f] median (IQR)	525 (350–850)	500 (325–800)	550 (350–865)	400 (290–600)

BMI, body mass index; CCS, Canadian Cardiovascular Society; CVA, cerebrovascular accident; NYHA, New York Health Association; TIA, transient ischaemic attack.

a Missing for 38 participants [14, 2, 8, 14 in each of the four groups (left to right across the table)].
b Missing for one participant [0, 0, 1, 0 in each of the four groups (left to right across the table)].
c Missing for two participants [0, 1, 1, 0 in each of the four groups (left to right across the table)].
d Missing for one participant [0, 0, 0, 1 in each of the four groups (left to right across the table)].
e Missing for three participants [0, 0, 1, 2 in each of the four groups (left to right across the table)].
f Missing for three participants [1, 0, 0, 2 in each of the four groups (left to right across the table)].

TABLE 60 Outcomes of participants by age of red blood cells transfused

Outcome	One + red blood cells > 21 days (*N* = 527)	No red blood cells > 21 days (*N* = 402)	Unknown red blood cells > 21 days (*N* = 452)	No red blood cell transfusions (*N* = 622)
Intra- and post-operative use of blood products				
Pre-randomisation red blood cell transfusion, *n/N* (%)	143/527 (27.1)	108/402 (26.9)	103/452 (22.8)	160/622 (25.7)
Post-randomisation (pre-primary outcome) red blood cell transfusions, *n/N* (%)				
No units	0/527 (0.0)	0/402 (0.0)	0/452 (0.0)	622/622 (100.0)
1 unit	178/527 (33.8)	239/402 (59.5)	173/452 (38.3)	0/622 (0.0)
2 units	172/527 (32.6)	107/402 (26.6)	130/452 (28.8)	0/622 (0.0)
3–4 units	124/527 (23.5)	48/402 (11.9)	99/452 (21.9)	0/622 (0.0)
> 4 units	53/527 (10.1)	8/402 (2.0)	50/452 (11.1)	0/622 (0.0)
FFP transfusions, *n/N* (%)	185/527 (35.1)	126/402 (31.3)	138/452 (30.5)	132/622 (21.2)
Platelet transfusions, *n/N* (%)	225/527 (42.7)	165/402 (41.0)	172/452 (38.1)	176/622 (28.3)
Cryoprecipitate transfusions, *n/N* (%)	68/527 (12.9)	34/402 (8.5)	56/452 (12.4)	43/622 (6.9)
Activated factor VII used, *n/N* (%)	5/527 (0.9)	2/402 (0.5)	0/452 (0.0)	5/622 (0.8)
Beriplex used, *n/N* (%)	24/527 (4.6)	20/402 (5.0)	21/452 (4.6)	35/622 5.6)
Minimum haemoglobin (g/dl),[a] median (IQR)	7.8 (7.1–8.4)	7.9 (7.3–8.5)	7.7 (7.1–8.3)	8.3 (7.8–8.6)
Primary outcome,* n/N *(%)				
Overall primary outcome	188/511 (36.8)	139/390 (35.6)	147/441 (33.3)	174/564 (30.9)
Infectious event	138/501 (27.5)	106/387 (27.4)	107/439 (24.4)	127/563 (22.6)
Sepsis	125/515 (24.3)	92/396 (23.2)	94/449 (20.9)	113/605 (18.7)
Wound infection	21/486 (4.3)	27/375 (7.2)	24/436 (5.5)	29/560 (5.2)
Ischaemic event	89/522 (17.0)	62/399 (15.5)	62/450 (13.8)	82/611 (13.4)
Permanent stroke	11/517 (2.1)	7/398 (1.8)	7/448 (1.6)	7/611 (1.1)
Suspected MI	5/514 (1.0)	1/396 (0.3)	0/447 (0.0)	1/611 (0.2)
Gut infarction	1/514 (0.2)	0/396 (0.0)	3/448 (0.7)	3/611 (0.5)
AKI	75/519 (14.5)	55/398 (13.8)	58/450 (12.9)	74/611 (12.1)
Other trial outcomes				
All-cause mortality, *n/N* (%)	24/527 (4.6)	10/402 (2.5)	17/452 (3.8)	17/622 (2.7)
Significant pulmonary morbidity, *n/N* (%)	68/518 (13.1)	52/400 (13.0)	72/449 (16.0)	51/614 (8.3)
Duration of ICU/HDU stay (hours), median (IQR)	66.5 (24.5–117)	48.1 (23.5–97.0)	60.3 (26.4–99.3)	32.6 (11.3–76.1)
Duration of post-randomisation hospital stay (hours), median (IQR)	7.0 (6.0–11.0)	7.0 (5.0–10.0)	7.0 (6.0–11.0)	6.0 (4.0–9.0)
Composite outcome				
Primary outcome or death, *n/N* (%)	196/511 (38.4)	142/390 (36.4)	157/441 (35.6)	176/564 (31.2)

a Missing for two participants [0, 0, 0, 2 in each of the four groups (left to right across the table)].

than the other groups but there were no clear trends in average post-randomisation haemoglobin levels between the three groups of transfused participants.

In terms of trial outcomes, the primary outcome occurred in 36.8% of participants transfused older blood, 35.6% of participants transfused only younger blood, 33.3% of those with unknown age of blood and 30.9% of those not transfused. More participants died in the groups transfused older blood (4.6%) and with unknown age of blood (3.8%) than those transfused only younger blood (2.5%) and those not transfused (2.7%). Finally, the composite outcome of primary outcome or death occurred in 38.4% of participants transfused older blood, 36.4% of participants transfused younger blood only, 35.6% of those with unknown age of blood and 31.2% of those not transfused.

Next steps

The results from *Descriptive analyses* suggest some evidence of a weak association between older blood and poorer outcome, particularly in terms of mortality; however, a major limitation is that no adjustment for confounding has been performed. Therefore, it is unclear from these descriptive analyses whether or not any differences observed are actually due to other factors, for example, the fact that participants transfused older blood received, on average, more red blood cells than those transfused only younger blood.

A further limitation of this work is that blood group was unfortunately not collected in the study and is not considered retrievable. It has been suggested that this could be an important confounding factor, especially if age of blood is defined in terms of giving older vs. younger blood. The rationale for this view is that the turnover of blood stores varies according to the blood group of the donated blood; for example, participants with rare blood groups may be more likely to have older blood.[60]

Therefore, an obvious next step would be to fit multivariate models addressing the confounding. This has not been done owing to the number of missing data on age of blood, which is of a sufficiently high level that any analyses ignoring missing data ('complete-case analyses') will be inefficient and possibly biased. Addressing this missing data problem is not straightforward. Multiple imputation techniques are most commonly used as they are considered most appropriate and flexible.[61] Imputation (and, therefore, subsequent modelling) could be implemented at the red blood cell unit level (i.e. by imputing the age of each unit of red blood cells) or at level of a participant (e.g. imputing whether a participant received any old blood or not). Further work is required to address the issue of whether imputation should be implemented at the red blood cell unit level or at the participant level.

Another consideration is alternative ways of defining age of blood at the participant level (as described in the methods), including the age of the oldest red blood cell transfused, the mean age of all red blood cells, the use of any blood older than 14 days, and the number or percentage of red blood cells given that are older than 14 or 21 days. These approaches will be affected to different extents by missing data; therefore, we do not intend to proceed with this until we have addressed the missing data problem described above.

Chapter 8 Discussion

Main findings: study conduct

Recruitment

Recruitment was slower than expected and the duration of recruitment had to be extended in order to reach the target sample size. Issues affecting recruitment have been described in *Chapter 3*, *Recruitment*. Throughout the trial the rate of recruitment remained frustratingly resistant to any actions the co-ordinating team took to increase it. It did not appear to increase as additional centres were recruited, nor when mid-term site visits were carried out to encourage centre staff to share good practice tips gleaned from the best recruiting centres and to discuss local circumstances that were perceived to be limiting recruitment. However, the UK Comprehensive Research Network made TITRe2 a special focus for their efforts and this is likely to explain the increase in recruitment in the second half of 2011.

Non-adherence to the allocated threshold

We identified non-adherence as a key issue at the outset and were able to put in place appropriate data collection (although time-consuming) to differentiate non-adherence into mild, moderate and severe. The importance of non-adherence was reinforced by the DMEC, both in terms of the threat to the overall power of the trial and also the possibility of differential non-adherence by group. The central trial team reported adherence to the DMEC regularly.

Even with our extreme awareness of the problem and a large investment in data collection, non-adherence was still prevalent in the trial. Fortunately, severe non-adherence occurred for only a small number of participants (9.7% in the restrictive group and 6.2% in the liberal group) and, therefore, good separation was maintained between groups with respect to red blood cells transfused and haemoglobin levels. In calculating the initial target sample size we assumed that no more than 35% of participants in the restrictive group and no less than 74% of participants in the liberal group would be transfused. Although the absolute rates differed, the transfusion rates (53% and 92%, respectively) achieved this separation in the rate of transfusion.

In a similar way to the rate of recruitment, non-adherence was resistant to our efforts to reduce its incidence through a continuous education and awareness campaign and, latterly, detailed feedback to centres about specific non-adherent instances. This resistance perhaps reflects the limited ability of these initiatives to overcome staff shortages on the ground, which was the factor that we believed to be mainly responsible. This leads to the question of whether or not we would advocate monitoring non-adherence in this level of detail, to which our answer is unequivocally yes. Despite non-adherence not being straightforward to predict, knowledge of non-adherence is vital. Even if non-adherence has been considered when justifying the target sample size, there is still a need to monitor its incidence carefully and ensure it is in line with the assumptions made.

The main drawback of trying to measure non-adherence is the demanding data collection required and, if we were to design the study again, we would investigate more streamlined methods of capturing these data, for example downloads of routine data from ICU software now commonly being used to manage patient care. Many reasons for non-adherence were missing and, although these were queried, relevant information was often difficult to retrieve. In addition, we believe the category ‘oversight’ was used as a default reason when a clinician was not asked to justify non-adherence at the time it occurred.

It is difficult to compare non-adherence rates from TITRe2 to rates observed in previous trials that randomised patients to different transfusion strategies. Two of the earliest studies defined non-adherence either only in terms of withheld transfusions[62] or extra transfusions.[37] The former study (838 participants) reported non-adherence for six participants (1.4%) in the restrictive group and 18 participants (4.3%) in

the liberal group, and the latter (the largest study in cardiac surgery patients to date[37]) reported four cases (all in the restrictive group) of non-adherence from 502 participants. Both studies reported markedly lower non-adherence rates than TITRe2, although comparisons are not sensible owing to the different definitions used, differences in the populations randomised (both trials included participants who did not breach the liberal threshold) and the limited information about non-adherence that was reported in both studies.

Two more recent studies considered non-adherence both in terms of extra and withheld transfusions. The FOCUS trial[13] investigated transfusion strategies following hip surgery; severe protocol deviations that were comparable with our definitions were reported in 9.0% of participants in the liberal strategy group and 5.6% in the restrictive strategy group. These rates are similar to our rates of severe non-adherence, although the differences between the randomised groups are in the opposite direction to TITRe2. This could be due to the different hypotheses being addressed as FOCUS hypothesised that giving transfusion would benefit patients. The second study was a pilot RCT of adherence to transfusion thresholds in cardiac surgery;[38] it used non-adherence definitions most comparable to TITRe2 and comprised a similar population. Among the 50 participants recruited, post-operative non-adherence was reported as 18% in the ICU and 0% on the ward in the restrictive group, and 31% in ICU and 86% on the ward in the liberal group. As in TITRe2 for any non-adherence, rates were higher in the liberal group than the restrictive group. The rate in the liberal group was substantially higher than TITRe2.

We believe that we are the first researchers to identify and classify, in detail, non-adherence to a transfusion strategy in a complicated trial setting, in which both the timing of randomisation and intervention were not at a fixed point in time. Adherence remains a key issue in trials comparing restrictive and liberal transfusion strategies and this study has led to better understanding of potential motivations and mechanisms for different types of non-adherence. Some of this understanding can be generalised to other trials with complex interventions. In particular, vigilance and reminders appeared to be the most successful ways to avoid non-adherence. We noted that non-adherence was less common in centres with successful research infrastructures (e.g. a well organised NHS research department, recruiting to multiple NIHR portfolio studies, well-integrated team of research nurses with expertise in managing cardiac surgery patients) and a high throughput of patients. It is clear that having fewer, high-recruiting, sites as opposed to lots of low-recruiting sites is preferable, as the constant presence of trial participants on the ICU or the ward is one of the best reminders to staff. Even if increased vigilance results from higher staffing levels, it is unclear whether or not this is cost-effective. Trials can suffer a large amount of non-adherence and still deliver meaningful results, as we believe has been the case in TITRe2.

Higher-than-expected frequency of the primary outcome

The higher-than-expected frequency of the composite primary outcome and the dominance of less serious events such as sepsis and milder AKI were the most substantive issues experienced. On the one hand, the higher overall frequency meant that the trial had more statistical power than anticipated; however, on the other hand, the dominance by less serious events had the potential to undermine the interpretation of the primary outcome. The question of whether or not to revise the primary outcome was debated by the DMEC before an application was made to extend the scheduled period of recruitment. The DMEC recommended that neither the primary outcome nor the target sample size should be changed (see *Strengths and limitations*).

Main findings: study results

Summary of findings of the trial

The TITRe2 trial tested the hypothesis that a restrictive red blood cell transfusion threshold is superior to a liberal threshold after adult cardiac surgery, in terms of post-operative morbidity and health service costs. We refuted this hypothesis because we observed no difference in the primary composite outcome between the liberal and restrictive groups. Pre-planned subgroup analyses showed no differences, contrary to beliefs that 'at-risk' groups should be transfused at different haemoglobin thresholds.

We carried out a number of planned sensitivity analyses of the primary outcome in order to test the robustness of the primary analysis. When we designed the trial we decided to include participants transfused before randomisation, for example in the operating theatre, as the question the trial sought to answer applied as much to these patients as others. Nevertheless, we recognised that by doing so we might dilute any effect of randomisation as transfusion was the 'exposure' of interest and transfusion before randomisation would be distributed similarly. As hypothesised, when we excluded this subgroup in a sensitivity analysis, the effect estimate for the primary outcome moved away from the null, favouring the liberal threshold.

A second sensitivity analysis was planned because of the observation (in the pre-specified interim analysis) that the majority of the primary outcome events were either sepsis or AKI. We considered that a treatment effect for more 'serious' events would better reflect our original intention in formulating the composite outcome but did not hypothesise that the effect estimate would move. Therefore, we were surprised to find that effect estimate moved to towards the null.

Two other sensitivity analyses were designed to address uncertainty about the ascertainment of AKI events (see *Chapter 2*, *Sensitivity analyses*). We did not hypothesise a change in the magnitude of the treatment effect for either analysis. Excluding AKI events that may have been reported erroneously did not move the effect estimate; however, including additional AKI events that we suspected had been missed did move the effect estimate away from the null, again favouring the liberal threshold. Although we had not hypothesised such a shift, this finding was consistent with the imbalance of qualifying AKI events (both among AKI events that had been reported and AKI events that we suspected had been missed) across the two groups. The small difference in the overall primary outcome event rate (2%) arose because participants in the restrictive group had a 2% higher frequency of AKI events (14% vs. 12%). Including the additional AKI events approximately doubled their frequency in both groups (approximately 28% vs. 24%), increasing the overall difference in the primary outcome from 2% to 4%.

All-cause mortality was the only secondary outcome for which the treatment effect suggested a difference between groups, with more participants dying in the restrictive group. There were no differences in other secondary outcomes, including unexpected SAEs and SAEs that did not qualify for the primary outcome. In the course of peer review of a manuscript reporting the main outcome results, it was suggested that we should carry out (the same) sensitivity analyses for all-cause-mortality. This suggestion was made owing to the potential importance of a difference in mortality and the difficulty in quantifying uncertainty around the observed difference, given that it was one among several secondary outcomes. However, only two of the sensitivity analyses were applicable: first, excluding deaths occurring in the first 24 hours after randomisation and, second, excluding participants who had red blood cells transfused before randomisation. In both analyses, the magnitude of the treatment effect favouring a liberal threshold increased as hypothesised (and its nominal statistical significance was maintained despite both analyses having less power).

Interpreting secondary analyses is challenging when several statistical tests are carried out.[40] Nevertheless, the higher frequency of deaths in the restrictive group is a cause for serious concern. It is not clear how anaemia attributable to the restrictive threshold may have resulted in an increased number of deaths. The difference in haemoglobin between groups was modest (1 g/dl) and assessment of causes of death or SAEs that preceded death did not demonstrate cause and effect, although expecting to deduce a causal mechanism in this way may be unrealistic based on a small number of deaths in a setting in which death typically occurs after a series of AEs.

The TITRe2 trial compared two active interventions, both of which probably reflected usual care although in different centres. Safety is considered here in terms of a restrictive threshold compared with a liberal one. There was a similarly small non-significant difference, again favouring the liberal threshold, in the frequency of all SAEs not included in the primary outcome (35.7% and 34.2% of participants in the restrictive and liberal groups, respectively). The trial did not have adequate power to distinguish any difference in the types of SAEs between groups. The IV analysis estimating the effect of red blood cell

transfusion (after randomisation and before the occurrence of the primary outcome or censoring) also provided the most direct test of the safety of transfusion among participants who were transfused, finding no evidence at all that transfusion increased the risk of the primary outcome or death.

Three observational analyses were planned investigating the effects of exposure to red blood cell transfusion, post-operative anaemia and 'old' red blood cells (that had been stored for longer than average). The main reasons for doing these analyses were:

(a) to try to replicate our observational finding[2] and the findings of other observational studies,[63] about the risks of transfusion in the trial cohort
(b) to try to estimate the effect of transfusion at different levels of anaemia
(c) to try to replicate previous reports (e.g. Dzik[60] and Koch *et al.*[64]) regarding the risk of poor clinical outcome being attributable to red blood cells stored for longer than average
(d) to contrast effect estimates from analyses using conventional and IV methods to adjust for confounding (added when drafting the SAP when recognised the opportunity that the trial afforded to do IV analyses).

The rationale (a) above for analysis may appear odd given that the main finding of the trial did not support our original trial hypothesis about the superiority of a restrictive threshold. Nevertheless, it is interesting to contrast the findings from this conventionally adjusted analysis with our previous observational estimate and the main trial finding (remembering that Murphy *et al.*[2] compared any versus no transfusion rather than different transfusion thresholds). The conventionally adjusted analysis showed a dose–response relationship between the odds of the composite poor outcome and increasing red blood cell transfusion, as did the previous observational analysis for ischaemic and infectious events, although the gradient of the relationship was shallower in TITRe2. However, it is very difficult to reconcile the dose–response relationship with the main trial finding, which found no difference in the frequency of the composite primary outcome between groups which received substantially different average volumes of red blood cells, forcing us to conclude that this conventionally adjusted result is subject to residual confounding.

We successfully estimated the effect of anaemia in conventionally adjusted models in analysis (b) and the effect estimates were consistent with our expectation – that is, as the nadir haemoglobin increased, the odds of a poor outcome decreased. However, we were unable to investigate how nadir haemoglobin modified the effect of red blood cell transfusion because of the intrinsic link between red blood cell transfusion and haemoglobin level, and the unpredictability of the temporal relationship between transfusion and the lowest haemoglobin level experienced by a patient.

We were unable to investigate the effect of duration of storage of red blood cells [analysis (c)] because (1) the duration of storage was often missing and (2) we did not have access to information about the blood groups of red blood cell donors and recipients, a likely important confounder. Missing duration of storage of red blood cell units transfused was especially critical because the occurrence of such missing data for a participant was associated with the number of red blood cell units transfused. Any simple attempt to deal with these missing data, for example excluding participants who received any red blood cell unit with missing duration of storage, would almost certainly introduce bias. The implications of imputing duration of storage based on participants' characteristics are uncertain and subject to ongoing analyses.

The IV analysis of the effect of red blood cell transfusion (d) also generated a striking three-way contrast with the results of the conventionally adjusted analyses (a) and the main trial finding. The estimate from the IV analysis was consistent with the main trial finding but different from the conventionally adjusted estimate, implying again that the conventionally adjusted estimate was subject to residual confounding. The conventionally adjusted estimates of the effect of lowest post-operative haemoglobin experienced were complex to interpret, suggesting that the effect varied according to the operation that a participant was undergoing and that the anticipated increased risk from anaemia was mainly apparent for non-CABG operations. The IV analysis could not consider this interaction; it did not find a statistically significant

increase in the odds of a poor outcome from anaemia but the point estimates increased with increasing anaemia.

Instrumental variable analyses of trials in which the random allocation is not congruent with exposure to a particular intervention (typically owing to non-adherence) are often reported as estimating 'the effect of treatment among the treated'. To this extent, the IV analysis provides the most direct estimate possible of the effect of red blood cell transfusion. Although the CIs are wide (and are unadjusted for nadir haemoglobin), the estimates of the IV analyses strongly suggest that transfusion after cardiac surgery setting is safe.

Balance of benefits against harms

Safety has been discussed above (see *Summary of findings of the trial*) and there was a small non-significant difference, favouring the liberal threshold, in the frequency of all SAEs not included in the primary outcome. The primary outcome was also a composite of SAEs; therefore, consideration of the balance between benefits and harms requires the primary outcome to be combined with deaths and all other SAEs. Combining all of these events increased the risk difference between groups (54.4% and 50.7% of participants in the restrictive and liberal groups, respectively); thus, although none of these differences was statistically significant, the liberal threshold appears to offer the better balance of benefits and harms.

Economic evaluation

The main findings from the economic evaluation are that there is very little difference between the groups in either costs or effects and great uncertainty around the cost-effectiveness results. There was very little difference in total costs per participant between the two groups. Participants in the restrictive group cost were, on average, £182 less than those in the liberal group. When a breakdown of total costs was considered, there was a clear difference in the costs associated with red blood cells between the two groups, as expected, but otherwise, cost components were very similar. (The differences in cost between groups were about the same when considering only the red blood cell costs; however, the difference in costs attributable to red blood cells was estimated more precisely than the overall difference in costs.) Total costs were lower when the time origin was moved from surgery to the point of randomisation, but the mean cost difference between groups did not change substantively. Varying unit costs in a sensitivity analysis made very little difference to the mean cost difference, reinforcing how similar resource use was between the groups. There were several outliers in the liberal group, which exerted a substantial influence on the average costs of participants in that treatment group and reversing the direction of the results described above when they were excluded.

A difference of approximately £200 between the groups is a modest cost difference (approximately 1% of total costs). However, as 34,174 cardiac surgery procedures were undertaken in the UK in 2012/13,[65] a difference of £200 in each procedure would have resulted in savings or additional costs of £6.8M. The effect of this cost difference, and whether it is a cost saving or additional cost, is clearly important for the NHS.

The difference between the groups for QALYs is particularly small, creating a very small denominator for the ICER. Dividing the difference in costs by a tiny number close to zero resulted in a very large ICER (–£428,064). The point estimate in our base-case analysis suggests that the restrictive threshold is dominant over the liberal threshold as it is both more effective (very slightly greater QALY gain) and less costly and, therefore, it is cost-effective. However, there is a great deal of uncertainty around this result. This point estimate is close to the origin and the bootstrap replicates of the cost and QALY differences covered all four quadrants of the cost-effectiveness plane. 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 liberal group was no longer favoured when costs were considered alongside life-years and the cost-effectiveness point estimate suggested that the restrictive threshold was still cost-effective compared with the liberal threshold when life-years were used as the outcome measure in a sensitivity analysis.

There was a single subgroup interaction for QALYs gained, which suggested that patients with chronic obstructive pulmonary disease or asthma may be a particularly vulnerable group with respect to transfusion at a restrictive threshold. This finding was consistent with the subgroup analyses of the primary outcome, in so much as the largest difference between thresholds arose for this subgroup (see *Figure 13*). It is also intuitive from a clinical perspective, in that patients with chronic respiratory diseases commonly develop a reactive polycythaemia to chronic hypoxia and that these patients would experience a smaller QALY gain when exposed to a more extreme degree of anaemia.

Comparison with results from similar studies

Here, we consider the findings of TITRe2 in the context of the results of other trials both in cardiac surgery populations and other populations. (We do not consider observational studies given that their findings are very likely to be affected by confounding; see *Chapter 7*.) A Cochrane systematic review including all RCTs comparing restrictive and liberal transfusion thresholds in surgical patients and the critically ill was published in 2012.[12] The authors concluded:

> *In patients who do not have acute coronary artery disease, blood transfusion can probably be withheld in the presence of haemoglobin levels as low as 7.0 g/dl to 8.0 g/dl as long as there is no notable bleeding. The benefits of minimising allogeneic red cell transfusion are likely to be greatest where there is doubt about the safety of the blood supply.*

but expressed caution about applying this conclusion to patients with coronary disease:

> *For the present we recommend the use of a restrictive transfusion trigger, but suggest using caution in patients from high-risk groups such as acute coronary syndrome as there is currently no evidence from randomised controlled trials to guide treatment.*

Our result is consistent with the findings of the review and also resonates with the caution expressed by the authors. Four additional trials have been published since the last literature search for the Cochrane review.[13,14,38,66] Given this caution, three of these trials are relevant to this discussion.[13,14,38] (Patients with acute coronary syndrome were excluded from the Transfusion Strategies for Acute Upper Gastrointestinal Bleeding trial,[66] the only contemporary trial to have demonstrated a benefit for restrictive transfusion.) The first of these RCTs was a single-centre pilot trial in high-risk cardiac surgery patients to assess adherence to the proposed transfusion thresholds (discussed in the context of adherence above).[38] The trial was very small, recruiting just 50 participants, but reported more AEs in the restrictive group. In the second of these RCTs, which recruited patients with hip fracture,[13] 63% had cardiovascular disease and the trial found no benefit of restrictive transfusion. The third of these RCTs was a feasibility trial of transfusion thresholds in patients with unstable coronary disease (MI). It also only recruited a small sample ($n = 110$) but reported a reduced risk of major cardiac morbidity or death of borderline statistical significance with more liberal transfusion.[14]

As part of our effort to put our trial results in context, we formally combined the results of five RCTs comparing restrictive versus liberal transfusion thresholds in cardiac surgery patients (see *Chapter 5*, *Meta-analysis*).[24–26,37,38] Three of these RCTs were included in the Carson review,[24,25,37] the other two were the pilot trial for TITRe2[26] and another pilot trial.[38] Mortality was the only outcome for which we could synthesise data across all trials, with the pooled estimate indicating an increase in mortality of borderline statistical significance for a restrictive threshold. It should be noted that TITRe2 randomised approximately 50% more participants than the total number randomised in all previous trials and contributed more than 50% of the weight of information in the meta-analysis. We have already described other limitations of this meta-analysis arising from differences in the design of the included trials (see *Chapter 5*, *Meta-analysis*),

including the possibility that previous trials underestimated their treatment effects by randomising participants who did not breach the liberal threshold. A further limitation is that mortality does not capture the full consequences of different transfusion thresholds.

In summary, although the result of our primary analysis implies non-inferiority of a restrictive threshold compared with a liberal one, we consider that the totality of evidence available at present (including the results of secondary analyses in TITRe2 and the evidence from other trials discussed above) supports the caution expressed in the Cochrane review. Therefore, we are very uncertain about recommending restrictive transfusion after cardiac surgery. The evidence does not lead us to recommend using a liberal threshold after cardiac surgery; however, we believe that it should lead to a new hypothesis that more liberal transfusion may be beneficial.

This new hypothesis is clinically plausible. TITRe2 differed from previous large trials of transfusion thresholds in that all participants had symptomatic cardiovascular disease;[67,68] moreover, a significant proportion will have developed oxygen supply dependency in the immediate post-operative period.[69,70] Cardiac surgery patients are, therefore, often at the limits of their cardiovascular reserve and may benefit from higher haemoglobin levels and enhanced oxygen delivery. Patients with symptomatic disease may represent a specific high-risk group when more liberal transfusion thresholds are to be recommended.

Patient and public involvement

The main impacts of PPI in the trial were with respect to:

- Developing information for participants.
- Making significant changes in the way in which trial follow-up as conducted and hence promoting the completeness of outcome data; specifically, PPI led to endorsement of the acceptability of postal follow-up and optimisation of the wording of items included in the questionnaire and their format.
- Discussion of the emerging findings from the trial based on the incomplete information available at the time.
- Disseminating information about the findings of the trial to participants (ongoing).

We found it difficult to involve patients in operational details of the trial. As previously described (see *Chapter 2*, *Patient and public involvement*), the trial needed to recruit anxious patients in an acute care setting. When patients were approached about the trial, they were, unsurprisingly, primarily concerned about the possible benefits and risks of withholding or giving extra transfusions.

We are aware that dissemination of the findings of the trial is also challenging. There is a risk that, despite the weight of the information contributed to the research question, the trial will be seen as inconclusive. The statistical issues are complex and it is challenging to find a lay form of words that reflects the findings while at the same time avoids tipping the reader to favour one or other transfusion threshold.

The challenges of carrying out meaningful PPI in the acute setting of cardiac surgery are ongoing because the trials unit that co-ordinated TITRe2 also manages a portfolio of early phase trials and other studies for the NIHR Bristol Cardiovascular Biomedical Research Unit. In particular, through the Biomedical Research Unit we are investing in PPI to improve the ways in which we approach potential participants to make the experience for research participants better, for example by minimising anxiety, to promote a fuller understanding about our trials and with the aspiration that this will enhance recruitment to these difficult-to-do studies.

Strengths and limitations

The TITRe2 trial has many strengths, most obviously its size compared with previous trials of transfusion thresholds in cardiac surgery patients; it randomised four times more participants than the next largest trial comparing liberal and restrictive transfusion thresholds after cardiac surgery.[24–26,37,38] The sample size was designed to take into account non-adherence, which was observed at a similar level to that expected. The higher-than-expected frequency of the primary outcome meant that the primary finding had more power than it was designed to have. By only randomising participants who breached the liberal threshold, we avoided diluting the treatment effect with similar numbers of participants in each group who would probably not have been transfused. This design contrasts with previous RCTs, which included such patients in their analysis populations.[24–26,37,38]

The TITRe2 was also highly pragmatic. Approximately half of all of the specialist cardiac surgery centres in the UK took part and the trial was conducted in a usual-care setting. We are confident that the findings of the trial can be applied to all cardiac surgery centres in the UK. Importantly, and to the great credit of participating units, the trial succeeded (with the help of very many staff in the NHS) in monitoring haemoglobin levels and treating participants according to their allocated thresholds. The separation in both the volumes of red blood cell transfusion and average haemoglobin levels between groups demonstrates the success of the trial in implementing the transfusion thresholds. Local research teams and the co-ordinating centre together achieved excellent completeness of follow-up, with just one of the planned outcomes, infectious events, having more than 5% of missing data. Assessors who were blind to the allocation verified or adjudicated all reported events that qualified for the primary outcome, although we suspect that AKI may have been under-ascertained (see below).

With hindsight, designing TITRe2 to test the superiority of a restrictive threshold may have been a mistake. Answering the question of whether or not a restrictive threshold is non-inferior to a liberal threshold might be considered more pressing. This limitation was assuaged to some extent by the additional power (better precision) of the primary analysis but we have not formally been able to address this question because we did not pre-specify and justify a non-inferiority margin at the outset. The totality of the findings from the trial, and other evidence, make a simple conclusion very difficult. Through no fault of the trial, it is likely that different readers will view the findings as supportive of either restrictive or liberal transfusion practice. The possible 40–60% increase in mortality with a restrictive threshold remains a major concern but a very much larger trial would be needed to provide a definitive answer about this effect.

At the outset, the trial was also presented as a comparison of a new intervention, that is a restrictive threshold, against a usual-care comparator of a liberal threshold. In fact, practice was shifting towards a more restrictive threshold during the course of applying for funding and during the trial, and usual care varied across participating centres (as previously and more recently documented).[5,71] Some readers may want to reverse this perspective to consider liberal compared with restrictive.

Although the trial had greater power than planned, the downside was dominance of the composite primary outcome by less serious events, sepsis and AKI, which was the consequence of implementing objectively verifiable criteria for these events. This limitation was addressed to some extent by a sensitivity analysis of more serious events, which occurred with a frequency of 14.8%, similar to that assumed when estimating the required sample size. Unexpectedly, in this sensitivity analysis the treatment effect for the primary outcome shifted to the null. This result is difficult to reconcile with a difference in mortality and we have no explanation for these divergent findings. Verification of data led us to suspect that AKI events had been underascertained by prospective data collection, leading to the sensitivity analysis including extra AKI events identified from routinely collected serial creatinine data. We believe that this limitation arose because of differences between centres in the baseline creatinine value they used to define AKI.[36] It was interesting that including the extra events generated the expected pyramidal distribution by AKI severity (most mild, least severe), which was not apparent in the distribution of AKI events in the primary analysis.

The main limitation in the conduct of the trial was our inability to blind health-care staff. However, the use of objective end points or adjudication by blinded personnel protected against detection bias. Non-adherence was a challenge throughout the trial but did not prevent us achieving substantial separation in red blood cell transfusion between the groups. Non-adherence that was classified as mild or moderate, despite occurring with greater frequency, was considered unlikely to alter transfusion frequency (as opposed to the average number of units transfused). The nature of protocol non-adherence differed by group but only affected the overall transfusion rate in a small percentage of participants and was similar by group. The question of how much impact the effect of non-adherence (severe or non-severe) has had on the outcome of the trial is difficult to quantify, although we note the consistency between the IV analysis and the main trial finding. A sensitivity analysis excluding non-adherent participants would have been biased because non-adherence arose for different reasons in the two groups, that is participants with non-adherent instances had different characteristics. The consequences of non-adherence are to dilute the treatment effect and, therefore, to provide a more conservative estimate.

Lessons for the future

Choosing specific restrictive and liberal thresholds in RCTs such as TITRe2 is particularly challenging. From the point of view of the feasibility of the trial, the thresholds need to be sufficiently different in order to investigate a clinically important target difference in outcome (whether specified in terms of a superiority or non-inferiority hypothesis) with a sample size that can be achieved in a reasonable duration of recruitment. However, the greater the separation of the thresholds, the more challenging it is to maintain adherence. Moreover, a comparison between any two thresholds (likely to be set in a way that encompasses most of the range of thresholds implemented in usual care) cannot answer the question 'What threshold is best?'. A modified version of the usual design would be to allocate participants to multiple groups with different thresholds, powered to detect a non-zero gradient in effect across thresholds. Although this design might be logistically more challenging to conduct, it might paradoxically promote recruitment and adherence as fewer participants would be exposed to the highest and lowest thresholds.

When applying for funding, we underestimated the number of data that would be necessary to collect. We make no apology for collecting these data as they supported our assessments of fidelity of implementing the intervention (haemoglobin levels and red blood cell transfusions) as well as non-adherence, which were aspects of the conduct of the trial that had been substantially neglected in the pilot. We undertook a careful appraisal of data collection early in the course of the trial and removed a few items that were considered to be unnecessary. The success of this process, both the initial specification of the data items and removal of some at a later stage, is demonstrated by our use of all of the data collected in analysing the trial findings and writing this report. The important lesson from the trial is that it was possible to collect the data required to monitor non-adherence.

We underestimated the number of data needed because the extent of data collection, particularly with respect to monitoring non-adherence, only became apparent when we were setting up the trial. Collecting information about all blood products transfused, nursing observations of temperature, heart rate and oxygen saturation (used to define sepsis), the lowest haemoglobin recorded each day (used to monitor non-adherence) and creatinine biochemistry each day (used to validate instances of AKI) was all time-consuming. However, the additional time needed was not simply to do with extracting more data, for example, research nurses often had to make repeated visits to participants to check information or liaise with doctors or nurses, given that randomisation and the intervention were not fixed in time.

When seeking extra time to recruit participants for the trial, we also sought extra funding for centres to cover the higher than expected research costs they were incurring. Once we had succeeded in persuading the funder of the need for this funding, implementation of the uplift of £80 per randomised participant (about 4 hours of research nurse time) was relatively straightforward through a variation to the site

contract. (The additional funding was paid for participants already randomised as well as participants randomised after the variation to the contract was implemented.)

Had we adopted a payment model in which each participating centre was given a set amount of funding, we would have faced a much more serious challenge in distributing the local research costs. Centres may have resisted an attempt to reduce the amount owing to lower than expected recruitment, on the grounds that we had underestimated the volume of work involved. Moreover, we originally intended to recruit four to eight centres but had recruited 17 by the end of the trial; we think that increasing the number of centres in this way (each participating for different lengths of time) would have been problematic. The total funding award in the extension for the uplift in research costs (£120,000) would also have represented substantially less per centre than we estimated a centre would (on average) generate per year (about £13,000 for the remainder of the trial for an extra centre compared with approximately £15,000 per year for the first group of centres).

We found it difficult to estimate the local research costs that a participating centre was likely to incur. Researchers have to do this task when writing the full application for a project and preparing a budget and may be tempted to reduce this cost, which is inevitably uncertain, rather than the cost of resources that they will use centrally to manage the trial (which they may believe they can estimate more confidently). The importance of the local research income to a centre for a study is likely to become more important in the future as NHS organisations increasingly compete for NIHR portfolio income in a region. If it is clear that 'boots on the ground' at participating centres are a rate-limiting step in delivering a trial, increasing the local research costs may be a relatively easy way to enhance recruitment. However, when multiple trials are competing for the same group of patients, there is also a risk that NHS organisations may cherry-pick the trials that generate the most income.

In TITRe2, although we believe that the primary factor determining the recruitment rate and quality of data for a centre was the commitment and research awareness of the local research team (evidenced by the impact of the absence of specific research nurses), the amount of local researcher time available to be spent on the project was also very important. Having a team of research nurses was helpful in maintaining recruitment and data collection over usual periods of annual leave. When this was not the case, such periods doubled the period over which recruitment slowed or stopped, as there was no point in recruiting participants in advance if no one was going to be available to collect the data. Similarly, there was no one available to recruit participants during the period of absence for the usual research nurse, so no recruited participants, for whom data collection was required, having surgery when he/she returned from leave (e.g. 1 week's annual leave typically affected recruitment for 3 weeks).

There is still debate about the best way to remunerate participating centres for local research costs and whether one or other method enhances recruitment. We believe that a 'fee' per participant randomised, as adopted in TITRe2, provides an incentive to recruit and most fairly rewards differential recruitment by centres. In most circumstances, we consider it preferable to providing, for example, funding to each centre for a fixed amount of time of a research nurse. As described in *Chapter 2*, *Contractual and financial arrangements*, we successfully implemented a system of activity reports using data submitted from centres, which were used by centres as the basis for invoices to the University of Bristol (the 'contractor'). However, with payment being made in arrears, this system can cause difficulties and delays in setting up centres that may be sceptical about recruitment rates and unable to deploy staff to work on a trial without advance funding. In current trials, we are using a mixed-economy method, awarding centres a fixed amount to put in place staff to start recruiting participants, then applying the fee-per-participant system. The mixed system will inevitably be somewhat less efficient if some centres are not successful in recruiting participants but this inefficiency may be worthwhile to reduce the average delay in centres starting to recruit. Another way to implement this principle would be initially to offer each centre a fixed amount of research nurse time and subsequently to adjust the funding depending on actual recruitment.

We believe that TITRe2 benefited substantially from efforts made by the cardiovascular specialty group of the UK Comprehensive Research Network. We are unable to describe what measures the Network instituted as they were applied discretely (which may explain their success) and were not disclosed to the trial team.

Other trials competing for the same target population was a final factor affecting recruitment and it was frustrating that the NIHR (across its varied programmes) funded new trials that competed for cardiac surgery patients during the course of TITRe2. Not surprisingly, centres employing chief investigators for these trials tended to prioritise recruitment to their home-grown trials over TITRe2, with a dramatic effect on recruitment at one or two sites. At any one time, specialty networks in the Comprehensive Research Network have an overview of NIHR-funded trials currently recruiting patients with particular conditions but this is after the trials have been funded. We are not aware that these networks feed information back to the NIHR about target populations that are currently 'over-researched' and when a new trial may struggle to recruit.

Future research

The most pressing question to answer is whether or not a liberal threshold is superior to a restrictive threshold in cardiac surgery patients who are likely to be at the limits of their cardiovascular reserve. A RCT has recently started to recruit in the Canada and the USA which will help to answer this question.[72] As with TITRe2, the TRICS-III trial is again comparing restrictive and liberal thresholds in patients having cardiac surgery with CPB and the researchers aim to randomise 3592 participants. Key differences between the trials are as follows:

- TRICS-III hypothesises a restrictive threshold to be non-inferior to a liberal threshold.
- TRICS-III is recruiting high-risk patients only (EuroSCORE of > 6).
- TRICS-III thresholds are slightly different and the thresholds are applied both during the operation and subsequently (restrictive < 7.5 g/dl intraoperatively or postoperatively; liberal < 9.5 g/dl intraoperatively or in the ICU and < 8.5 g/dl postoperatively on the ward).
- TRICS-III has a primary composite outcome consisting only of events that we considered to be serious in our sensitivity analysis (i.e. death, MI, kidney failure requiring dialysis or stroke; expected frequency and non-inferiority margin are not stated in the registration details).

Although not explicitly testing the hypothesis that a liberal transfusion threshold is superior, TRICS-III is recruiting patients who are most likely to be at the limit of their cardiovascular reserve. The weight of information contributed by this trial to a future meta-analysis will be substantial, although it is unclear whether the researchers are randomising preoperatively or only when a participant breaches the liberal threshold. Until this trial concludes, we do not see any particular merit in pursuing an individual participant data meta-analysis of the existing trials. In our opinion, the only benefit of such an analysis would be investigation of relevant subgroups but, even if achievable, these analyses would have low power. A more fruitful approach would be to persuade previous triallists to reanalyse their trial datasets after excluding from both restrictive and liberal groups all participants who did not breach the liberal threshold. These analyses would make these trials more similar to TITRe2 and test the hypothesis that the results of these trials currently underestimate the treatment effects. The revised treatment effects should be combined in a further (aggregate) meta-analysis of mortality. An initiative of this kind might also allow meta-analyses of other outcomes with higher frequencies, which would provide estimates with greater precision.

With respect to the investment already made in TITRe2, we believe that further analyses of the data may be able to estimate the effects of transfusion at different haemoglobin levels and to estimate the effect of longer versus shorter duration of storage of red blood cells (although we are aware that a RCT is currently testing this[73,74]). *Chapter 7*, *Red blood cells and haemoglobin levels*, *Next steps* and *Chapter 7*, *Age of blood*, *Next steps* have already described the analyses that we propose to pursue.

There are two key areas of further health economic research that would be worthwhile. In this report, we have described a within-trial analysis up to 3 months, consistent with the main analysis of clinical outcomes. It would be useful to extrapolate the information about costs and effects obtained for the trial and to explore different time horizons including a life-time time horizon. With respect to quality of life, the EQ-5D-3L questionnaire was used in the trial because the 5-level version had not been validated at the time. The 5-level version has been designed to be able to discriminate changes in health-related quality of life better than the 3-level questionnaire. Given such small differences between the restrictive and liberal groups, it would be interesting to investigate whether or not the use of the 5-level questionnaire in current cardiac and blood transfusion studies could detect larger differences between trial groups.

Chapter 9 Conclusion

We conclude that both TITRe2 and totality of evidence available at present indicate that a restrictive transfusion threshold is definitely not superior, and probably not inferior, to a liberal threshold. In terms of the economic component of the trial, we also conclude that there is no difference between the two thresholds. However, the same evidence makes it difficult to recommend restrictive transfusion after cardiac surgery, despite the reduction in costs that this might achieve by lowering the consumption of allogeneic red blood cells. A new hypothesis, that more liberal transfusion may be beneficial after cardiac surgery, needs to be investigated.

Acknowledgements

The trial was funded by the UK NIHR Health Technology Assessment programme (reference 06/402/94). Reeves is part funded by the NIHR Bristol Biomedical Research Unit in Cardiovascular Disease and this award also supported the research nurse team in Bristol. Angelini and Murphy are British Heart Foundation (BHF) Professors of Cardiac Surgery and Rogers is a BHF Reader in Medical Statistics.

Contributions of authors

Barnaby C Reeves (chief investigator, Professor of Health Services Research and Co-Director of the Clinical Evaluation and Trials Unit) and **Gavin J Murphy** (BHF Professor of Cardiac Surgery) conceived the trial.

Katie Pike (research associate in medical statistics) and **Rachel L Nash** (NIHR Predoctoral Research Methods Fellow) prepared reports during the trial and **Katie Pike** carried out the statistical analyses, under the supervision of **Chris A Rogers** (BHF Reader in Medical Statistics and Co-Director of the Clinical Evaluation and Trials Unit).

Rachel CM Brierley (trial co-ordinator), **Alice Miles** (trial coordinator), **Barnaby C Reeves**, **Chris A Rogers** and **Gavin J Murphy** managed the conduct of the trial with expert clinical input as required from **Gianni D Angelini** (BHF Professor of Cardiac Surgery), **Andrew D Mumford** (reader in haematology) and **Alan Cohen** (Consultant Anaesthetist).

Elizabeth A Stokes (researcher in health economics) and **Sarah Wordsworth** (Associate Professor in Health Economics) carried out the health economic analyses.

Barnaby C Reeves was the chief investigator and **Gavin J Murphy** the lead clinical investigator.

Barnaby C Reeves, **Gavin J Murphy**, **Chris A Rogers** and **Sarah Wordsworth** designed the trial.

Barnaby C Reeves, **Gavin J Murphy**, **Chris A Rogers**, **Gianni D Angelini** and **Sarah Wordsworth** wrote the application for funding to do the trial.

Katie Pike, **Barnaby C Reeves**, **Sarah Wordsworth**, **Elizabeth A Stokes** and **Gavin J Murphy** drafted the report.

All authors reviewed the report for important intellectual content and approved the final version.

Publications

Brierley RC, Pike K, Miles A, Wordsworth S, Stokes EA, Mumford AD, *et al.* A multi-centre randomised controlled trial of transfusion indication threshold reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery: study protocol. *Transfus Apher Sci* 2014;**50**:451–61.

Pike K, Nash RL, Murphy GJ, Reeves BC, Rogers CA. Transfusion Indication Threshold Reduction (TITRe2) randomised controlled trial in cardiac surgery: statistical analysis plan. *Trials* 2015;**16**:54.

Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, *et al.* Liberal or restrictive transfusion after cardiac surgery: TITRe2 randomized trial. *New Engl J Med* 2015;**372**:997–1008.

Reeves BC, Rogers CA, Murphy GJ. Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;**373**:193.

Pike K, Maishman RL, Brierley RCM, Rogers CA, Murphy GJ, Reeves BC. Adherence to transfusion strategies in a randomized controlled trial: experiences from the TITRe2 trial. *Br J Haematol* 2016; in press. http://dx.doi.org/10.1111/bjh.14220

Stokes EA, Wordsworth S, Bargo D, Pike K, Rogers CA, Brierley RCM, *et al.* Are lower levels of red blood cell transfusion more cost-effective than liberal levels after cardiac surgery? Findings from the TITRe2 randomised controlled trial. *BMJ Open* 2016:**6**:e011311.

Reeves BC, Pike K, Murphy GJ, Sterne JAC, Rogers CA. Effects of red cell transfusion after cardiac surgery: estimates from multivariable and instrumental variable analyses of data from the TITRe2 trial. Submitted to *Lancet Haematol*.

Data sharing statement

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the Medical Research Council Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. We propose that a minimum requirement with respect to scientific quality should be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. A second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK Research Ethics Committee or other similar, approved ethics review body.

References

1. Habib RH, Zacharias A, Schwann TA, Riordan CJ, Engoren M, Durham SJ, *et al.* Role of hemodilutional anemia and transfusion during cardiopulmonary bypass in renal injury after coronary revascularization: implications on operative outcome. *Crit Care Med* 2005;**33**:1749–56. http://dx.doi.org/10.1097/01.CCM.0000171531.06133.B0
2. Murphy GJ, Reeves BC, Rogers CA, Rizvi SI, Culliford L, Angelini GD. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. *Circulation* 2007;**116**:2544–52. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.698977
3. Karkouti K, Wijeysundera DN, Beattie WS. Risk associated with preoperative anemia in cardiac surgery: a multicenter cohort study. *Circulation* 2008;**117**:478–84. http://dx.doi.org/10.1161/CIRCULATIONAHA.107.718353
4. Bennett-Guerrero E, Zhao Y, O'Brien SM, Ferguson TB Jr, Peterson ED, Gammie JS, *et al.* Variation in use of blood transfusion in coronary artery bypass graft surgery. *JAMA* 2010;**304**:1568–75. http://dx.doi.org/10.1001/jama.2010.1406
5. Murphy MF, Murphy GJ, Gill R, Herbertson M, Allard S, Grant-Casey J. *National Comparative Audit of Blood Transfusion: 2011 Audit of Blood Transfusion in Adult Cardiac Surgery*. Birmingham: NHS; 2013. URL: http://hospital.blood.co.uk/media/26859/nca-2011_use_of_blood_in_adult_cardiac_surgery_report.pdf (accessed 30 July 2015).
6. Wells AW, Llewelyn CA, Casbard A, Johnson AJ, Amin M, Ballard S, *et al.* The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfus Med* 2009;**19**:315–28. http://dx.doi.org/10.1111/j.1365-3148.2009.00933.x
7. Brierley RCM, Pike K, Miles A, Wordsworth S, Stokes EA, Mumford AD, *et al.* A multi-centre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery: study protocol. *Transfus Apher Sci* 2014;**50**:451–61. http://dx.doi.org/10.1016/j.transci.2014.02.020
8. Corwin HL, Parsonnet KC, Gettinger A. RBC transfusion in the ICU. Is there a reason? *Chest* 1995;**108**:767–71. http://dx.doi.org/10.1378/chest.108.3.767
9. Stover EP, Siegel LC, Parks R, Levin J, Body SC, Maddi R, *et al.* Variability in transfusion practice for coronary artery bypass surgery persists despite national consensus guidelines: a 24-institution study. Institutions of the Multicenter Study of Perioperative Ischemia Research Group. *Anesthesiology* 1998;**88**:327–33. http://dx.doi.org/10.1097/00000542-199802000-00009
10. Koch CG, Li L, Duncan AI, Mihaljevic T, Cosgrove DM, Loop FD, *et al.* Morbidity and mortality risk associated with red blood cell and blood-component transfusion in isolated coronary artery bypass grafting. *Crit Care Med* 2006;**34**:1608–16. http://dx.doi.org/10.1097/01.CCM.0000217920.48559.D8
11. Karkouti K, Wijeysundera DN, Yau TM, McCluskey SA, Chan CT, Wong PY, *et al.* Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. *Anesthesiology* 2011;**115**:523–30. http://dx.doi.org/10.1097/ALN.0b013e318229a7e8
12. Carson JL, Carless PA, Hebert PC. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev* 2012;**4**:CD002042. http://dx.doi.org/10.1002/14651858.cd002042.pub3

13. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, *et al.* Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med* 2011;**365**:2453–62. http://dx.doi.org/10.1056/NEJMoa1012452

14. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, *et al.* Liberal versus restrictive transfusion thresholds for patients with symptomatic coronary artery disease. *Am Heart J* 2013;**165**:964–71. http://dx.doi.org/10.1016/j.ahj.2013.03.001

15. Carson JL, Carless PA, Hebert PC. Outcomes using lower vs higher hemoglobin thresholds for red blood cell transfusion. *JAMA* 2013;**309**:83–4. http://dx.doi.org/10.1001/jama.2012.50429

16. Bolton-Maggs PHB, Poles D, Watt A, Thomas D, Cohen H, on behalf of the Serious Hazards of Transfusion (SHOT) Steering Group. *The 2012 Annual SHOT Report*. 2013. URL: www.shotuk.org/wp-content/uploads/2013/08/SHOT-Annual-Report-2012.pdf (accessed 30 July 2015).

17. Greinacher A, Fendrich K, Brzenska R, Kiefel V, Hoffmann W. Implications of demographics on future blood supply: a population-based cross-sectional study. *Transfusion* 2011;**51**:702–9. http://dx.doi.org/10.1111/j.1537-2995.2010.02882.x

18. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activity-based costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010;**50**:753–65. http://dx.doi.org/10.1111/j.1537-2995.2009.02518.x

19. Ferraris VA, Brown JR, Despotis GJ, Hammon JW, Reece TB, Saha SP, *et al.* 2011 update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthetists blood conservation clinical practice guidelines. *Ann Thorac Surg* 2011;**91**:944–82. http://dx.doi.org/10.1016/j.athoracsur.2010.11.078

20. Napolitano LM, Kurek S, Luchette FA, Anderson GL, Bard MR, Bromberg W, *et al.* Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009;**37**:3124–57. http://dx.doi.org/10.1097/CCM.0b013e3181b39f1b

21. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, *et al.* Red blood cell transfusion: a clinical practice guideline from the AABB*. *Ann Intern Med* 2012;**157**:49–58. http://dx.doi.org/10.7326/0003-4819-157-1-201206190-00429

22. World Health Organization (WHO). *Global Forum for Blood Safety: Patient Blood Management. Priorities for Action*. Dubai: WHO; 2011. URL: www.who.int/bloodsafety/events/gfbs_01_pbm/en/ (accessed 24 February 2014).

23. Farmer SL, Towler SC, Leahy MF, Hofmann A. Drivers for change: Western Australia Patient Blood Management Program (WA PBMP), World Health Assembly (WHA) and Advisory Committee on Blood Safety and Availability (ACBSA). *Best Pract Res Clin Anaesthesiol* 2013;**27**:43–58. http://dx.doi.org/10.1016/j.bpa.2012.12.007

24. Johnson RG, Thurer RL, Kruskall MS, Sirois C, Gervino EV, Critchlow J, *et al.* Comparison of two transfusion strategies after elective operations for myocardial revascularization. *J Thorac Cardiovasc Surg* 1992;**104**:307–14.

25. Bracey AW, Radovancevic R, Riggs SA, Houston S, Cozart H, Vaughn WK, *et al.* Lowering the hemoglobin threshold for transfusion in coronary artery bypass procedures: effect on patient outcome. *Transfusion* 1999;**39**:1070–7. http://dx.doi.org/10.1046/j.1537-2995.1999.39101070.x

26. Murphy GJ, Rizvi SIA, Battaglia F, Culliford L, Rogers CA, Cohen A, *et al.* A pilot randomized controlled trial of the effect of transfusion- threshold reduction on transfusion rates and morbidity after cardiac surgery. *Transfus Altern Transfus Med* 2007;**9**(Suppl. 1):41–2.

27. Wilson AP, Treasure T, Sturridge MF, Gruneberg RN. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. *Lancet* 1986;**1**:311–13. http://dx.doi.org/10.1016/S0140-6736(86)90838-X

28. Wilson AP, Weavill C, Burridge J, Kelsey MC. The use of the wound scoring method 'ASEPSIS' in postoperative wound surveillance. *J Hosp Infect* 1990;**16**:297–309. http://dx.doi.org/10.1016/0195-6701(90)90002-6

29. Gibbons C, Bruce J, Carpenter J, Wilson AP, Wilson J, Pearson A, *et al.* Identification of risk factors by systematic review and development of risk-adjusted models for surgical site infection. *Health Technol Assess* 2011;**15**(30). http://dx.doi.org/10.3310/hta15300

30. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, *et al.* Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007;**11**:R31. http://dx.doi.org/10.1186/cc5713

31. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;**16**:199–208. http://dx.doi.org/10.1016/0168-8510(90)90421-9

32. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd edn. New Jersey, NJ: Lawrence Erlbaum Associates; 1988.

33. Pike K, Brierley R, Rogers CA, Murphy GJ, Reeves BC. Adherence in a randomised controlled trial comparing liberal and restrictive red blood cell (RBC) transfusion protocols after cardiac surgery (TITRe2). *Trials* 2011;**12**(Suppl. 1):A131. http://dx.doi.org/10.1186/1745-6215-12-S1-A131

34. Pike K, Nash RL, Murphy GJ, Reeves BC, Rogers CA. Transfusion Indication Threshold Reduction (TITRe2) randomised controlled trial in cardiac surgery: statistical analysis plan. *Trials* 2015;**16**:54. http://dx.doi.org/10.1186/s13063-015-0564-x

35. Tooze JA, Grunwald GK, Jones RH. Analysis of repeated measures data with clumping at zero. *Stat Methods Med Res* 2002;**11**:341–55. http://dx.doi.org/10.1191/0962280202sm291ra

36. Englberger L, Suri RM, Li Z, Casey ET, Daly RC, Dearani JA, *et al.* Clinical accuracy of RIFLE and Acute Kidney Injury Network (AKIN) criteria for acute kidney injury in patients undergoing cardiac surgery. *Crit Care* 2011;**15**:R16. http://dx.doi.org/10.1186/cc9960

37. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, *et al.* Transfusion requirements after cardiac surgery: the TRACS randomized controlled trial. *JAMA* 2010;**304**:1559–67. http://dx.doi.org/10.1001/jama.2010.1446

38. Shehata N, Burns LA, Nathan H, Hebert P, Hare GM, Fergusson D, *et al.* A randomized controlled pilot study of adherence to transfusion strategies in cardiac surgery. *Transfusion* 2012;**52**:91–9. http://dx.doi.org/10.1111/j.1537-2995.2011.03236.x

39. Patel NN, Avlonitis VS, Jones HE, Reeves BC, Sterne JAC, Murphy GJ. Indications for red cell transfusion in cardiac surgery: a systematic review and meta-analysis of randomized controlled trials and observational studies [published online ahead of print 16 November 2015]. *Lancet Haematol* 2015. http://dx.doi.org/10.1016/S2352-3026(15)00198-2

40. Schulz KF, Grimes DA. Multiplicity in randomised trials I: endpoints and treatments. *Lancet* 2005;**365**:1591–5. http://dx.doi.org/10.1016/S0140-6736(05)66461-6

41. NICE. *Social Value Judgements: Principles for the Development of NICE Guidance*. 2nd edn. London: NICE; 2008. URL: www.nice.org.uk/media/default/About/what-we-do/Research-and-development/Social-Value-Judgements-principles-for-the-development-of-NICE-guidance.pdf (accessed 30 July 2015).

42. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. *BMJ* 1996;**313**:275–83. http://dx.doi.org/10.1136/bmj.313.7052.275

43. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes*. 3rd edn. New York, NY: Oxford University Press; 2005.

44. NICE. *Guide to the Methods of Technology Appraisal 2013*. London: NICE; 2013. URL: www.nice.org.uk/article/pmg9/resources/non-guidance-guide-to-the-methods-of-technology-appraisal-2013-pdf (accessed 30 July 2015).
45. Department of Health. *National Schedule of Reference Costs 2012–13*. London: Department of Health; 2013.
46. NHS Blood and Transplant. *NHS Blood and Transplant Price List 2012–2013*. 2012. URL: http://hospital.blood.co.uk/products/ (accessed 28 September 2012).
47. Department of Health Commercial Medicines Unit. Electronic Marketing Information Tool (eMIT). *Drugs and Pharmaceutical Electronic Market Information (eMit)*. URL: http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ (accessed 10 February 2014).
48. Joint Formulary Committee. *British National Formulary*. 66 edn. London: BMJ Group and Pharmaceutical Press; 2013.
49. Curtis L. *Unit Costs of Health and Social Care 2013*. Canterbury, University of Kent: Personal Social Services Research Unit; 2013.
50. Dolan P, Gudex C, Kind P, Williams A. *A Social Tariff for Euroqol: Results from a UK General Population Survey*. York: University of York; 1995.
51. White IR, Royston P, Wood AM. Multiple imputation using chained equations: issues and guidance for practice. *Stat Med* 2011;**30**:377–99. http://dx.doi.org/10.1002/sim.4067
52. Rubin DB. *Multiple Imputation For Non-Response In Surveys*. New York, NY: John Wiley & Sons; 1987.
53. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ* 2005;**14**:487–96. http://dx.doi.org/10.1002/hec.944
54. Dakin HA, Wordsworth S, Rogers CA, Abangma G, Raftery J, Harding SP, *et al.* Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial. *BMJ Open* 2014;**4**:e005094. http://dx.doi.org/10.1136/bmjopen-2014-005094
55. Murphy GJ, Pike K, Rogers CA, Wordsworth S, Stokes EA, Angelini GD, *et al.* Liberal or restrictive transfusion after cardiac surgery. *N Engl J Med* 2015;**372**:997–1008. http://dx.doi.org/10.1056/NEJMoa1403612
56. Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model. *Health Technol Assess* 2006;**10**(44). http://dx.doi.org/10.3310/hta10440
57. Joint Formulary Committee. *British National Formulary*. 58 edn. London: BMJ Group and Pharmaceutical Press; 2009.
58. Briggs A, Clark T, Wolstenholme J, Clarke P. Missing . . . presumed at random: cost-analysis of incomplete data. *Health Econ* 2003;**12**:377–92. http://dx.doi.org/10.1002/hec.766
59. Greenland S. An introduction to instrumental variables for epidemiologists. *Int J Epidemiol* 2000;**29**:1102. http://dx.doi.org/10.1093/oxfordjournals.ije.a019909
60. Dzik W. Fresh blood for everyone? Balancing availability and quality of stored RBCs. *Transfus Med* 2008;**18**:260–5. http://dx.doi.org/10.1111/j.1365-3148.2008.00870.x

61. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al.* The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;**61**:344–9. http://dx.doi.org/10.1016/j.jclinepi.2007.11.008

62. Hebert PC, Wells G, Blajchman MA, Marshall J, Martin C, Pagliarello G, *et al.* A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Eng J Med* 1999;**340**:409–17. http://dx.doi.org/10.1056/NEJM199902113400601

63. Reeves BC, Murphy GJ. Increased mortality, morbidity, and cost associated with red blood cell transfusion after cardiac surgery. *Curr Opin Cardiol* 2008;**23**:607–12. http://dx.doi.org/10.1097/HCO.0b013e328310fc95

64. Koch CG, Li L, Sessler DI, Figueroa P, Hoeltge GA, Mihaljevic T, *et al.* Duration of red-cell storage and complications after cardiac surgery. *N Engl J Med* 2008;**358**:1229–39. http://dx.doi.org/10.1056/NEJMoa070403

65. Blue Book Online. *How Many [Cardiac Surgery] Operations are Carried Out Each Year?* 2013. URL: http://bluebook.scts.org (accessed 30 July 2015).

66. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, *et al.* Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med* 2013;**368**:11–21. http://dx.doi.org/10.1056/NEJMoa1211801

67. Task Force on Myocardial Revascularisation of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Association for Percutaneous Cardiovascular Interventions (EAPCI), Wijns W, Kolh P, Danchin N, Di Mario C, *et al.* Guidelines on myocardial revascularization. *Eur Heart J* 2010;**31**:2501–55. http://dx.doi.org/10.1093/eurheartj/ehq277

68. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ECS), European Association for Cardio-Thoracic Surgery (EACTS), Vahanian A, Alfieri O, Andreotti F, *et al.* Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J* 2012;**33**:2451–96. http://dx.doi.org/10.1093/eurheartj/ehs109

69. Casutt M, Seifert B, Pasch T, Schmid ER, Turina MI, Spahn DR. Factors influencing the individual effects of blood transfusions on oxygen delivery and oxygen consumption. *Crit Care Med* 1999;**27**:2194–200. http://dx.doi.org/10.1097/00003246-199910000-00021

70. Utoh J, Moriyama S, Okamoto K, Kunitomo R, Hara M, Kitamura N. The effects of cardiopulmonary bypass on postoperative oxygen metabolism. *Surg Today* 1999;**29**:28–33. http://dx.doi.org/10.1007/BF02482966

71. Wells AW, Mounter PJ, Chapman CE, Stainsby D, Wallis JP. Where does blood go? Prospective observational study of red cell transfusion in north England. *BMJ* 2002;**325**:803. http://dx.doi.org/10.1136/bmj.325.7368.803

72. Clinical Trials Registry. *Transfusion Requirements in Cardiac Surgery III (TRICS-III).* URL: http://clinicaltrials.gov/show/NCT02042898 (accessed 30 July 2015).

73. Lacroix J, Hébert P, Fergusson D, Tinmouth A, Blajchman MA, Callum J, *et al.* The Age of Blood Evaluation (ABLE) randomized controlled trial: study design. *Transfus Med Rev* 2011;**25**:197–205. http://dx.doi.org/10.1016/j.tmrv.2011.03.001

74. Lacroix J, Hébert PC, Fergusson DA, Tinmouth A, Cook DJ, Marshall JC, *et al.* Age of transfused blood in critically ill adults. *N Engl J Med* 2015;**372**:1410–18. http://dx.doi.org/10.1056/NEJMoa1500704

75. Joint Formulary Committee. *British National Formulary.* 47 edn. London: BMJ Group and Pharmaceutical Press; 2004.

76. Lord J, Willis S, Eatock J, Tappenden P, Trapero-Bertran M, Miners A, *et al.* Economic modelling of diagnostic and treatment pathways in National Institute for Health and Care Excellence clinical guidelines: the Modelling Algorithm Pathways in Guidelines (MAPGuide) project. *Health Technol Assess* 2013;**17**(58). http://dx.doi.org/10.3310/hta17580

77. Gray AJ, Goodacre S, Newby DE, Masson MA, Sampson F, Dixon S, *et al.*, on behalf of the 3CPO study investigators. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. *Health Technol Assess* 2009;**13**(33). http://dx.doi.org/10.3310/hta13330

78. NICE. *NICE Medical Technology Guidance 8: The VeriQ System for Assessing Graft Flow During Coronary Artery Bypass Graft Surgery*. 2011. URL: http://guidance.nice.org.uk/mtg8 (accessed 30 July 2015).

79. NICE. *Nutrition Support in Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition*. Costing Report. Implementing NICE Guidance in England. NICE Clinical Guideline no. 32. 2006. URL: www.nice.org.uk/guidance/cg32/resources/costing-report-194884669 (accessed 10 November 2015).

80. NHS Business Services Authority, NHS Prescription Services. *Drug Tariff. The Electronic Drug Tariff*. Department of Health; 2014. URL: www.ppa.org.uk/ppa/edt_intro.htm (accessed 21 February 2014).

81. NHS Direct National Health Services Trust. *NHS Direct National Health Services Trust Annual Report and Accounts 2012/13*. London: The Stationery Office; 2013. URL: www.gov.uk/government/publications/nhs-direct-national-health-service-trust-annual-report-and-accounts-2012-to-2013 (accessed 30 July 2015).

Appendix 1 Transfusion Indication Threshold Reduction study investigators

Trial sites

Blackpool Victoria Hospital and Lancaster University
Investigators: Mr Augustine Tang and Dr Palaniappan Saravanan. Research team: Charlotte Waterhouse.

Royal Sussex County Hospital, Brighton
Investigator: Dr Robert Kong. Research team: Nicola Skipper.

University Hospitals NHS Foundation Trust, Bristol
Investigator: Professor Gavin Murphy (until August 2012)/Professor Gianni Angelini (from August 2012). Research team: Emma Hopkins and Penny Lambert.

University Hospital Coventry and Warwickshire NHS Trust, Coventry
Investigator: Mr Sunil K Bhudia. Research team: Denise Gocher.

Castle Hill Hospital, Hull
Investigator: Dr Sean Bennett. Research team: Neil Smith and Adam Walker.

Derriford Hospital, Plymouth
Investigators: Dr Mark Bennett and Mr Malcolm Dalrymple-Hay. Research team: Maxine Pearse.

Essex Cardiothoracic Centre, Basildon
Investigator: Professor Andrew J Ritchie. Research team: Emily Redman and Amanda Solesbury.

Royal Infirmary of Edinburgh, Edinburgh
Investigator: Mr Vipin Zamvar.

Hammersmith Hospital, London
Investigator: Dr Geoffrey Lockwood. Research team: Dr Francesca Fiorentino, Alima Rahman.

King's College Hospital NHS Foundation Trust
Investigator: Dr Gudrun Kunst. Research team: Georgina Parsons and Fiona Wade-Smith.

The Leeds Teaching Hospitals NHS Trust
Investigator: Dr Michael H Cross. Research team: Stuart Elliot and Zoe Beardow.

Glenfield Hospital, Leicester
Investigator: Professor Tom Sypt. Research team: Martina Williams.

Liverpool Heart and Chest Hospital Foundation Trust
Investigator: Mr Brian Fabri (until December 2012)/Mr Mark Field (from January 2013). Research team: Ian Kemp and Andrea Young.

The James Cook University Hospital, Middlesbrough
Investigator: Dr Nick Stratford. Research team: Heather Robinson.

Freeman Hospital, Newcastle
Investigator: Mr Stephen Clark. Research team: Sarah Rowling and Hazel Forsyth.

University Hospital Southampton Foundation Trust
Investigator: Dr Ravi Gill. Research team: Beverley Wadhams and Kim de Courcy-Golder.

New Cross Hospital, Wolverhampton
Investigators: Dr Ian Morgan. Research team: Emma Greatbach and Alex Ng.

Resource centres

Trial management centre, Clinical Trials and Evaluation Unit, University of Bristol
Professor Barnaby C Reeves, Dr Chris A Rogers, Dr Rachel CM Brierley, Dr Alice Miles, Wendy Underwood, Dr Lucy A Culliford, Jonathan Evans, Katie Pike, Rachel Nash, David Hutton, Emma Hopkins, Penny Lambert, Kate Rajakaruna, Kim Wright, Jenny Wilcox and Rachel Wyatt.

Health Economics Research Centre, University of Oxford
Dr Sarah Wordsworth, Elizabeth A Stokes and Danielle Bargo.

Adjudication Committee
Dr Tom W Johnson, Dr Sally Tomkins and Mr Jon Anderson.

NHS Blood and Transplant
Dr Edwin Massey and Ian Millar.

Appendix 2 Transfusion Indication Threshold Reduction committees

Data Monitoring and Safety Committee

Professor Gordon Murray (chairperson), Professor Tim Walsh and Professor Domenico Pagano.

Trial Steering Committee

Mr Patrick Magee (chairperson, until his death in May 2011), Professor John Pepper (chairperson, from June 2011), Dr Duncan Young, Dr Edwin Massey, Dr Gordon Taylor and Karin Smyth.

Appendix 3 Additional health economic evaluation information

Unit costs and resource use assumed for complications

Note that unit costs not in 2012/13 prices have been inflated to 2012/13 prices using the HCHS inflation index.[48]

TABLE 61 Unit costs for surgery, inpatient stays and blood products

Resource	Unit cost (£)	Reference
Cardiac surgery and reoperations		
CABG	6714	NHS Reference Costs 2012/13.[45] 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 *Inpatient stay* row, *Cardiac ward day*, in this table), and £227 was subtracted for blood products based on data from an audit of blood transfusion in cardiac surgery (NHSBT, 2011[5]). An average cost for the codes was then generated, weighted by activity
Valve	7336	NHS Reference Costs 2012/13.[45] Elective inpatients. HRG codes EA17 (single valve) and EA52 (more than one 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 (NHSBT, 2011[5]). An average cost for the codes was then generated for single and more than one valve procedures, weighted by activity. Finally these two 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.[45] 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 (NHSBT, 2011[5]). An average cost for the codes was then generated, weighted by activity
Other	8298	NHS Reference Costs 2012/13.[45] 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 (NHSBT, 2011[5]). 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
Reoperations ≥ 3 hours, including blood, excluding LOS	9719	As 'other' cardiac procedure above, with £1421 for blood products added back in

continued

TABLE 61 Unit costs for surgery, inpatient stays and blood products (*continued*)

Resource	Unit cost (£)	Reference
Inpatient stay		
Cardiac ward day	392	NHS Reference Costs 2012/13.[45] 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.[45] Critical Care Services – Adult: Critical Care Unit (XC07Z, 0 organs supported)
CICU day	1190	NHS Reference Costs 2012/13.[45] 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.[45] 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.[45] Non-elective inpatient excess bed-day cost across all activities
Blood products		
Red blood cells	123.31	NHSBT Price List 2012/13[46]
Red blood cell administration cost, first unit	22	Primary data collection of the nursing time and consumables associated with requesting blood and administering transfusions undertaken with collaborators on the TOPPS trial, funded by NHSBT. Preliminary analyses show it takes 49 minutes of nursing time and £6 of consumables to request and administer the first unit of red blood cells
Red blood cell administration cost, subsequent units	5	As above (see *Resource* row, *Red blood cell administration cost, first unit*, in this table); analyses found it took 15 minutes of nursing time to administer subsequent units (no additional consumables)
FFP	27.46	NHSBT Price List 2012/13[46]
Platelets	209.30	NHSBT Price List 2012/13[46]
Cryoprecipitate	189.19	NHSBT Price List 2012/13[46]

TOPPS, Trial of prophylactic vs. no prophylactic platelet transfusions.

TABLE 62 Unit costs for blood saving techniques, fluids and medications in theatre/CICU/HDU

Resource	Assumed quantity	Unit cost (£)	Reference
Tranexamic acid	5 g intravenously	15.50	BNF 66, 2013[48]
Trasylol	6 million Kallikrein Inhibitor Units intravenously	316.83	Davies *et al.*[56] using data from BNF 47, 2004.[75] Costs have been inflated using the HCHS inflation index
Intraoperative/post-operative cell salvage		176	Davies *et al.*[56] Costs have been inflated using the HCHS inflation index
Activated factor VII	5 mg intravenously	2486.60	Transfusion Laboratory of the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, 2013, personal communication
Human prothrombin complex (Beriplex, CSL Behring UK Ltd)	1500 IU intravenously	420	Transfusion Laboratory at a district general hospital, South Central, 2014, personal communication
HES	1500 ml intravenously	40.60	BNF 58, 2009.[57] Costs have been inflated using the HCHS inflation index
Human albumin solution (Zenalb, Bio Products Laboratory Ltd)	500 ml intravenously	36	Transfusion Laboratory at a district general hospital, South Central, 2014, personal communication
Gelofusine	1500 ml intravenously	7.92	Finance Department, teaching hospital, South Central, 2013, personal communication
Inotropes	Noradrenaline 1 mg/hour for 5 days	57.30	eMIT, 2014[47]
Hartmann's solution (compound sodium lactate)	1500 ml intravenously	2.67	Finance Departmen, teaching hospital, South Central, 2013, personal communication
Gelatin (Isoplex, Beacon Pharmaceuticals)	1500 ml intravenously	22.07	BNF 66, 2013[48]

HES, hydroxyethyl starch; IU, international units.

TABLE 63 Unit costs for antibiotics

Drug name	Route	Assumed dose/frequency per day	Daily cost (£)	Source	Daily cost (£) from BNF[47] for sensitivity analyses
Amikacin	i.v.	500 mg 3 × day	18.42	eMIT[47]	
Amoxicillin	Oral	500 mg 4 × day	0.10	eMIT[47]	0.31
Amoxicillin	i.v.	500 mg 4 × day	1.46	eMIT[47]	2.20
Aztreonam	i.v.	1 g 3 × day	28.20	BNF[48]	
Benzylpenicillin	i.v.	1.2 g 4 × day	7.56	BNF[48]	
Caspofungin	i.v.	70 mg first day, 50 mg 1 × day subsequent days	416.78 day 1, 327.67 thereafter	BNF[48]	
Cefalexin	Oral	250 mg 4 × day	0.11	eMIT[47]	
Cefotaxime	i.v.	1 g 2 × day	1.22	eMIT[47]	
Ceftazidime	i.v.	1 g 3 × day	2.56	eMIT[47]	
Ceftriaxone	i.v.	1 g 1 × day	0.53	eMIT[47]	
Cefuroxime	i.v.	750 mg 3 × day	1.37	eMIT[47]	
Cefuroxime 1.5 g	i.v.	1.5 g 3 × day	2.13	eMIT[47]	
Cefuroxime 750 mg	i.v.	750 mg 3 × day	1.37	eMIT[47]	
Chloramphenicol	i.v.	1 g 4 × day	5.56	BNF[48]	
Ciprofloxacin	Oral	500 mg 2 × day	0.05	eMIT[47]	0.15
Ciprofloxacin	i.v.	400 mg 2 × day	2.02	eMIT[47]	39.58
Clarithromycin	Oral	250 mg 2 × day	0.13	eMIT[47]	
Clarithromycin	i.v.	500 mg 2 × day	5.24	eMIT[47]	
Clindamycin	Oral	150 mg 4 × day	0.24	eMIT[47]	
Clindamycin	i.v.	600 mg 3 × day	7.27	eMIT[47]	
Co-amoxiclav	Oral	375 mg 3 × day	0.21	eMIT[47]	0.32
Co-amoxiclav 625 mg	Oral	625 mg 3 × day	0.22	eMIT[47]	
Co-amoxiclav	i.v.	600 mg 3 × day	1.64	eMIT[47]	3.63
Co-amoxiclav 1.2 g	i.v.	1.2 g 3 × day	1.91	eMIT[47]	
Colomycin nebs (Colistimethate sodium)	Oral	1 million units 2 × day	3.36	BNF[48]	
Colistimethate sodium	i.v.	1 million units 2 × day	3.36	BNF[48]	
Co-trimoxazole	Oral	960 mg 2 × day	0.49	eMIT[47]	
Co-trimoxazole	i.v.	960 mg 2 × day	7.12	BNF[48]	
Daptomycin	i.v.	350 mg 1 × day	62.00	BNF[48]	
Demeclocycline	Oral	150 mg 4 × day	11.64	BNF[48]	
Doxycycline	Oral	200 mg first day, 100 mg 1 × day subsequent days	0.07 day 1, 0.03 thereafter	eMIT[47]	0.28 day 1, 0.14 thereafter
Ertapenem	i.v.	1 g 1 × day	31.65	BNF[48]	
Erythromycin	Oral	250 mg 4 × day	0.11	eMIT[47]	0.24
Erythromycin	i.v.	Erythromycin lactobionate 1 g 4 × day	43.92	BNF[48]	

TABLE 63 Unit costs for antibiotics (*continued*)

Drug name	Route	Assumed dose/frequency per day	Daily cost (£)	Source	Daily cost (£) from BNF[47] for sensitivity analyses
Flucloxacillin	Oral	250 mg 4 × day	0.11	eMIT[47]	
Flucloxacillin	i.v.	0.25 g 4 × day	1.68	eMIT[47]	4.92
Fluconazole	Oral	400 mg first day, 200 mg 1 × day subsequently	0.19 day 1, 0.09 thereafter	eMIT[47]	
Fluconazole	i.v.	400 mg first day, 200 mg 1 × day subsequently	1.80 day 1, 0.94 thereafter	eMIT[47]	
Fusidic acid	Oral	500 mg 3 × day	1.81	BNF[48]	
Gentamicin	i.v.	80 mg 3 × day	1.57	eMIT[47]	5.85
Imipenem	i.v.	500 mg 4 × day	17.67	eMIT[47]	
Levofloxacin	Oral	500 mg 1 × day	0.23	eMIT[47]	
Levofloxacin	i.v.	500 mg 1 × day	1.87	eMIT[47]	
Linezolid	Oral	600 mg 2 × day	89.00	BNF[48]	
Linezolid	i.v.	600 mg 2 × day	89.00	BNF[48]	
Meropenem	i.v.	0.5 g 3 × day	7.86	eMIT[47]	24.00
Metronidazole	Oral	400 mg 3 × day	0.05	eMIT[47]	0.21
Metronidazole	i.v.	500 mg 3 × day	1.20	eMIT[47]	9.30
Nitrofurantin	Oral	50 mg 4 × day	5.23	BNF[48]	
Piperacillin/tazobactam	i.v.	4.5 g 3 × day	5.68	eMIT[47]	
Rifampicin	Oral	300 mg 3 × day	0.42	eMIT[47]	
Rifampicin	i.v.	600 mg 3 × day	7.66	eMIT[47]	
Oseltamivir (Tamiflu®, Roche pharmaceuticals)	Oral	75 mg 2 × day	3.08	BNF[48]	
Teicoplanin	i.v.	400 mg 2 × day for three doses, subsequently 400 mg 1 × day	12.24 day 1, 6.12 thereafter	eMIT[47]	14.64 day 1, 7.32 thereafter
Temocillin	i.v.	1 g 2 × day	50.90	BNF[48]	
Timentin	i.v.	3.2 g 3 × day	15.99	BNF[48]	
Trimethoprim	Oral	200 mg 2 × day	0.03	eMIT[47]	0.14
Vancomycin	i.v.	0.5 g 2 × day	2.32	eMIT[47]	12.50

i.v., intravenous; nebs, nebulisers.

TABLE 64 Unit costs for regular medications

Recorded on CRF	Assumed drug	Assumed route	Assumed dose/frequency per day	Daily cost (£) from BNF[47]
Digoxin	Digoxin	Oral	125 µg daily	0.04
Diuretics	Furosemide	Oral	40 mg daily	0.03
Beta-blockers	Atenolol	Oral	25 mg daily	0.03
Calcium antagonists	Amlodipine	Oral	5 mg daily	0.03
Aspirin	Aspirin	Oral	75 mg daily	0.03
Oral nitrates	Isosorbide dinitrate	Oral	80 mg daily	0.98
Angiotensin 2 blockers	Losartan	Oral	25 mg daily	0.04
ACE inhibitors	Ramipril	Oral	5 mg daily	0.04
Warfarin	Warfarin sodium	Oral	3 mg daily	0.03
Clopidogrel	Clopidogrel	Oral	75 mg daily	0.06
Statins	Simvastatin	Oral	40 mg daily	0.04
Antiarrhythmic	Amiodarone	Oral	200 mg daily	0.06
Heparin/clexane	Enoxaparin sodium	S/C	20 mg daily	2.27
Intravenous glyceryl trinitrate/nitrates	Glyceryl trinitrate	i.v.	25 mg daily	6.49
$FeSO_4$	Ferrous Sulphate	Oral	200 mg (65 mg iron) 3 × day	0.11

ACE, angiotensin-converting enzyme; i.v., intravenous; S/C, subcutaneous.

TABLE 65 Resource use assumed for complications and total costs

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 echocardiography, 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, intravenous fluids	275.49	Reoperations already captured
Intestinal obstruction/perforation	Laparotomy, parental nutrition	2893	Reoperations already captured

TABLE 65 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Post-operative haemorrhage	Chest radiograph	41	Reoperations already captured. Assume no additional costs for participants who have a reoperation on the same day/ following day as post-operative haemorrhage
ARDS	Transoesophageal echocardiography, three chest radiographs	395	Reintubation and intensive care already captured
Reintubation/ventilation	Transoesophageal echocardiography, three chest radiographs	395	
Initiation of mask CPAP	CPAP, chest radiograph	539	
Tracheostomy	Tracheostomy, chest radiograph	5354	
Pneumothorax requiring chest drainage	Chest radiograph, chest drain	4218	
Pleural effusion requiring drainage	Chest radiograph, chest drain	4218	
Pacing	Temporary pacemaker	3073	
SVT/AF requiring treatment	Amiodarone	4.79	
Deep-vein thrombosis	Duplex scan of leg veins, intravenous heparin	202.43	Warfarin already captured
VF/VT requiring intervention	Transoesophageal echocardiography, emergency coronary angiography, chest radiograph	2007	Emergency reoperations and reintubation captured elsewhere
Low cardiac output requiring management (including IABP)	Transoesophageal echocardiography, chest radiograph	313	
Wound dehiscence requiring rewiring/treatment	Minor treatment (£161), or VAC therapy if stated (£3501)	161 or 3501	Assume reoperation covers this complication if reoperation the same day or next day
Cardiac tamponade	Transoesophageal echocardiography, chest radiograph	313	Reoperations and red blood cells already captured
Other GI complications			
Abdominal distention/small bowel dilatation/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 i.v. for dehydration	3592	
Duodenal ulcer	Endoscopy	676	

continued

TABLE 65 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
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	
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	
Laparoscopy	Laparoscopy	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 owing to abdominal aortic aneurysm repair	CT scan	62	
Rectal bleed	Endoscopy	676	
Upper GI bleed owing to transoesophageal echocardiography	Endoscopy	676	
Other pulmonary complications – all assumed to have two chest radiographs, add £82 to all			
Suspected chest infection	No additional treatment	0	Antibiotics and reintubation already captured
Aspiration pneumonia/ pneumonia	No additional treatment	0	Antibiotics and reintubation already captured
BIPAP commenced	BIPAP	498	
Basal atelectasis	Chest radiographs, physiotherapy	180	CPAP already captured
Basal respiratory wheeze	Nebulised 0.9% saline (10 ml) or salbutamol (2.5 mg) 4 times daily	1035	
Bronchopneumonia	No additional treatment	0	Antibiotics and reintubation already captured
Fluid overload	No additional treatment	0	Antibiotics and reintubation already captured
Left and right haemothorax/ haemothorax requiring chest drainage	Chest drain	4177	
Heart failure	Diuretics	0.15	Reintubation already captured

TABLE 65 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Increasing oxygen requirements, chest examination	Physiotherapy	139	CPAP and reintubation already captured
Infection	No additional treatment	0	Antibiotics and reintubation already captured
Left pneumothorax	Chest radiograph	41	
Lower respiratory tract infection	No additional treatment	0	Antibiotics and reintubation already captured
Overloaded	Diuretics	0.15	Reintubation already captured
Pericardial effusion/pericardial effusions with atelectasis	No treatment in mild cases	0	Reoperation and reintubation already captured
Pleuritic pain	Analgesia	6	
Pneumonia and respiratory failure	No additional treatment	0	Antibiotics and reintubation already captured
Pulmonary oedema	Diuretics	0.15	Reintubation already captured
Right lower lobe collapse and atelectasis changes on chest radiograph	Chest radiograph, physiotherapy	180	CPAP and reintubation already captured
Reduced air entry to bases/ respiratory distress/respiratory failure	Physiotherapy	139	CPAP and reintubation already captured
Respiratory arrest	No additional treatment	0	Reintubation already captured
Slight decrease in entry in both bases	Physiotherapy	139	CPAP and reintubation already captured
(Small) pleural effusion left side/ right side/bilateral	No treatment	0	
Surgical emphysema	Chest drain, chest radiograph	4218	
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 reintubation already captured
Other arrhythmia complications – all assumed to have two ECGs, add £106 to all			
AV block/first 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	14,564	
Heart block-paced	No additional treatment	0	Pacing already captured
Arrhythmia	Amiodarone	4.79	

continued

TABLE 65 Resource use assumed for complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumptions
Asystole/P wave asystole/cardiac arrest/pulseless electrical activity arrest	CPR	1491	Reintubation already captured
Asystole with permanent pacemaker insertion	Permanent pacemaker	14,564	
Atrial flutter	Amiodarone	4.79	
Bradycardia/intermittent 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	
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	Reintubation already captured
New AF	No additional treatment	0	Pacing already captured
Permanent pacemaker implanted	Permanent pacemaker	14,564	
SVT/flutter	Amiodarone	4.79	
Sinus tachycardia	No treatment	0	
Type B Wolff–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	

AF, atrial fibrillation; AV, aortic valve; BIPAP, bilevel positive airway pressure; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; i.v., intravenous; SVT, supraventricular tachycardia; TIA, transient ischaemic attack; VAC, vacuum-assisted closure; VF, ventricular fibrillation; VT, ventricular tachycardia.
Resource use assumed for complications and total costs are shown here, unit costs and sources are shown in *Table 66*.
VAC therapy comprises a vacuum (negative pressure) device applied to wounds that are infected.

TABLE 66 Unit costs for complications

Treatment/action	Unit cost (£)	Source for cost information
24-hour Holter monitor	204	NHS Reference Costs 2012/13.[45] Day cases. EA47Z electrocardiogram monitoring and stress testing. 320 cardiology. Lower quartile cost
Antibiotics (piperacillin/tazobactam, 4.5 g i.v. 3 × day for 5 days)	28.40	eMIT[47]
Amiodarone (1.2 g i.v., then oral 200 mg 3 × day for 1 week, 2 × day for 1 week)	4.79	eMIT[47]
Analgesia (morphine sulphate, 10 mg i.v. every 4 hours for 5 days)	6	eMIT[47]
Antinausea medication (ondanestron, 4 mg i.v. for 5 days)	0.63	eMIT[47]
BIPAP	498	As CPAP
Cardioversion	808	Lord *et al.*[76] Costs have been inflated using the HCHS inflation index
Chest drain	4177	NHS Reference Costs 2012/13[45]
Chest radiograph	41	Finance Department, teaching hospital, South Central, 2012, personal communication. Costs have been inflated using the HCHS inflation index
Coronary angiography	1694	NHS Reference Costs 2012/13[45]
CPAP	498	Grey *et al.*[77] Costs have been inflated using the HCHS inflation index
CPR	1491	NHS Reference Costs 2012/13[45]
CT scan	62	NHS Reference Costs 2012/13.[45] Diagnostic Imaging – Direct Access. RA08 A Computerised Tomography Scan, one area, no contrast, 19 years and over. 100 general surgery
Diuretics (furosemide 40 mg orally for 5 days)	0.15	BNF[48]
Drainage of pus under local anaesthesia	426	NHS Reference Costs 2012/13.[45] Elective inpatients. JC43 A Minor Skin Procedures, 13 years and over. 320 Cardiology
Drainage of pus under general anaesthesia	1919	NHS Reference Costs 2012/13.[45] Elective inpatients. JC43 A Minor Skin Procedures, 13 years and over. 172 Cardiac Surgery
Duplex scan of leg veins	155	NHS Reference Costs 2012/13.[45] Diagnostic Imaging – Outpatients. RA10Z Computerised Tomography Scan, one area, pre and post contrast. 172 Cardiac Surgery
ECG	53	NHS Reference Costs 2012/13.[45] Directly Accessed Diagnostic Services. EA47Z Electrocardiogram Monitoring and stress testing
Echocardiography – transthoracic	121	NHS Reference Costs 2012/13.[45] Diagnostic Imaging – Outpatients. RA60 A Simple Echocardiogram, 19 years and over. 172 Cardiac Surgery
Echocardiography – transoesophageal	272	NHS Reference Costs 2012/13.[45] Day Cases. EA45Z Complex Echocardiogram, including Transoesophageal and Fetal Echocardiography. 320 Cardiology. Lower quartile cost
Endoscopy	676	NHS Reference Costs 2012/13[45]
Fluoroscopy	115	NHS Reference Costs 2012/13.[45] Diagnostic Imaging – Outpatients. RA16Z Contrast Fluoroscopy Procedures, less than 20 minutes. 172 Cardiac Surgery

continued

TABLE 66 Unit costs for complications (*continued*)

Treatment/action	Unit cost (£)	Source for cost information
Haemofiltration (assume for 2 days)	1438	NHS Reference Costs 2012/13.[45] Renal Dialysis at Base. LE01 A. Haemodialysis for Acute Kidney Injury, 19 years and over
IABP – used in sensitivity analysis	2776	NICE Medical Technology Guidance 8, 2011.[78] Costs have been inflated using the HCHS inflation index
Intravenous fluids (gelofusine, 1500 ml)	13.49	BNF[48]
Insulin (1000 units for 5 days)	138.60	BNF[48]
i.v. heparin (initial 5000 units, then 15,000 units every 12 hours for 5 days)	47.43	BNF[48]
Isolation room, stool culture and i.v. for dehydration	3592	NHS Reference Costs 2012/13[45]
Omeprazole (i.v. omeprazole 40 mg for 3 days, then 40 mg oral daily for 5 days)	12.68	BNF,[48] eMIT[47]
Laparoscopy	2693	As laparotomy
Laparotomy	2693	NHS Reference Costs 2012/13[45]
Laxatives, enemas (bisacodyl, 5 mg; sodium citrate, assume for 5 days)	2.25	BNF,[48] eMIT[47]
Minor treatment for wound dehiscence	161	NHS Reference Costs 2012/13.[45] Elective inpatients. JC43 A 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.[45] 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[45]
Nebulised 0.9% saline (10 ml) or salbutamol (2.5 mg) 4 times daily	1035	NHS Reference Costs 2012/13[45]
Parenteral nutrition (assume 5 days)	200	NICE, Nutrition Support in Adults: Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition Costing Report, 2006.[79] Costs have been inflated using the HCHS inflation index
Permanent pacemaker	14,564	NHS Reference Costs 2012/13[45]
Physiotherapy/rehabilitation	139	NHS Reference Costs 2012/13.[45] Elective inpatients. DZ30Z Chest Physiotherapy. 340 Respiratory Medicine
Speech and language therapy review	109	NHS Reference Costs 2012/13.[45] 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.[45] 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.[45] 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

TABLE 66 Unit costs for complications (*continued*)

Treatment/action	Unit cost (£)	Source for cost information
Tracheostomy	5313	NHS Reference Costs 2012/13[45]
Ultrasound	67	NHS Reference Costs 2012/13.[45] 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
Negative Pressure Wound Therapy	3501	NHS Reference Costs 2012/13.[45] Elective inpatients. JC42 A 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

BIPAP, bilevel positive airway pressure; CPR, cardiopulmonary resuscitation; IABP, intra-aortic balloon pump; i.v., intravenous.

TABLE 67 Unit costs for reattending hospital

Resource	Unit cost (£)	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
Ward day for readmissions	265	NHS Reference Costs 2012/13.[45] Non-elective inpatient excess bed-day cost across all activities
ICU day for readmissions	1168	NHS Reference Costs 2012/13.[45] Critical Care Services – Adult: Critical Care Unit (weighted average of XC01Z–XC07Z, 0–6 organs supported)
ED attendance, leading to admission	154	NHS Reference Costs 2012/13.[45] ED services, excluding dental care. Weighted average of all admitted codes
ED attendance, not leading to admission	101	NHS Reference Costs 2012/13.[45] ED services, excluding dental care. Weighted average of all non-admitted codes
Ambulance to hospital	230	NHS Reference Costs 2012/13.[45] Ambulance services, ASS02, see and treat and convey

TABLE 68 Resource use assumed for readmission complications and total costs

Complication	Treatment/action	Cost (£)	Assumption
Antibiotics			
Site = respiratory	Antibiotics, chest radiograph	69.40	
Site = surgical wound	Antibiotics, chest radiograph, CT scan	131.40	
Site = blood	Antibiotics	28.40	
Site = other – endocarditis	Antibiotics, chest radiograph, CT scan	131.40	
Site = other – infective endocarditis	Antibiotics, chest radiograph, CT scan, transthoracic echocardiography	252.40	
Site = other – respiratory tract infection	Antibiotics, chest radiograph	69.40	
Site = other – wound	Antibiotics, chest radiograph, CT scan	131.40	
Site = other – all others including UTI	Antibiotics	28.40	
Deep-vein thrombosis	Duplex scan of leg veins, i.v. heparin, warfarin	203.78	
Cardiac tamponade	Transoesophageal echocardiography, chest radiograph, two red blood cells	559.62	Reoperations captured elsewhere
Other GI complications			
Barrett's oesophagus	Endoscopy	676	
Dehydration, hypovolaemia secondary to 3 days of diarrhoea	i.v. fluids	13.49	
Gastroenteritis	i.v. fluids	13.49	
Oesophageal ulcer	Endoscopy	676	
Peritonitis	Laparotomy, CT scan	2755	
Vomiting related to amiodarone. Medication changed	i.v. fluids	13.49	
Other pulmonary complications: all assumed to have two chest radiographs and an ECG – add £135 to all			
Suspected/possible pulmonary embolism – diagnosed with pleuritic chest pain	CT scan, transthoracic echocardiography	183	
Acute shortness of breath – treated with diuretics	Diuretics, transthoracic echocardiography	121.15	
Breathing difficulties at routine outpatients. Kept in overnight for breathing assessment	Transthoracic echocardiography	121	
Breathlessness and cough	Transthoracic echocardiography	121	
Chest pain and shortness of breath	Transthoracic echocardiography	121	
Chest pain on inspiration/coughing	CT scan	62	
Cough	No treatment	0	
Dyspnoea	Transthoracic echocardiography	121	
End stage heart failure	Diuretics, transthoracic echocardiography	121.15	

TABLE 68 Resource use assumed for readmission complications and total costs (*continued*)

Complication	Treatment/action	Cost (£)	Assumption
Failed extubation	No additional treatment	0	Covered in ICU cost
Left hydropneumothorax	Chest ultrasonography, chest drain	4244	
Musculoskeletal chest pain	Analgesia	6	
Pleural effusion and bilateral pedal oedema	Chest ultrasonography, diuretic therapy	67.15	
Pleural effusion not requiring drainage	Chest ultrasonography	67	
Pleural effusion treated with increased dose of furosemide	Furosemide (80 mg)	0.30	
Pleuritic left lung (not requiring drainage)	Analgesia	6	
Pulmonary fibrosis	No treatment	0	
Right sided pleural effusion and empyema, ultrasonography-guided drainage, 2 units blood transfused, treated with i.v. antibiotics	Chest drain, 2 units red blood cells, i.v. antibiotics	4452.02	
Severe chest pain, possible pulmonary embolism but ruled out following investigations	Transthoracic echocardiography, CT pulmonary angiogram (CT chest)	183	
Shortness of breath	Transthoracic echocardiography	121	
Shortness of breath owing to fluid overload, diuretics increased	Transthoracic echocardiography, furosemide (80 mg)	121.30	
Sudden onset of shortness of breath, small right pleural effusion	Transthoracic echocardiography	121	
Other arrhythmia complications: all assumed to have two ECGs – add £106 to all			
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
Other thromboembolic complications			
Pulmonary embolus	Transthoracic echocardiography, CT pulmonary angiogram (CT chest), i.v. heparin for 5 days, warfarin	231.78	
Apical thrombus	Transthoracic echocardiography, i.v. heparin for 5 days, warfarin	169.78	
Possible bilateral renal infarcts	CT scan, i.v. heparin, warfarin	110.78	
Small leg thrombus	Ultrasonography of leg, i.v. heparin, warfarin	115.78	

AF, atrial fibrillation; i.v. intravenous; UTI, urinary tract infection.
Resource use assumed for readmission complications and total costs are shown here, unit costs and sources are shown in *Table 69*. Resource use and costs for readmission complications as inpatient complications if not reported here.

TABLE 69 Unit costs for readmission complications (not previously presented)

Treatment/action	Unit cost (£)	Reference
Diuretics (furosemide 80 mg orally for 5 days)	0.30	BNF[48]
Warfarin (3 mg daily, assumed given for half of follow up time, 45 days)	1.35	BNF[48]

TABLE 70 Unit costs for outpatient appointments

Specialty	Unit cost (£)	Service code	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
Anticoagulation service	25	324	These are all sourced from NHS Reference Costs 2012–13.[45] They are all average costs for each specialty (costs taken from the Total – Outpatient Attendances page of the NHS Reference Costs 2012–13, Total activity section)
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	
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 GI surgery	120	106	
Urology	101	101	
Vascular surgery	142	107	

TABLE 71 Unit costs for other outpatient attendances

Resource	Unit cost (£)	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
Renal/dialysis	157	NHS Reference Costs 2012/13.[45] Renal Dialysis at Base. LD02 A Hospital Haemodialysis or Filtration, with Access via Arteriovenous Fistula or Graft, 19 years and over
Outpatient endoscopy	676	As endoscopy, previously given (see *Table 66*)
ECG	53	As previously given (see *Table 66*)
Electrocardiogram monitoring and stress testing	204	As 24-hour Holter monitor (see *Table 66*)
CT scan	62	As previously given (see *Table 66*)
Echocardiography scan – transthoracic	121	As previously given (see *Table 66*)
MRI scan	248	As previously given (see *Table 66*)
Chest radiography	41	As previously given (see *Table 66*)
Chest radiography and ultrasonography	108	As previously given (see *Table 66*)
Sigmoidoscopy	164	NHS Reference Costs 2012/13.[45] Procedures in Outpatients. FZ57Z Diagnostic or Therapeutic, Rigid Sigmoidoscopy, 19 years and over. 104 Colorectal Surgery

TABLE 72 Costs for resource use associated with SAEs (not previously presented)

Treatment/action	Unit cost (£)	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
Bladder cystoscopy	129	NHS Reference Costs 2012/13.[45] Procedures in Outpatients. LB15E Minor Bladder Procedures, 19 years and over. 101 Urology
Colonoscopy	257	NHS Reference Costs 2012/13.[45] Procedures in Outpatients. FZ51Z Diagnostic Colonoscopy, 19 years and over. 100 General Surgery
Diverticulitis	686	NHS Reference Costs 2012/13.[45] 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.[45] Day Cases. EA47Z Electrocardiogram Monitoring and stress testing. 320 Cardiology
Fasciotomy	6182	NHS Reference Costs 2012/13.[45] 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 (see *Table 66*)
Groin scan/procedure of lymphatic system	3191	NHS Reference Costs 2012/13[45]
Oesophagogastroduodenoscopy	676	As endoscopy (see *Table 66*)
Leg amputation	13,353	NHS Reference Costs 2012/13.[45] Non-elective inpatients. QZ11D Amputations with CC Score 8–13. 107 Vascular Surgery
Recatheterisation	1534	NHS Reference Costs 2012/13[45]
Stoma bag system	63.38	NHS Electronic Drug Tariff.[80] Part IXC – Stoma Appliances (Colostomy Sets). Weighted average of all sets
Tesio catheter insertion under fluoroscopy	325	NHS Reference Costs 2012/13[45]
Uroscopy	129	NHS Reference Costs 2012/13.[45] Procedures in Outpatients. LB15E Minor Bladder Procedures, 19 years and over. 101 Urology

TABLE 73 Unit costs for post-discharge community health and social care contacts

Resource	Unit cost (£)	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
GP at surgery	34	Unit Costs of Health and Social Care 2013;[49] 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;[49] 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;[49] 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;[49] 10.1, Community Nurse. Using data from NHS Reference Costs 2011/12,[45] the mean average cost for a face-to-face contact in district nursing services for 2012/2013 was £39, with an IQR of £33 to £46. Costs have been uprated using the HCHS pay and prices inflator
Other NHS or social services		
Cardiac rehabilitation/ exercise class	42	NHS Reference Costs 2012/13;[45] Total – Outpatient Attendances. 327 – Cardiac Rehabilitation
Cardiac nurse	70	NHS Reference Costs 2012/13;[45] Community Health Services – Nursing, N11AF, Specialist Nursing – Cardiac Nursing/Liaison, Adult, Face to face
Diabetic nurse	70	NHS Reference Costs 2012/13;[45] Community Health Services – Nursing, N15AF, Specialist Nursing – Diabetic Nursing/Liaison, Adult, Face to face
Anticoagulation service	10	NHS Reference Costs 2012/13;[45] 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;[49] 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;[45] Non Consultant Led Outpatient Attendances; Non-Admitted Non-Face to Face Attendance, Follow-up, 327 – Cardiac Rehabilitation
Dietitian	71	NHS Reference Costs 2012/13;[45] Community Health Services – Allied Health Professionals. A03 – Dietician
Health-care support worker	16	Unit Costs of Health and Social Care 2013;[49] 10.5, Clinical support worker nursing (community). £30 per hour of home visiting. Contact assumed to be for 32.9 minutes[a]
Occupational therapist	53	Unit Costs of Health and Social Care 2013;[49] 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 IQR of £30 to £64. Costs have been uprated using the HCHS pay and prices inflator
Physiotherapist	34	Unit Costs of Health and Social Care 2013;[49] 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 IQR of £28 to £38. Costs have been uprated using the HCHS pay and prices inflator
Social worker	87.19	Unit Costs of Health and Social Care 2013;[49] 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]

continued

TABLE 73 Unit costs for post-discharge community health and social care contacts (*continued*)

Resource	Unit cost (£)	Reference: sheet from which costs were taken, specific HRG code and/or specialty code from which costs were taken
Other NHS or social services at home		
Cardiac rehabilitation/nurse	70	NHS Reference Costs 2012/13;[45] Community Health Services – Nursing. N11AF Specialist Nursing – Cardiac Nursing/Liaison, Adult, Face to face
Phone call to cardiology	49	NHS Reference Costs 2012/13;[45] Outpatients. WF01C, Non-Admitted Non-Face to Face Attendance, Follow-up. 320 – Cardiology
Carer	8.50	Unit Costs of Health and Social Care 2013;[49] 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% of a home care workers' time was spent travelling. Assume 30-minute visit
Community matron	68	NHS Reference Costs 2012/13;[45] 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;[49] 10.2 Nurse (mental health), £65 per hour of face-to-face contact, excluding qualifications. Contact assumed to be for 32.9 minutes[a]
Dietitian	71	NHS Reference Costs 2012/13;[45] Community Health Services – Allied Health Professionals. A03 – Dietician
Occupational therapist	73	Unit Costs of Health and Social Care 2013;[49] 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 IQR of £50 to £86. Costs have been updated using the HCHS pay and prices inflator
Paramedic	174	NHS Reference Costs 2012/13;[45] Ambulance Services. ASS01 – See and treat or refer
Physiotherapist	47	Unit Costs of Health and Social Care 2013;[49] 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 IQR of £37 to £52. Costs have been uprated using the HCHS pay and prices inflator
Social worker	87.19	Unit Costs of Health and Social Care 2013;[49] 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;[45] Community Health Services – Nursing, N29AF, Other Specialist Nursing, Adult, Face to face
Respiratory nurse	75	NHS Reference Costs 2012/13;[45] 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[81]
Indoor and outdoor grab rails	91	Unit Costs of Health and Social Care 2013;[49] 7.3.1, social services access improvements
Mobile shower chair	55	Unit Costs of Health and Social Care 2013;[49] 7.3.1, social services shower

AF, atrial fibrillation; LA, local authority.

a When 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;[49] section 13.1).

A detailed breakdown of total average costs per participant

TABLE 74 Detailed breakdown of total average costs per participant to 3 months from surgery for both trial groups

Resource use	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
Red blood cells			
Red blood cells	257 (12)	379 (13)	–122 (18)
Red blood cell administration	30 (1)	48 (1)	–17 (2)
Total red blood cells	**287 (13)**	**427 (15)**	**–140 (19)**
Cardiac procedure			
Initial cardiac surgery	7309 (18)	7313 (18)	–4 (26)
Blood products			
FFP	27 (2)	26 (2)	1 (2)
Platelets	135 (7)	134 (7)	1 (10)
Cryoprecipitate	43 (5)	39 (4)	4 (7)
Total blood products	**206 (12)**	**199 (11)**	**7 (16)**
Inpatient complications			
Primary outcome			
Antibiotics for infectious complication	21 (5)	14 (2)	7 (5)
Stroke	3 (1)	3 (1)	0 (1)
Suspected MI	6 (3)	13 (5)	–7 (6)
Gut infarction	11 (6)	3 (3)	8 (6)
AKI – stage 3	86 (11)	73 (10)	13 (15)
Other complications			
Reoperation	636 (70)	704 (75)	–67 (102)
Reintubation	28 (4)	29 (4)	–1 (5)
Tracheostomy	182 (32)	176 (31)	6 (45)
Mask CPAP	68 (6)	65 (7)	3 (9)
Pneumothorax requiring chest drainage	59 (16)	55 (15)	4 (22)
Pleural effusion requiring drainage	245 (32)	248 (36)	–3 (48)
Pacing	946 (48)	956 (47)	–9 (67)
SVT/AF requiring treatment	2 (0)	2 (0)	0 (0)
VF/VT requiring intervention	44 (11)	16 (6)	28 (13)
Low cardiac output	33 (3)	35 (4)	–1 (5)
SAEs	17 (7)	12 (5)	5 (9)
Other inpatient complications	296 (54)	311 (54)	–15 (76)
Total complications and SAEs	**2684 (137)**	**2714 (146)**	**–30 (200)**

continued

TABLE 74 Detailed breakdown of total average costs per participant to 3 months from surgery for both trial groups (*continued*)

Resource use	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
Inpatient LOS			
CICU	1359 (138)	1330 (158)	29 (210)
HDU	1916 (72)	1890 (74)	25 (104)
Ward	2221 (59)	2287 (68)	–66 (90)
ICU	8 (8)	17 (12)	–9 (14)
Another unit/hospital	351 (51)	368 (51)	–17 (72)
Total LOS	**5854 (201)**	**5892 (221)**	**–38 (299)**
Blood saving techniques			
Tranexamic acid	13 (0)	13 (0)	0 (0)
Trasylol	13 (2)	11 (2)	2 (3)
Intraoperative cell salvage	85 (3)	88 (3)	–4 (4)
Post-operative cell salvage	10 (1)	8 (1)	2 (2)
Beriplex	22 (3)	20 (3)	–2 (4)
Factor VIIa	17 (7)	12 (6)	5 (9)
Total blood saving techniques	**159 (9)**	**152 (8)**	**7 (12)**
Fluids in theatre/CICU/HDU			
Inotropes	36 (1)	35 (1)	1 (1)
Gelofusine	7 (0)	7 (0)	0 (0)
HES	9 (1)	9 (1)	0 (1)
Other fluids	3 (0)	3 (0)	0 (0)
Total fluids	**55 (1)**	**55 (1)**	**0 (2)**
Readmissions to hospital			
LOS (ward and ICU)	446 (58)	447 (50)	–1 (76)
Complications and SAEs	271 (38)	259 (40)	12 (55)
Readmission via ED and/or ambulance	52 (4)	47 (4)	5 (6)
Total readmissions	**770 (85)**	**753 (78)**	**17 (116)**
ED attendances			
Total ED visits	9 (1)	8 (1)	1 (1)
Ambulance to ED	7 (1)	4 (1)	3 (2)
Total ED	**16 (2)**	**12 (2)**	**4 (3)**
Outpatient appointments			
Cardiac surgery outpatient visits	131 (5)	151 (6)	–20 (8)
Cardiology outpatient visits	37 (2)	33 (2)	4 (3)
Other outpatient visits	32 (4)	30 (4)	2 (5)
Ambulance to appointment	1 (0)	2 (1)	0 (1)
Total outpatients	**202 (6)**	**216 (7)**	**–14 (9)**

TABLE 74 Detailed breakdown of total average costs per participant to 3 months from surgery for both trial groups (*continued*)

Resource use	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
Other health and social care contacts			
GP at surgery	68 (2)	71 (2)	–3 (3)
GP at home	37 (3)	32 (2)	5 (4)
Practice nurse	18 (1)	18 (1)	0 (2)
District nurse	96 (8)	86 (7)	10 (11)
Other contacts	160 (9)	160 (12)	0 (15)
Total other contacts	**378 (14)**	**366 (16)**	**12 (21)**
Total costs	**17,945 (332)**	**18,127 (357)**	**–182 (488)**

AF, atrial fibrillation; HES, hydroxyethyl starch; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
Costs do not always sum to totals owing to rounding.

Changes in the use of regular medications between admission to and discharge from the cardiac surgery unit

Information on regular medications taken by participants was recorded on CRF Form D2 for two time points (1) on admission to the cardiac surgery unit (baseline) and (2) at discharge from the cardiac surgery unit. In the main costing analyses, we assumed that any medications participants were on at discharge, they took for the 3-month follow-up and were costed for 3 months.

In this separate analysis, we summarised the number of participants on each medication at baseline and at discharge, and the change in the use of medications. We then costed the medications participants were on at baseline and at discharge for a period of 1 week to get an insight into the costs of their regular use. Comparisons were then made between the costs of these medications taken at baseline and at discharge from hospital, to determine whether or not there were significant changes before and after surgery. There was very little missing data for the use of regular medications at baseline and at discharge. Complete information was available for all drugs at both time points for 1990 of the 2003 participants and, therefore, a complete case analysis was performed.

Table 75 shows the number of participants on each medication at baseline and at discharge, and the change between the time points for each transfusion group. There was quite a lot of change in the use of medications before and after surgery. The use of diuretics, aspirin, warfarin and antiarrhythmics increased considerably in both groups from baseline to discharge, whereas the use of calcium antagonists, oral nitrates and angiotensin-converting enzyme (ACE) inhibitors reduced after surgery in both groups. The use of $FeSO_4$ increased after surgery, but to a much greater extent in the restrictive group than the liberal group.

Table 76 shows the mean weekly costs per participant in each group for each of the medications at baseline and at discharge. The daily unit cost for each of the drugs is also shown and most are very inexpensive. Costs have reduced after surgery – mean total costs are similar in both groups, approximately £4 at baseline and £2 at discharge. The reduction in costs after surgery is driven by the reduced costs of oral nitrates and intravenous glyceryl trinitrate in both groups, and also by the reduced cost of heparin in the liberal group.

TABLE 75 The number of participants on each regular medication at baseline and discharge, for each transfusion group

	Restrictive threshold, $n = 992$			Liberal threshold, $n = 998$		
Drug name	Baseline, frequency (%)	Discharge, frequency (%)	Discharge vs. baseline, frequency (%) difference	Baseline, frequency (%)	Discharge, frequency (%)	Discharge vs. baseline, frequency (%) difference
Digoxin	44 (4)	38 (4)	–6 (–1)	57 (6)	54 (5)	–3 (–0)
Diuretics	336 (34)	634 (64)	298 (30)	360 (36)	652 (65)	292 (29)
Beta blockers	590 (59)	668 (67)	78 (8)	588 (59)	671 (67)	83 (8)
Calcium antagonists	228 (23)	101 (10)	–127 (–13)	247 (25)	106 (11)	–141 (–14)
Aspirin	597 (60)	754 (76)	157 (16)	606 (61)	777 (78)	171 (17)
Oral nitrates	222 (22)	27 (3)	–195 (–20)	217 (22)	26 (3)	–191 (–19)
Angiotensin 2 blockers	116 (12)	55 (6)	–61 (6)	114 (11)	60 (6)	–54 (–5)
ACE inhibitors	453 (46)	338 (34)	–115 (–12)	425 (43)	328 (33)	–97 (10)
Warfarin	108 (11)	263 (27)	155 (16)	119 (12)	251 (25)	132 (13)
Clopidogrel	187 (19)	141 (14)	–46 (–5)	162 (16)	152 (15)	–10 (–1)
Statins	713 (72)	726 (73)	13 (1)	720 (72)	757 (76)	37 (4)
Anti-arrhythmic	24 (2)	284 (29)	260 (26)	29 (3)	273 (27)	244 (24)
Heparin	33 (3)	33 (3)	0 (0)	54 (5)	33 (3)	–21 (–2)
Intravenous glyceryl trinitrate	23 (2)	2 (0)	–21 (–2)	21 (2)	9 (1)	–12 (–1)
$FeSO_4$	29 (3)	154 (16)	125 (13)	37 (4)	63 (6)	26 (3)

ACE, angiotensin-converting enzyme.

TABLE 76 Weekly costs per participant for regular medications at baseline and at discharge

Drug name	Daily unit cost (£)	Restrictive threshold, *n* = 992			Liberal threshold, *n* = 998		
		Baseline, mean cost (£)	Discharge, mean cost (£)	Discharge vs. baseline, mean cost (£) difference	Baseline, mean cost (£)	Discharge, mean cost (£)	Discharge vs. baseline, mean cost (£) difference
Digoxin	0.04	0.01	0.01	0.00	0.02	0.02	0.00
Diuretics	0.03	0.07	0.13	0.06	0.08	0.14	0.06
Beta-blockers	0.03	0.12	0.14	0.02	0.12	0.14	0.02
Calcium antagonists	0.03	0.05	0.02	–0.03	0.05	0.02	–0.03
Aspirin	0.03	0.13	0.16	0.03	0.13	0.16	0.04
Oral nitrates	0.98	1.54	0.19	–1.35	1.49	0.18	–1.31
Angiotensin 2 blockers	0.04	0.03	0.02	–0.02	0.03	0.02	–0.02
ACE inhibitors	0.04	0.13	0.10	–0.03	0.12	0.09	–0.03
Warfarin	0.03	0.02	0.06	0.03	0.03	0.05	0.03
Clopidogrel	0.06	0.08	0.06	–0.02	0.07	0.06	0.00
Statins	0.04	0.20	0.20	0.00	0.20	0.21	0.01
Antiarrhythmic	0.06	0.01	0.12	0.11	0.01	0.11	0.10
Heparin	2.27	0.53	0.53	0.00	0.86	0.53	–0.33
Intravenous glyceryl trinitrate	6.49	1.05	0.09	–0.96	0.96	0.41	–0.55
$FeSO_4$	0.11	0.02	0.12	0.10	0.03	0.05	0.02
Total cost		**4.00**	**1.95**	**–2.05**	**4.19**	**2.19**	**–1.99**

Costs do not always sum to total cost due to rounding.

The costs of these medications are low but it is important to bear in mind that these are weekly costs, whereas participants are likely to be on these medications for a long time. Furthermore, people on long-term medication are likely to have additional health-care appointments, for example people on warfarin have regular monitoring checks, so costs are incurred to the NHS beyond the drug costs.

Non-NHS costs: did these differ between trial groups?

The primary perspective of the evaluation was that of the UK NHS and Personal Social Services. However, data were collected on some types of non-NHS costs and if resource use differed between the trial groups for these non-NHS costs, we planned to include these costs in a wider perspective in a sensitivity analysis. The main non-NHS resource collected was participants' means of travel to hospital for readmissions or visits after discharge. We investigated whether or not resource use for travel to hospital differed between trial groups, to determine whether or not it was important to conduct a sensitivity analysis around this.

On the follow-up questionnaire, participants were asked to record how they travelled to hospital for each readmission, ED 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 ED visits recorded and for 1387 of the outpatient appointments recorded. These responses are shown in *Table 77*.

TABLE 77 Means of transport for hospital attendances post discharge

Means of transport	Randomised to restrictive threshold, frequency (%)	Randomised to liberal threshold, frequency (%)	Restrictive vs. liberal threshold, % 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)[a]	0 (0)	3
Transport to ED	**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)[b]	8 (1)[c]	0

OP, outpatient.
a One walked, two already at hospital, one charity.
b Three walked, three charity, one motorcycle.
c Five walked, two charity, one hospital car.

For readmissions to hospital, approximately 50% of participants were taken by ambulance, the majority of other participants travelled at their own expense, most frequently being taken by a friend or relative by car. The proportion of participants travelling by each means is very similar between the trial groups. Relatively few ED visits were recorded by participants, 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 participants travelled at private expense, the majority being taken by a friend or relative by car or driving himself or herself. The proportion of participants 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.

Sensitivity analyses

Sensitivity analyses around unit costs

TABLE 78 Sensitivity analyses performed around unit costs

Sensitivity analysis	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	£1608 general ICU £1190 CICU £619 HDU £392 cardiac ward £265 another unit/hospital ward (£1168 if known to be ICU)	Alter bed-day costs in first admission by ± 25% and 50%
4	Bed-days in readmissions	£1168 ICU £265 ward	Alter readmission ICU/ward costs by ± 25% and 50%
5	Stroke	£139 for physiotherapy and diagnostics as recorded (CT scan £62; MRI scan £248)	£705 (taken from Reference Costs,[45] see *Table 66*)
6	Wound dehiscence	Covered by reoperation if the two dates are the same; otherwise £161 unless VAC therapy is stated then £3501	Assume VAC 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	± 25% and 50%
10	Tracheostomy	£5354 (includes one radiograph)	± 25% and 50%

continued

TABLE 78 Sensitivity analyses performed around unit costs (*continued*)

Sensitivity analysis	Resource/complication	Unit costs used in base-case analysis	Alternative strategies for sensitivity analysis
11	Reoperations	£6608 if operation takes < 3 hours and £8298 if ≥ 3 hours. 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[47] when available, otherwise BNF;[48] see *Table 63*	Increase costs by 100%
13	Antibiotics	eMIT[47] when available, otherwise BNF;[48] see *Table 63*	Cost most common antibiotics (those received by 20 or more participants) using BNF;[48] see *Table 62*
14	Antibiotics	eMIT[47] when available, otherwise BNF;[48] see *Table 63*	For antibiotics participants receive orally or intravenously, cost all as oral
15	Antibiotics	eMIT[47] when available, otherwise BNF;[48] see *Table 63*	For antibiotics participants receive orally or intravenously, cost all as intravenous
16	Outpatient visits	See *Tables 70* and *71*	± 25% and 50%

IABP, intra-aortic balloon pump; VAC, vacuum-assisted closure.

TABLE 79 Results of sensitivity analyses around unit costs

Sensitivity analysis	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
Base case	17,945 (332)	18,127 (357)	–182 (488)
SA1 (ward stay, cardiac unit)	17,226 (327)	17,386 (352)	–161 (480)
SA2 (ward stay, beyond index cardiac admission)	18,267 (346)	18,476 (370)	–208 (507)
SA3 (bed-days, first admission)			
+ 25%	19,409 (377)	19,600 (408)	–191 (556)
–25%	16,482 (289)	16,654 (308)	–173 (422)
+ 50%	20,872 (423)	21,073 (460)	–201 (625)
–50%	15,018 (248)	15,181 (261)	–163 (360)
SA4 (bed-days, readmissions)			
+ 25%	18,057 (336)	18,239 (360)	–182 (493)
–25%	17,834 (329)	18,016 (355)	–182 (484)
+ 50%	18,168 (341)	18,350 (363)	–182 (498)
–50%	17,722 (326)	17,904 (353)	–182 (481)
SA5 (stroke)	17,954 (333)	18,137 (358)	–182 (489)
SA6 (wound dehiscence)	18,022 (337)	18,200 (361)	–178 (494)
SA7 (low cardiac output)	18,248 (341)	18,439 (369)	–192 (502)

TABLE 79 Results of sensitivity analyses around unit costs (*continued*)

Sensitivity analysis	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive vs. liberal threshold, mean cost (£) difference (SE)
SA8 (chest drain)	17,712 (324)	17,905 (348)	–193 (475)
SA9 (pacing)			
+25%	18,182 (336)	18,366 (361)	–184 (493)
–25%	17,709 (329)	17,888 (355)	–180 (484)
+50%	18,419 (340)	18,605 (364)	–187 (498)
–50%	17,472 (326)	17,649 (352)	–177 (480)
SA10 (tracheostomy)			
+25%	17,991 (337)	18,171 (362)	–180 (495)
–25%	17,900 (327)	18,083 (352)	–183 (481)
+50%	18,036 (342)	18,215 (367)	–179 (502)
–50%	17,854 (323)	18,039 (348)	–185 (474)
SA11 (reoperations)			
£6608	17,930 (331)	18,115 (356)	–185 (486)
£8298	18,092 (339)	18,296 (366)	–203 (499)
SA12 (antibiotics)	17,968 (334)	18,143 (358)	–175 (490)
SA13 (antibiotics, BNF)	18,004 (335)	18,190 (361)	–186 (492)
SA14 (antibiotics, oral)	17,943 (332)	18,126 (357)	–182 (488)
SA15 (antibiotics, i.v.)	17,948 (332)	18,131 (358)	–183 (488)
SA16 (outpatient visits)			
+25%	17,995 (332)	18,181 (357)	–185 (488)
–25%	17,895 (332)	18,074 (357)	–178 (488)
+50%	18,045 (332)	18,234 (357)	–189 (488)
–50%	17,845 (333)	18,020 (358)	–175 (488)

i.v., intravenous; SA, sensitivity analysis.
Costs do not always sum to total cost due to rounding.

Costs from randomisation

Costs for 3 months from randomisation rather than from surgery have been calculated for each participant. Events that occurred before randomisation were excluded: the cardiac procedure and blood saving techniques in theatre [tranexamic acid, aprotinin (Trasylol, The Nordic group) and cell salvage]. Costs associated with post-operative cell saver were included only if participants were randomised within 4 hours of surgery. The costs of red blood cells given pre-randomisation and complications occurring pre-randomisation were excluded. For events which may have started before randomisation but extended beyond randomisation, such as LOS 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 and the costs of these products were excluded.

Any events occurring within 3 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 than the costs to 3 months from surgery.

Tables 80 and *81* present the mean resource use and mean costs to 3 months from randomisation. Participants in the restrictive group received on average one less unit of red blood cells than participants in the liberal group; other resource use was similar between the groups. In terms of costs, the reduced use of red blood cells in the restrictive group resulted in a cost difference of –£141 in red blood cells between the groups, which is largely what drives the difference in total costs between the groups of –£134.

TABLE 80 Resource use per participant to 3 months from randomisation

Resource use component	Randomised to restrictive threshold ($n = 1000$), frequency (%) or mean (SE)	Randomised to liberal threshold ($n = 1003$), frequency (%) or mean (SE)	Restrictive vs. liberal threshold, % or mean (SE) difference
Red blood cells, number of units/participant	***1.49 (0.08)***	***2.49 (0.09)***	***–1.00 (0.12)***
Blood products, number of units/participant			
FFP	1.00 (0.06)	0.95 (0.06)	0.05 (0.08)
Platelets	0.65 (0.03)	0.64 (0.03)	0.01 (0.05)
Cryoprecipitate	0.23 (0.03)	0.21 (0.02)	0.02 (0.04)
Inpatient complications *Primary outcome, number (%) of participants*			
Antibiotics for infectious complication	319 (32%)	322 (32%)	0%
Stroke	11 (1%)	14 (1%)	0%
Suspected MI	2 (0%)	4 (0%)	0%
Gut infarction	5 (1%)	1 (0%)	0%
AKI, stage 3	47 (5%)	45 (4%)	0%

TABLE 80 Resource use per participant to 3 months from randomisation (*continued*)

Resource use component	Randomised to restrictive threshold ($n = 1000$), frequency (%) or mean (SE)	Randomised to liberal threshold ($n = 1003$), frequency (%) or mean (SE)	Restrictive vs. liberal threshold, % or mean (SE) difference
Other complications, number of events/participant			
Reoperation	0.07 (0.01)	0.08 (0.01)	–0.01 (0.01)
Reintubation	0.05 (0.01)	0.06 (0.01)	–0.01 (0.01)
Tracheostomy	0.03 (0.01)	0.03 (0.01)	0.00 (0.01)
Mask CPAP	0.10 (0.01)	0.09 (0.01)	0.01 (0.02)
Pneumothorax requiring chest drainage	0.01 (0.00)	0.01 (0.00)	0.00 (0.00)
Pleural effusion requiring drainage	0.06 (0.01)	0.06 (0.01)	0.00 (0.01)
Pacing	0.09 (0.01)	0.06 (0.01)	0.03 (0.01)
SVT/AF requiring treatment	0.35 (0.02)	0.33 (0.02)	0.02 (0.03)
VF/VT requiring intervention	0.02 (0.01)	0.01 (0.00)	0.01 (0.01)
Low cardiac output	0.03 (0.01)	0.03 (0.01)	0.01 (0.01)
Inpatient LOS, days/participant			
CICU	0.89 (0.11)	0.86 (0.13)	0.03 (0.17)
HDU	2.75 (0.12)	2.71 (0.12)	0.04 (0.17)
Ward	5.49 (0.15)	5.68 (0.17)	–0.19 (0.22)
Another unit/hospital	1.26 (0.18)	1.36 (0.21)	–0.09 (0.28)
Blood saving techniques, number (%) of participants			
Post-operative cell salvage[a]	24 (2%)	20 (2%)	0%
Readmissions to hospital			
LOS, days/participant	1.39 (0.15)	1.48 (0.16)	–0.09 (0.22)
ED attendances			
Total ED visits, number/participant	0.08 (0.01)	0.07 (0.01)	0.01 (0.01)
Outpatient appointments, number/participant			
Cardiac surgery outpatient visits	0.44 (0.02)	0.51 (0.02)	–0.07 (0.03)
Cardiology outpatient visits	0.28 (0.02)	0.26 (0.02)	0.02 (0.03)
Other outpatient visits	0.17 (0.02)	0.17 (0.02)	–0.01 (0.03)
Other health-care contacts, number/participant			
GP at surgery	1.99 (0.07)	2.10 (0.08)	–0.11 (0.10)
GP at home	0.43 (0.05)	0.38 (0.03)	0.05 (0.06)
Practice nurse	1.55 (0.15)	1.57 (0.13)	–0.02 (0.18)
District nurse	2.40 (0.22)	2.18 (0.21)	0.22 (0.30)

AF, atrial fibrillation; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.
a Included if participant randomised within 4 hours of surgery.

TABLE 81 Breakdown of total average costs per participant from randomisation to 3 months for both trial groups

Cost component	Randomised to restrictive threshold ($n = 1000$), mean cost (£) (SE)	Randomised to liberal threshold ($n = 1003$), mean cost (£) (SE)	Restrictive versus liberal threshold, mean cost (£) difference (SE)
Red blood cells	208 (11)	349 (13)	–141 (17)
Inpatient episode			
Other blood products	206 (12)	199 (11)	7 (16)
Complications and SAEs	1694 (120)	1663 (128)	31 (175)
LOS[a]	5274 (198)	5318 (219)	–45 (295)
Blood saving techniques	43 (8)	36 (7)	7 (10)
Regular medications	26 (2)	29 (2)	–3 (3)
Total	7243 (286)	7245 (322)	–2 (430)
Post discharge			
Readmissions	780 (87)	765 (79)	15 (117)
ED visits	16 (2)	12 (2)	4 (3)
Outpatient appointments	202 (6)	219 (7)	–17 (9)
Other medical/social care	376 (13)	369 (17)	7 (21)
Total	1374 (92)	1365 (83)	9 (124)
Total costs	**8825 (310)**	**8959 (340)**	**–134 (460)**

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

Inpatient resource use for red blood cells, LOS and complications reduces when we consider resource use from randomisation rather than from surgery (see *Table 80* and *Chapter 6*, *Table 37*). The differences between the groups are similar for both analyses, but units of red blood cells transfused reduce by 0.6 units when we consider resource use from randomisation rather than from surgery, and CICU stay reduces by 0.25 days and HDU stay by 0.34 days. The number of complications experienced by participants also reduces, particularly for pacing, supraventricular tachycardia/atrial fibrillation requiring treatment, and low cardiac output.

Subgroup analyses

TABLE 82 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 (SE)	Mean QALY difference (SE)	ICER	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (SE)	Mean QALY difference (SE)	ICER
Isolated CABG							***Other operation types***						
£14,663 (£356), *n* = 408	0.1853 (0.0023)	£15,218 (£406), *n* = 408	0.1819 (0.0022)	–£555 (£540)	0.0034 (0.0031)	Restrictive dominant (–£161,423)	£20,208 (£483), *n* = 592	0.1765 (0.0020)	£20,122 (£519), *n* = 595	0.1784 (0.0021)	£86 (£709)	–0.0019 (0.0029)	Liberal dominant (–£44,221)
< 75 years							***≥ 75 years***						
£17,146 (£367), *n* = 714	0.1813 (0.0018)	£17,290 (£437), *n* = 680	0.1796 (0.0019)	–£144 (£571)	0.0017 (0.0025)	Restrictive dominant (–£86,221)	£19,940 (£702), *n* = 286	0.1774 (0.0029)	£19,889 (£609), *n* = 323	0.1800 (0.0029)	£51 (£929)	–0.0026 (0.0040)	Liberal dominant (–£19,818)
No diabetes							***Diet, oral medication or insulin-controlled diabetes***						
£17,365 (£352), *n* = 802	0.1827 (0.0016)	£17,701 (£363), *n* = 802	0.1815 (0.0018)	–£336 (£506)	0.0012 (0.0024)	Restrictive dominant (–£277,188)	£20,296 (£869), *n* = 198	0.1699 (0.0039)	£19,826 (£1035), *n* = 201	0.1729 (0.0039)	£469 (£1351)	–0.0029 (0.0056)	Liberal dominant (–£160,777)
No lung disease[a]							***Chronic pulmonary disease or asthma***[a]						
£17,648 (£330), *n* = 889	0.1833 (0.0016)	£18,150 (£399), *n* = 861	0.1806 (0.0017)	–£502 (£518)	0.0028 (0.0022)	Restrictive dominant (–£181,346)	£20,325 (£1389), *n* = 111	0.1564 (0.0048)	£17,987 (£715), *n* = 142	0.1736 (0.0041)	£2338 (£1562)	–0.0172 (0.0064)	Liberal dominant (–£135,981)
eGFR > 60 ml/minute							***eGFR ≤ 60 ml/minute***						
£17,342 (£381), *n* = 715	0.1820 (0.0017)	£17,293 (£400), *n* = 698	0.1824 (0.0018)	£48 (£552)	–0.0004 (0.0024)	Liberal dominant (–£117,537)	£19,460 (£661), *n* = 285	0.1757 (0.0031)	£20,077 (£729), *n* = 303	0.1735 (0.0032)	–£617 (£984)	0.0022 (0.0044)	Restrictive dominant (–£275,536)

continued

TABLE 82 Costs, QALYs and cost-effectiveness results for each of the subgroups (*continued*)

'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 (SE)	Mean QALY difference (SE)	ICER	Mean costs (SE)	Mean QALYs (SE)	Mean costs (SE)	Mean QALYs (SE)	Mean cost difference (SE)	Mean QALY difference (SE)	ICER
Males							***Females***						
£17,982 (£421), *n* = 693	0.1836 (0.0019)	£18,367 (£468), *n* = 680	0.1823 (0.0020)	–£386 (£629)	0.0012 (0.0026)	Restrictive dominant (–£314,941)	£17,863 (£519), *n* = 307	0.1728 (0.0026)	£17,622 (£511), *n* = 323	0.1741 (0.0028)	£241 (£728)	–0.0013 (0.0039)	Liberal dominant (–£183,713)
Good ventricular function							***Moderate or poor ventricular function***						
£17,667 (£371), *n* = 787	0.1831 (0.0016)	£17,582 (£404), *n* = 771	0.1827 (0.0017)	£85 (£549)	0.0004 (0.0022)	£210,032	£18,854 (£706), *n* = 204	0.1711 (0.0039)	£20,287 (£785), *n* = 221	0.1700 (0.0041)	–£1432 (£1056)	0.0011 (0.0054)	Restrictive dominant (–£1,332,993)

a The interaction term between subgroups for QALYs was statistically significant ($p = 0.003$).

Appendix 4 Transfusion Indication Threshold Reduction case report forms

TITRe2 **A1**

PATIENT ASSESSMENT FOR TRIAL ELIGIBILITY & CONSENT CHECKLIST

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

CONFIRMATION OF TRIAL ELIGIBILITY

	Yes	No		Yes	No
Aged ≥ 16 years	☐	■	Critical limb ischaemia?	■	☐
Undergoing cardiac surgery?	☐	■	Undergoing emergency surgery?	■	☐
System of beliefs prevents them from having blood and blood products (e.g. Jehovah's Witness)?	■	☐	Currently participating in any other interventional clinical study?	■	☐
Congential or acquired platelet, red cell or clotting disorder?	■	☐	Patient able to give fully informed consent for the study (e.g. no learning or language difficulties)?	☐	■
Ongoing or recurrent sepsis?	■	☐			

NOTE: IF ANY ■ ARE TICKED THEN PATIENT IS NOT ELIGIBLE FOR THE TRIAL

- If patient is <u>not</u> eligible, please enter reason(s) for ineligibility to the screening log *(destroy this page if completed or partially completed)*.
- If patient <u>is</u> eligible and wishes to take part, obtain written consent before proceeding.

AFTER PATIENT HAS CONSENTED:

Once consent is obtained, please ensure the following are carried out with patient present:

Remind the patient about the 3-month follow-up questionnaire and record patient's phone number *(include dialling code)*: _____

Please record patient's address and postcode *(for postal questionnaire)* _____

_____

Postcode __ __ __ __ __ __ __

	Yes	No
Does the patient wish to be informed of the results of the study once it has ended?	☐	☐
Does the patient wish to know their treatment allocation (if randomised) once the study has ended?	☐	☐
GP letter sent to the patient's GP?	☐	☐

Checklist of tasks for site to complete at registration:

Study registration sticker & blue clip attached and randomisation form added to patient's notes?	☐	Patient given a *copy* of their signed consent form to keep?	☐
Patient given baseline EQ5D booklet to complete prior to surgery?	☐	Patient given a copy of the PIS to keep?	☐

This section can be completed without patient present (tick box when task is complete):

<u>Original</u> signed patient consent form filed in patient's CRF folder	☐	<u>Copy</u> of the sent GP letter filed in patient's CRF folder	☐
		<u>Copy</u> of the GP letter filed in patient's notes	☐
<u>Copy</u> of the signed patient consent form filed in patient's notes	☐	<u>Copy</u> of the Patient Information Sheet filed in patient's notes	☐
<u>Fax</u> the signed patient consent form to the co-ordinating centre in Bristol (0117 342 3288)	☐	Details of patient's consent added to screening log	☐

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, 22/03/2012

** Names must appear on the site signature & delegation log*

TITRe2 A2

PATIENT DETAILS AT REGISTRATION –all consented patient (con)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

PATIENT AND GP DETAILS

Date of Birth __ __ /__ __ /__ __ __ __ *dd/mm/yyyy*

Sex: Male ☐ Female ☐

Height ☐☐☐ cm

Weight ☐☐☐.☐ kg

GP Name _____

GP Address _____

_____

_____

GP Postcode __ __ __ __ __ __ __

NHS Number __ __ __ __ __ __ __ __ __ __ OR CHI Number *(for Scottish centres)* __ __ __ __ __ __ __ __ __ __

Operative priority: Elective ☐ Urgent ☐

Baseline (pre-operative) blood tests:

Haemoglobin (Hb) ☐☐.☐ g / dL Haematocrit (Hct) ☐☐.☐ % Creatinine ☐☐☐☐ µmol / L

EUROSCORE

LV function: Good *(> 50%)* ☐ Moderate *(30 - 50%)* ☐ Poor *(< 30%)* ☐

	Yes	No
Surgery on thoracic aorta *(for disorder of ascending, arch or descending aorta)*	☐	☐
Chronic pulmonary disease / asthma? *(longterm use of bronchodilators or steroids)*	☐	☐
Extracardiac arteriopathy? *(claudication, carotid occlusion or > 50% stenosis , previous or planned surgery on the abdominal aorta, limb arteries or carotids)*	☐	☐
Neurological dysfunction? *(disease severely affecting ambulation or day-to-day functioning)*	☐	☐
Previous cardiac surgery? *(pericardium opened)*	☐	☐
Active endocarditis? *(on antibiotics)*	☐	☐
Critical preoperative state? *(VT, VF, aborted sudden death, pre-operative cardiac massage, IPPV, inotropes, IABP or ARF (oliguria < 10 ml/h))*	☐	☐
Unstable angina? *(IV nitrates until arrival in operating theatre)*	☐	☐
Recent MI? *(< 90 days pre-surgery)*	☐	☐
Pulmonary hypertension? *(Systolic PA > 60 mmHg)*	☐	☐
Postinfarct septal rupture?	☐	☐

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 3.0, 31/01/2011

** Names must appear on the site signature & delegation log*

TITRe2 A3

PATIENT DETAILS AT REGISTRATION – (con)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

OTHER MEDICAL HISTORY

NYHA class: *(Tick one only)*

- I ☐ *No symptoms and no limitations in ordinary physical activity.*
- II ☐ *Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.*
- III ☐ *Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.*
- IV ☐ *Severe limitations. Experiences symptoms even while at rest.*

Angina class (CCS): *(Tick one only)*

- 0 ☐ *No angina. Asymptomatic.*
- I ☐ *Angina with strenuous / prolonged exertion. Ordinary activity such as walking does not cause angina.*
- II ☐ *Slight limitation of activity. Events such as rapid walking or climbing stairs, emotional stress cause angina.*
- III ☐ *Marked limitation of activity. Walking or climbing stairs in normal conditions at normal pace cause angina.*
- IV ☐ *Inability to carry out any physical activity without discomfort, anginal symptoms may be present at rest.*

Diabetes?	Diet ☐	Oral medication ☐	Insulin ☐	No ☐				
Pacemaker?	Permanent ☐	Temporary ☐	No ☐					
Heart rhythm?	Heart block ☐	Atrial fibrillation / flutter ☐	Sinus ☐					
Smoker?	Yes ☐	Ex-smoker (>1 month) ☐	No ☐	*NB. Ex-smoker (<1 month) is considered as a smoker*				
Haemofiltration / dialysis?	Yes ☐	No ☐						
CVA / TIAs?	Yes ☐	No ☐						
Coronary disease?	Single ☐	Double vessel ☐	Triple vessel ☐	None ☐	Not investigated ☐			
Disease in left main stem *(> 50% stenosis)*?	Yes ☐	No ☐						

	Yes	No
IV nitrates until theatre?	☐	☐
Unfractionated heparin intravenously within 6 h of surgery?	☐	☐
Low molecular weight heparin (clexane, tinzaparin) at therapeutic dose within 12 h preoperatively?	☐	☐
Inotropes until theatre?	☐	☐
Aspirin within 5 days pre-operatively?	☐	☐
Clopidogrel within 5 days pre-operatively?	☐	☐

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 3.0, 27/07/2010

* *Names must appear on the site signature & delegation log*

TITRe2

A4

RANDOMISATION FORM

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

SECTION 1: TRIAL ELIGIBILITY AT RANDOMISATION

Has patient's haemoglobin fallen to < 9.0 g/dL OR the haematocrit fallen to < 27? **Yes** ☐ **No** ☐
(Please randomise patient in either of the above cases)

NOTE: If **NO** is ticked, then patient is **NOT ELIGIBLE** for randomisation.

Date and time Hb < 9.0 g/dL ***OR*** Hct < 27 recorded: __ __ /__ __ /__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)*

Qualifying Hb value ☐☐ . ☐ g / dL OR Qualifying Hct value ☐☐ . ☐ %

If patient is eligible for randomisation, please enter date of birth, hospital number and 'operation type' below (this information is required for randomisation) and then complete randomisation at: http://www.sealedenvelope.com/titre2

Date of Birth *(dd/mm/yyyy)* __ __ /__ __ /__ __ __ __

Hospital number _____

Operation type: CABG only ☐ CABG and Valve ☐ Valve only ☐ Other ☐

SECTION 2: AFTER RANDOMISATION, COMPLETE THE SECTION BELOW:

Randomisation number (generated by computer at randomisation): ☐☐☐☐☐

Treatment allocation:

Group 1: 'Liberal' *(transfuse if Hb < 9.0 g / dL **OR** Hct < 27)* ☐

Group 2: 'Restrictive' *(transfuse if Hb <7.5 g / dL **OR** Hct < 22)* ☐

Please ensure the correct colour coded clip (indicating treatment allocation) is attached to be visible on patient's chart or notes as follows:

*Please tick **ONE** of the below when completed:*

Group 1: 'Liberal' - **GREEN LABEL** ☐ OR Group 2: 'Restrictive' - **ORANGE LABEL** ☐

Name of person who randomised patient *(please print)*: _____

Is the clinician responsible for this patient at time of randomisation willing for the patient to be treated at this time in accordance with the allocated protocol group? * Yes ☐ No ☐

Name of clinician consulted for decision *(please print)* _____

Grade of clinician consulted for decision: Consultant ☐ Registrar ☐ Other ☐

Note to person randomising: please file this completed Randomisation Form in the patient's notes for the attention of the research co-ordinator.

*Note to research co-ordinator: If responsible clinician not in agreement with patient being treated according to protocol at this time , please ensure the relevant form in CRF Section E is completed to document this

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, 24/07/2009

** Names must appear on the site signature & delegation log*

TITRe2 B1

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)* __ __ /__ __ /__ __ __ __

Version 5.0, 01/09/2011

** Names must appear on the site signature & delegation log*

TITRe2 B2

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		*How many breaches occurred since randomisation/ last transfusion, before blood was prescribed?
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*

TITRe2 C1

DETAILS OF PERI-OPERATIVE PERIOD - (rand)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

OPERATION DETAILS

Responsible consultant surgeon (initials) ☐☐☐
First Operator (initials) ☐☐☐
Date of operation *(dd/mm/yyyy)* __ __ /__ __ /__ __ __ __
Start of operation *(time entered theatre)* *(24 hour clock)* __ __ : __ __
End of operation (time) *(24 hour clock)* __ __ : __ __

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: ☐

Valve(s) replaced / repaired:
Aortic Yes ☐ No ☐
Mitral Yes ☐ No ☐
Tricuspid Yes ☐ No ☐
Pulmonary Yes ☐ No ☐

Harvest site(s):
Right arm Yes ☐ No ☐
Left arm Yes ☐ No ☐
Right leg Yes ☐ No ☐
Left leg Yes ☐ No ☐
LIMA Yes ☐ No ☐
RIMA Yes ☐ No ☐
Other Yes ☐ No ☐

Blood saving techniques: Tranexamic acid Yes ☐ No ☐ Trasylol Yes ☐ No ☐ Cell Saver Yes ☐ No ☐

POST-OPERATIVE DETAILS

Total chest tube drainage at 4 h ☐☐☐☐ *ml*
Total chest tube drainage at 12 h ☐☐☐☐ *ml*
Was post-op cell salvage used? Yes ☐ No ☐

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 ± 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: ☐☐☐☐ µmol / L
Day 2: Creatinine ☐☐☐☐ µmol / L N/A ☐
Day 3: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 4: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 5: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 6: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 7: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 8: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 9: Creatinine: ☐☐☐☐ µmol / L N/A ☐
Day 10: Creatinine: ☐☐☐☐ µmol / L N/A ☐

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 7.0, 01/09/2011

TITRe2 C2

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 __ __ /__ __ /__ __ __ __ *dd/mm/yyyy*

N/A - patient discharged/died by day 3 ☐

N/A - patient not randomised by day 3 ☐

	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*

TITRe2 C3

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*

TITRe2 C4

ASEPSIS ASSESSMENT DAY 8 - (rand)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

ASEPSIS WOUND ASSESSMENT - Day 8

'Day 8' inspection *(If unable to complete on day 8, please complete as close to day*

Date performed __ __ /__ __ /__ __ __ __ *dd/mm/yyyy*

N/A - patient discharged/died by day 8 ☐

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
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*

TITRe2 C5

SUMMARY OF INFECTIOUS POST-OPERATIVE COMPLICATIONS - (rand)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

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 ☐	
Heart rate > 90 beats per minute?	Yes ☐	No ☐	Unrecorded ☐	
Respiratory rate > 20 breaths per minute?	Yes ☐	No ☐	Unrecorded ☐	Was infection subsequently confirmed by positive culture?
$PaCO_2$ < 32 mmHg or < 4.3 kPa?	Yes ☐	No ☐	Unrecorded ☐	
WBC count > 12,000 / mm^3 or < 4,000 / mm^3?	Yes ☐	No ☐	Unrecorded ☐	Yes ☐ No ☐

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 ☐	
Heart rate > 90 beats per minute?	Yes ☐	No ☐	Unrecorded ☐	
Respiratory rate > 20 breaths per minute?	Yes ☐	No ☐	Unrecorded ☐	Was infection subsequently confirmed by positive culture?
$PaCO_2$ < 32 mmHg or < 4.3 kPa?	Yes ☐	No ☐	Unrecorded ☐	
WBC count > 12,000 / mm^3 or < 4,000 / mm^3?	Yes ☐	No ☐	Unrecorded ☐	Yes ☐ No ☐

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 ☐	
Heart rate > 90 beats per minute?	Yes ☐	No ☐	Unrecorded ☐	
Respiratory rate > 20 breaths per minute?	Yes ☐	No ☐	Unrecorded ☐	Was infection subsequently confirmed by positive culture?
$PaCO_2$ < 32 mmHg or < 4.3 kPa?	Yes ☐	No ☐	Unrecorded ☐	
WBC count > 12,000 / mm^3 or < 4,000 / mm^3?	Yes ☐	No ☐	Unrecorded ☐	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)* __ __ /__ __ /__ __ __ __

Version 4.0, 27/07/2010

* *Names must appear on the site signature & delegation log*

TITRe2 C6

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 ☐	CT Yes ☐ No ☐ 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 ☐	Laparotomy Yes ☐ No ☐ 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 ☐	AKIN criteria Stage 1, 2 or 3 (see box below for definitions) Yes ☐ No ☐

If **Yes to Acute kidney injury,** please specify most severe stage experienced *(complete on discharge):* ☐

Stage 1: *Serum creatinine increase ≥ 0.3mg/dl (≥ 26.4µmol/l) or increase to 1.5-fold to 2-fold from baseline† OR urine output < 0.5ml/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

**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*

TITRe2 C7

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)

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.

			Date and time first documented in notes		If time is unknown please indicate time of day				SAE*		Number of events
Complication* *(see TITRe 2 trial manual, section 10, for full definitions)*	Yes	No	Date *(dd/mm/yyyy)*	Time *(24 hour clock)*	*AM*	*PM*	*Overnight*	*Unknown*	Yes	No	*(enter 0 if none)*
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)* __ __ /__ __ /__ __ __ __

Version 6.0, 31/01/2011

* *Names must appear on the site signature & delegation log*

TITRe2 D1

PATIENT DETAILS AT DISCHARGE - (rand)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

PATIENT MOVEMENT BETWEEN WARDS

Date and time first admitted to CICU/HDU post-operatively: __ __/__ __/__ __ __ __ (dd/mm/yyyy) __ __ : __ __ (24 hour clock) N/A ☐ *(Tick N/A if not applicable)*

Date and time of extubation *(Use H5 if patient was re-extubated)*: __ __/__ __/__ __ __ __ (dd/mm/yyyy) __ __ : __ __ (24 hour clock) N/A* ☐ *(*i.e. N/A if patient dies whilst intubated)*

Patient discharged from CICU/HDU to: General ICU ☐ Ward ☐ Patient died ☐ Home ☐ Other ☐

Date and time first admitted to general ICU (if applicable): __ __/__ __/__ __ __ __ (dd/mm/yyyy) __ __ : __ __ (24 hour clock) N/A ☐

Date and time first admitted to ward (if applicable): __ __/__ __/__ __ __ __ (dd/mm/yyyy) __ __ : __ __ (24 hour clock) N/A ☐

If time admitted to ward not known, please indicate time of day: AM ☐ PM ☐ Overnight ☐

READMISSIONS TO CICU/HDU / GENERAL ICU / WARD *(If >2 readmissions, use H5)*

How many times was the patient readmitted? *(if none, enter 0)* ☐ *If **>0**, please complete section below ± H5, if **0**, go to status at discharge*

				dd/mm/yyyy	(24 hour clock)
Date and time patient 1st readmitted to:	CICU/HDU ☐	General ICU ☐	Ward ☐	__ __/__ __/__ __ __ __	__ __ : __ __
Date and time patient 2nd readmitted to:	CICU/HDU ☐	General ICU ☐	Ward ☐	__ __/__ __/__ __ __ __	__ __ : __ __

DETAILS AT DISCHARGE

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*: __ __/__ __/__ __ __ __ (dd/mm/yyyy) ***OR*** Ongoing ☐
- Home ☐
- Other hospital ☐ → Give name _____
- Other ☐ → *Specify (e.g. died)* _____

**Note: please ensure that deaths are reported on the study SAE form (Section F)*

QUESTIONS FOR PATIENT AT DISCHARGE (if possible)

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 ☐

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 10.0, 22/03/2012

** Names must appear on the site signature & delegation log*

TITRe2 D2

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	☐	☐			
Clopidogrel	☐	☐			

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	☐	☐			
Clopidogrel	☐	☐			

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*

TITRe2

E1

GIVING A RBC TRANSFUSION IN BREACH OF PROTOCOL - (rand)

Centre Code ☐☐☐ Patient Name ____________________ Patient Study ID ☐☐☐☐☐☐

COMPLETE A SECTION BELOW EACH TIME A UNIT OF RBC IS TRANSFUSED, IN CONTRAVENTION OF THE ALLOCATED THRESHOLD *(Use additional pages for E1 if required.)*

NB. On any given date, if >1 unit is transfused in contravention of allocated group, for the same reason and under direction of the same clinician, one section can be completed for multiple units. Otherwise, complete a separate section for each unit.

UNIT NUMBER(S) ☐ ☐ ☐ *(Enter unit number(s) listed on B2 OR H2 that this completed section applies to)*

*Immediately prior to prescription:

Hb recorded* ☐☐.☐ g / dL

OR Hct recorded* ☐☐.☐ %

Indicate why these RBC units were transfused in breach of the allocated threshold *(see E (info) for definitions)*

Excessive blood loss ☐ Sepsis ☐ Physiological indicators of oxygen debt ☐ Oversight / Error ☐

Other ☐ *Specify:* ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

UNIT NUMBER(S) ☐ ☐ ☐ *(Enter unit number(s) listed on B2 OR H2 that this completed section applies to)*

*Immediately prior to prescription:

Hb recorded* ☐☐.☐ g / dL

OR Hct recorded* ☐☐.☐ %

Indicate why these RBC units were transfused in breach of the allocated threshold *(see E (info) for definitions)*

Excessive blood loss ☐ Sepsis ☐ Physiological indicators of oxygen debt ☐ Oversight / Error ☐

Other ☐ *Specify:* ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

UNIT NUMBER(S) ☐ ☐ ☐ *(Enter unit number(s) listed on B2 OR H2 that this completed section applies to)*

*Immediately prior to prescription:

Hb recorded* ☐☐.☐ g / dL

OR Hct recorded* ☐☐.☐ %

Indicate why these RBC units were transfused in breach of the allocated threshold *(see E (info) for definitions)*

Excessive blood loss ☐ Sepsis ☐ Physiological indicators of oxygen debt ☐ Oversight / Error ☐

Other ☐ *Specify:* ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

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 3.0, 31/01/2011

** Names must appear on the site signature & delegation log*

TITRe2 **E*(Info)***

RBC TRANSFUSION FORM - Information sheet

REASONS FOR RED BLOOD CELL TRANSFUSION OUT OF PROTOCOL (FOR USE WITH FORM E1)

Reason for Red Blood Cell Transfusion

IN ACCORDANCE WITH ASSIGNED RED BLOOD CELL TRANSFUSION THRESHOLDS

Hb < 9.0 g / dL / Hct < 27 if in control group
OR
Hb < 7.5 g / dL / Hct < 22 if in restrictive group

Other indications for red blood cell transfusions (outside assigned thresholds)

EXCESSIVE BLOOD LOSS

Defined as **ONE OF** (a), (b) or (c):
(a) > 4 ml kg^{-1} h^{-1} in any one hour
(b) > 2 ml kg^{-1} h^{-1} for two consecutive hours
(c) > 5 ml kg^{-1} h^{-1} in the first four hours post-op
PLUS
MABP < 60 mmHg **OR**
MABP < 75 mmHg in hypertensive patients **OR**
Tachycardia > 120 bpm

PHYSIOLOGICAL INDICATORS OF OXYGEN DEBT

Defined as one or more of the following:
PvO_2 < 32 mmHg
O_2ER > 50%
SvO_2 < 50%

SEPSIS

Defined as culture positive or suspected infection **AND** antibiotics **AND** at least two or more of the following conditions:
Temperature > 38 °C or < 36 °C
Heart rate > 90 beats / min
Respiratory rate > 20 breaths / min or $PaCO_2$ < 32 mmHg or < 4.3 kPa
WBC count > 12,000 / mm^3 or < 4000 / mm^3

Derived from Madjdpour and Spahn, British Journal of Anaesthesia 2005; 95:33-52

Version 3.0, 26/02/2010

TITRe2

E2

WITHHOLDING A RBC TRANSFUSION IN BREACH OF PROTOCOL - (rand)

Centre Code ☐☐☐ **Patient Name** ____________________ **Patient Study ID** ☐☐☐☐☐☐

PLEASE COMPLETE A SECTION BELOW EACH TIME A RBC TRANSFUSION IS NOT GIVEN, IN CONTRAVENTION OF THE ALLOCATED THRESHOLD *(Use additional pages for E2 if required)*

Date and time Hb / Hct fell below allocated threshold __ __/__ __/__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)* **OR** Breach Hb recorded ☐☐.☐ g / dL Breach Hct recorded ☐☐.☐ %

Please give details of why the RBC transfusion was NOT given in accordance with the protocol:

Oversight / Error ☐ Clinician preference *(specify below)* ☐ Other *(specify below)* ☐

Specify: ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

Date and time Hb / Hct fell below allocated threshold __ __/__ __/__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)* **OR** Breach Hb recorded ☐☐.☐ g / dL Breach Hct recorded ☐☐.☐ %

Please give details of why the RBC transfusion was NOT given in accordance with the protocol:

Oversight / Error ☐ Clinician preference *(specify below)* ☐ Other *(specify below)* ☐

Specify: ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

Date and time Hb / Hct fell below allocated threshold __ __/__ __/__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)* **OR** Breach Hb recorded ☐☐.☐ g / dL Breach Hct recorded ☐☐.☐ %

Please give details of why the RBC transfusion was NOT given in accordance with the protocol:

Oversight / Error ☐ Clinician preference *(specify below)* ☐ Other *(specify below)* ☐

Specify: ____________________

Name of the clinician making decision: ____________________ N/A ☐

Job title of the clinician making decision: ____________________ N/A ☐

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 3.0, 31/01/2011

** Names must appear on the site signature & delegation log*

Sponsor Ref: CS/2007/2695
REC Ref: 08/H0606/125

TITRe2 F1

SAE INITIAL REPORT FORM—Complete ONE form per SAE (rand)

Centre Code ☐☐☐ **Patient Study ID** ☐☐☐☐☐☐

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
Resulted in death * **Please provide copy of PM report or death certificate*	☐	☐
Is / was life-threatening	☐	☐
Resulted in persistent or significant disability / incapacity	☐	☐
Required hospitalisation	☐	☐
Prolonged an ongoing hospitalisation	☐	☐
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 ☐ 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*) __ __ /__ __ /__ __ __ __

Version 5.0, 04/03/2010

* *Names must appear on the site signature & delegation log*

Sponsor Ref: CS/2007/2695
REC Ref: 08/H0606/125

TITRe2 F2

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

Sponsor Ref: CS/2007/2695
REC Ref: 08/H0606/125

TITRe2 F3

SAE FOLLOW-UP FORM—Complete ONE form per SAE (rand)

Centre Code ☐☐☐ **Patient Study ID** ☐☐☐☐☐☐

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)

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 Initiaal 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*

TITRe2 G1

DISCONTINUATION OF TREATMENT (rand) & WITHDRAWAL FORM - (con)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

Has the responsible clinician decided to permanently discontinue the patient's treatment according to the allocated protocol group? Yes ☐ No ☐ If **Yes**, complete Section 1

Has the patient withdrawn consent? Yes ☐ No ☐ If **Yes**, complete Section 2

SECTION 1: DISCONTINUATION OF TREATMENT ACCORDING TO ALLOCATED PROTOCOL GROUP

Please complete this section for any patient for whom a decision has been made by the responsible consultant to permanently discontinue treatment according to the allocated protocol group, and return the form to the co-ordinating centre in Bristol immediately.

Name of clinician _____

Please give reason for discontinuation: _____

_____

_____

Date of discontinuation of protocol treatment __ __/__ __/__ __ __ __ *dd/mm/yyyy*

Time of discontinuation __ __ : __ *(24 hour clock)* Time not recorded ☐

Was treatment according to protocol permanently discontinued: Before surgery? ☐ After surgery but before randomisation? ☐ After randomisation? ☐

NB. Permanent discontinuation of protocol treatment due to clinician decision is NOT classed as a withdrawal from the trial. Data should still be collected for these patients according to the protocol unless the patient withdraws their consent. Please ensure all TITRe 2 clips are removed from patient's notes.

SECTION 2: WITHDRAWAL FROM TRIAL

Please complete this section for any patient withdrawing from the trial after giving consent and return it to the co-ordinating centre in Bristol immediately.

Please give reason for withdrawal (if known): _____

_____

_____

Date of withdrawal from trial __ __/__ __/__ __ __ __ *dd/mm/yyyy*

Time of withdrawal __ __ : __ *(24 hour clock)* Time not recorded ☐

Did the patient withdraw from the trial:

Before surgery? ☐ After surgery but before randomisation? ☐ After randomisation? ☐

Is the patient happy for data routinely collected about them by the NHS to still be collected and used in this study?

Yes ☐ No, patient withdraws all consent ☐ No, consultant no longer wants patient included ☐

Is the patient happy to participate in completion of follow-up questionnaires?

Yes ☐ No, patient withdraws all consent ☐

If YES, continue data collection from patient's medical notes according to the protocol (but do not carry out any further ASEPSIS wound inspections).

If NO, stop all data collection and return forms to the co-ordinating centre in Bristol.

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, 27/07/2010

** Names must appear on the site signature & delegation log*

TITRe2

H1

EXTENSION FOR FORM B1 (OPTIONAL DAILY CHECKS FOR ALL PATIENTS) - (con)

Centre Code ☐☐☐ **Patient Name** _______________ **Patient Study ID** ☐☐☐☐☐☐

LOWEST Hb, Hct AND RBC TRANSFUSION FOR EACH DAY POST-OPERATIVELY ***(extension from B1)***

Please complete the lowest Hb and Hct and whether or not the patient received a RBC transfusion for each day the patient was in hospital after their 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**
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐
___				☐	☐

For all RANDOMISED patients, please give further details of ALL RBC transfusions in Section E

For randomised participants only please use this form to monitor breaches of protocol allocation (giving or not giving transfusion in contravention of allocated group). If there are any instances of this, please complete relevant form (in Section E)

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, 22/03/2012

** Names must appear on the site signature & delegation log*

TITRe2 H2

EXTENSION FORM FOR B2 (RBC TRANSFUSION FORM) - (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.)*

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).

Only complete cells below if 'Reason for transfusion given' is "Per protocol" (code F)

Unit	Unit Batch No	Date of transfusion *(dd/mm/yyyy)* / Time of transfusion *(24 hour clock)*	Reason (use code from table below)	Date and time of breach that triggered prescription *dd/mm/yyyy 24 hour clock*	Hb/Hct at "trigger" breach: Hb	Hb/Hct at "trigger" breach: Hct	RBC prescribed <24 hours since "trigger" breach: Yes	RBC prescribed <24 hours since "trigger" breach: No	*How many breaches occurred since randomisation/last transfusion, before blood was prescribed?
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					
__		____/____/_____ __ __ : __ __		____/____/_____ __ __ : __ __					

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 that occurred before most recent breach)*

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, 31/01/2011

** Names must appear on the site signature & delegation log*

TITRe2 H3

EXTENSION FOR FORMS C2, C3 OR C4 (ASEPSIS ASSESSMENT) - (rand)

Centre Code ☐☐☐ **Patient Name** _____ **Patient Study ID** ☐☐☐☐☐☐

ASEPSIS WOUND ASSESSMENT EXTENSION FORM FROM PAGE C2, C3 OR C4

This is an extension sheet for form *(tick one)*: C2 (Day 3) ☐ C3 (Day 5) ☐ C4 (Day 8) ☐

Date performed *(dd/mm/yyyy)* __ __ /__ __ /__ __ __ __

3rd 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†	☐	☐	____/____/_____

4th 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†	☐	☐	____/____/_____

5th 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 3.0, 26/02/2010

* *Names must appear on the site signature & delegation log*

TITRe2 H4

EXTENSION FOR FORM C1 (OPTIONAL PATIENT DETAILS AT DISCHARGE) - (rand)

Centre Code ☐☐☐ Patient Name ______________________________ Patient Study ID ☐ «s ☐☐☐☐

HIGHEST CREATININE ON EACH POST-OPERATIVE DAY OF HOSPITAL STAY *(Randomised patients only)*

Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐
Day ___	Creatinine: ☐☐☐☐	μmol / L	N/A ☐

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, 22/03/2012

** Names must appear on the site signature & delegation log*

TITRe2 H5

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* __ __ : __ __ *(24 hour clock)*

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* __ __ : __ __ *(24 hour clock)*

Date/time of re-admission to ward __ __ /__ __ /__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)*

Date/time of re-admission to CICU/HDU __ __ /__ __ /__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)*

Date/time of re-admission to ward __ __ /__ __ /__ __ __ __ *dd/mm/yyyy* __ __ : __ __ *(24 hour clock)*

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.

Code	Date started *(dd/mm/yyyy)*:	SAE* Yes	SAE* No
☐	__ __ /__ __ /__ __ __ __	☐	☐
☐	__ __ /__ __ /__ __ __ __	☐	☐
☐	__ __ /__ __ /__ __ __ __	☐	☐
☐	__ __ /__ __ /__ __ __ __	☐	☐
☐	__ __ /__ __ /__ __ __ __	☐	☐

COMPLICATION CODES:

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,
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

*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*

Appendix 5 Statistical analysis plan

For further information on the statistical analysis plan, please see Pike *et al.*[34]

List of abbreviations

Acronym	Details
AE	Adverse event
AKI	Acute kidney injury
AKIN	Acute kidney injury network
ARDS	Acute respiratory distress syndrome
BMI	Body mass index
CABG	Coronary artery bypass graft
CCS	Canadian cardiovascular society
CI	Confidence interval
CICU	Cardiac intensive care unit
CPAP	Continuous positive airway pressure
CPB	Cardiopulmonary bypass
CRF	Case report form
CT	Computed tomography
CVA	Cerebrovascular accident
DOB	Date of birth
eGFR	Estimated glomerular filtration rate
FFP	Fresh frozen plasma
GMR	Geometric mean ratio
HDU	High dependency unit
HR	Hazard ratio
ICU	Intensive care unit
IQR	Inter quartile range
ITT	Intention to treat
IV	Intravenous
LIMA	Left internal mammary artery
LV	Left ventricular
MAR	Missing at random
MD	Mean difference
MI	Myocardial infarction
MRI	Magnetic resonance imaging
NYHA	New York heart association
OR	Odds ratio
PH	Proportional hazards
PIL	Patient information leaflet
PT	Preferred term
RBC	Red blood cell
RCT	Randomised controlled trial
RIMA	Right internal mammary artery

Acronym	Details
RRT	Renal replacement therapy
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SIRS	Systemic inflammatory response syndrome
SOC	System organ class
SVT	Supraventricular tachycardia
TIA	Transient ischaemic attack
TR	Time ratio
VF	Ventricular fibrillation
VT	Ventricular tachycardia
WBC	White blood cell

1 INTRODUCTION TO SAP

1.1 Scope

This document details information regarding the statistical analysis of the TITRe2 trial and covers all of the analysis of trial data outlined in the study protocol, with the exception of the health economic analyses.

1.2 Editorial changes

Any changes made to this Statistical Analysis Plan (SAP) after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The trial statistician should authorise this document.

2 STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

TITRe2 is a UK wide, multi-centre, open randomised controlled trial (RCT).

Two thresholds for red blood cell (RBC) transfusion following cardiac surgery are compared: a "restrictive" threshold whereby transfusions are given if the haemoglobin (Hb) level is below 7.5g/dL (or haematocrit (Hct) < 22) and a "liberal" threshold whereby transfusions are given if the Hb < 9g/dL (or Hct < 27).

2.2 Study objectives

Objectives of the RCT are to:

A. Estimate the difference in the risk of a post-operative infection or ischaemic event between restrictive and liberal transfusion thresholds.
B. Compare the effects of restrictive and liberal transfusion thresholds with respect to a range of secondary outcomes.
C. Estimate the cost-effectiveness of the restrictive compared to the liberal Hb transfusion threshold and describe this in terms of a cost-effectiveness acceptability curve.

This SAP covers objectives A and B.

2.3 Primary outcome

The primary outcome is a binary composite outcome of any serious infectious or ischaemic event in the first 3 months after randomisation. The qualifying events listed below will be included, along with the manner in which they will be verified:

Infectious events	*Definition / method of verification*
Sepsis during index admission	Defined by the following two conditions, both of which must be satisfied for sepsis to be documented: (a) Antibiotic treatment for suspected infection, ***and*** (b) The presence of SIRS[1] within 24 hours prior to start of antibiotic treatment
Wound infection	ASEPSIS[**1**] score >20. Wounds will be assessed at least once during a participant's hospital stay and details of the ASEPSIS assessment added to the study CRF. A questionnaire will be posted for self-completion, or will be administered by telephone, at 3 months to identify wound infections arising after discharge.[**2**]
Ischaemic events	***Definition / method of verification***
Permanent stroke	Clinical report of brain imaging (computerised tomography (CT) or magnetic resonance imaging (MRI)), in association with new onset focal or generalised neurological deficit (defined as deficit in motor, sensory or co-ordination functions).
Myocardial infarction (MI)	Elevated post-operative peak serum Troponin I or T, verified by an adjudication committee. Further details are given on the following page.
Acute kidney injury (AKI)	AKI Network criteria for AKI, stage 1, 2 or 3 (see below)[**3**] ***Stage 1:*** serum creatinine increase ≥0.3mg/dl (≥ 26.4µmol/l), OR >1.5 and ≤2-fold serum creatinine increase compared to the pre-operative serum creatinine (baseline) value, OR urine output <0.5ml/kg for 6 hours. ***Stage 2:*** >2 and ≤3-fold serum creatinine increase compared to the pre-operative serum creatinine (baseline) value, OR urine output <0.5ml/kg for >12 hours. ***Stage 3:*** >3-fold serum creatinine increase compared to the pre-operative serum creatinine (baseline) value, 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 urine output <0.3 ml/kg per hour for 24 hours or anuria for 12 hours, OR need for renal replacement therapy (RRT) irrespective of AKI stage at time of RRT. The time of onset of AKI, used to determine whether the event occurred pre-randomisation, is the first time that the patient triggers for AKI regardless of whether this is due to urine output or serum creatinine. The AKI stage recorded is the highest stage reached by the patient post-operatively but pre-

[1] SIRS - systemic inflammatory response syndrome. SIRS is central to the diagnosis of infective complications. It will be defined as ≥2 of the following conditions: temperature >38°C or <36°C; heart rate >90 beats/minute; respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg or $PaCO_2$ <4.3 kPa; WBC count >12,000/mm^3 or <4,000/mm^3. Blood test results and temperature will be classified using standard reference ranges.

	discharge.
Gut infarction	Laparotomy or post mortem

Events occurring post-discharge only contribute to the primary outcome if the potentially qualifying event resulted in admission to hospital or death. The exception to this is post-discharge wound infections, which are ascertained using the ASEPSIS post-discharge surveillance assessment. Other suspected infectious events treated in the community that did not cause readmission to hospital will not be recorded because they cannot be validated and are less serious than peri-operative infections.

Events suspected to qualify for the primary outcome but not supported by objective evidence will be referred to an independent adjudication committee whose members will be blinded to the random allocation. In practice this will amount to MIs only, as for all other elements documentary objective evidence has been collated and verified by research nurses blinded to the random allocation at the co-ordinating centre. Therefore the adjudication committee will be required to reach a final decision about whether patients with a suspected MI have actually had an MI, based on patient history, Troponin levels and preoperative and postoperative ECGs. The adjudication committee will consist of three clinical specialists, and agreement between two of the three specialists will be required to reach a final decision.

2.4 Secondary outcomes

Secondary outcomes are listed in the study protocol as:

- Units of RBCs and other blood components transfused during a participant's hospital stay
- Proportion of patients experiencing an infectious event
- Proportion of patients experiencing an ischaemic event
- EQ5D [**4**]
- Duration of intensive care unit (ICU) / high dependency unit (HDU) post-operative stay
- Duration of post-operative hospital stay
- All-cause mortality
- Significant pulmonary morbidity, comprising (i) initiation of non-invasive ventilation (e.g. continuous positive airway pressure (CPAP) ventilation), (ii) re-intubation/ventilation, or (iii) tracheostomy
- Cumulative resource use, cost, and cost-effectiveness

The latter outcome listed above is not covered by this SAP.

2.5 Changes to the study objectives during the course of the study

Some minor changes have been made to the study over the course of the trial:

- A protocol amendment was made to include Troponin T in addition to Troponin I in defining MI, and remove the defined threshold for MI in the study protocol. The highest troponin level for all patients with a suspected MI is collected and a definitive definition of MI will be decided upon after blinded review by the adjudication committee (see section 2.3).
- One of the secondary outcomes (significant pulmonary morbidity) was added part way through the trial.
- In the study protocol one of the intended subgroup analyses is pre-operative renal impairment, defined by pre-operative creatinine ≤177 μmol/l vs creatinine >177 μmol/l. However during the course of the trial use of pre-operative creatinine for risk stratification has been totally superseded by estimated Glomerular Filtration Rate (eGFR). Therefore the subgroup analysis on renal impairment has been amended to eGFR ≤60ml/min vs eGFR >60ml/min (note this has not been covered by a protocol amendment).
- The timings of all primary and secondary outcomes have been clarified as occurring post-randomisation, rather than post-operative.

All required data for the changes/additions were already being collected.

3 STUDY POPULATION

The study population is all adult patients (aged 16 or over) undergoing non-emergency elective cardiac surgery (this includes non-emergency cases admitted from home or non-emergency inpatient cases). Eligibility criteria are as inclusive as possible to promote the applicability of the evidence obtained during the trial.

The planned sample size is 2000 randomised patients. A graph showing recruitment trends over time will be given as well as centre-specific screening data.

3.1 Flow of participants

Participant flow will be described via a flowchart.

3.1.1 Whilst in hospital

Participants consent to the study pre-surgery if they meet all of the pre-consent eligibility criteria and give written consent. They are then randomised if at any point post-surgery they meet the post-consent eligibility criteria (Hb falls below 9g/dL or Hct below 27%). This means that a significant proportion of patients (~45%) consent to the study but are not randomised.

For randomised patients the duration of intervention in the trial is the duration of the patient's care under the consultant cardiac surgeon or a maximum of 3 months after the date of randomisation, whichever is shorter. Almost always, the duration of care under the cardiac surgeon will be the period of hospitalisation after surgery. The majority of data collection is undertaken whilst the participant is an in-patient.

3.1.2 Follow-up

After patients have been discharged from hospital they are followed up at further time points:

- At approximately six weeks post-operatively they are sent an EQ5D questionnaire.
- At approximately three months post-operatively they are contacted by telephone or post to complete a questionnaire including the following elements: a) adverse events (AEs) occurring after discharge; b) questions to identify surgical wound infections occurring after discharge (ASEPSIS post-discharge surveillance questionnaire)[**1**]; c) health economics / resource use questionnaire; d) questions determining whether a participant is aware of his/her random allocation. At this point they are also asked to complete a further EQ5D questionnaire.
- Patients that consent but are not randomised are also sent an EQ5D questionnaire at approximately three months post-operatively.

The duration of follow-up in the trial is until the three month follow-up assessment questionnaires have been completed or until 3 months after randomisation if a participant does not complete the questionnaires.

3.1.3 Follow-up windows

Although the follow-up times are planned at six weeks and three months post-operatively, occasionally data collection is delayed. When this occurs the following rules will be used to determine whether data should be included in analyses:

- EuroQol EQ5D: to determine suitable time frames within which data will be used, the distribution of time between questionnaire completion and operation date will be examined by group, blinded to allocation, separately for each time point. If the

distributions differ between the groups, pre-specified windows will be used: a) for pre-operative questionnaires a window of within 3 months pre-operatively; b) for the 6 week assessment a window of 4-10 weeks after the operation date; c) for the 3 month assessment a window of 10-20 weeks after the operation date. If the distributions are balanced across the two groups, any times that appear to be extreme outliers (identified by eye) will be excluded but all other data collected will be used.

- Three month telephone/postal questionnaire: the questionnaire specifically asks about the three month post-operative period and staff completing the telephone questionnaires are trained to only record information regarding this period, therefore data from all questionnaires will be used. Where dates of events are recorded (this is the case for AEs and the majority of resource use questions), any events inadvertently recorded that occurred more than three months post randomisation will not be included in any analyses. If dates are missing the event will be assumed to have occurred within the three month follow up period.

3.2 Comparisons of patients characteristics

3.2.1 Comparisons of non-consented and consented patients

The only characteristics available for patients that do not consent to the study are age and sex. These characteristics will be described for the following groups of patients:

- Non-consented (including PIL not sent, not approached, ineligible, did not consent and other reason for exclusion from study)
- Consented

This will only be done for sites known to have complete screening data; we anticipate these sites to be Bristol, Southampton and Leicester. Completeness of screening data is ascertained from knowledge about site-specific screening processes, and reflects whether the site screens the majority of patients admitted for cardiac surgery or predominantly those who are considered for inclusion in the trial. Screening log data for Bristol will be supplemented with data from institutional cardiac surgery databases, to identify any patients not recorded on the screening log but who could potentially have been considered for TITRe2. No formal statistical comparisons will be made.

3.2.2 Comparisons of non-randomised (but consented) and randomised patients

Characteristics that will be described include: all pre-operative characteristics, operation type, post-operative Hb/Hct values, blood products transfused, status (alive/dead) at end of surgery and hospital discharge, and EQ5D scores pre-operatively and at 3 months post-operative. These characteristics will be described for the following groups of patients:

- Consented patients considered for randomisation but not randomised (i.e. all consented patients including those randomised in error and excluding: patient/clinician withdrawals pre-surgery, patients who died pre-surgery or surgery was not performed, other reasons not considered for randomisation).
- Randomised patients included in the analysis population (i.e. all randomised patients, excluding: those randomised in error, or patients who withdrew and were unhappy for data collected to be used).

In both groups of patients, the excluded patients do not have the relevant data collected and so cannot be included in the comparisons.

No formal statistical comparisons will be made. Note that comparisons of resource use will be carried out by the health economists and so is not covered in the scope of this SAP.

3.3 Randomisation

Participants are randomised (1:1 allocation) to either the liberal or restrictive group using an internet-based system (Sealed Envelope Ltd). Cohort minimisation is used to minimise imbalance of: a) centre and b) operation type (classified as CABG, Valve, CABG+ Valve and Other).

3.4 Withdrawals

There are two types of study withdrawal, which are documented on a specific case report form (CRF):

- Patient withdrawal: patients can withdraw from the study at any time (including post-consent but prior to randomisation). Reasons for withdrawal are collected along with:
  a) whether data already collected can be used
  b) whether the patient is happy to participate in follow-up
- Clinician decision to discontinue treatment according to protocol: clinicians can decide to discontinue the patient's treatment at any time (this can include post-consent but prior to randomisation, which may happen if a patient's condition changes and the clinician feels decisions about the patient's care should not depend upon the study protocol) . This does not constitute a withdrawal and data collection continues as planned (unless the patient also withdraws their consent) but transfusions are no longer required to be given according to the study protocol.

Withdrawals and treatment discontinuations are summarised by treatment allocation, if applicable.

Unless patients were unhappy for data collected to be used, data on all withdrawals or treatment discontinuations will be included in the study analyses on an intention to treat basis (ITT), see **section 3.6**.

3.5 Protocol deviations

3.5.1 Non-compliance with randomisation protocol

The following types of protocol deviation will be considered:

- Patient did not meet one or more of the pre-consent study eligibility criteria but was consented into the study.
- Patient did not meet the post-consent eligibility criteria (i.e. Hb did not drop below 9g/dL or Hct below 27%) but was randomised.
- Patient was randomised more than 24 hours after meeting the post-consent inclusion criteria (i.e. randomised more than 24 hours after Hb dropping below 9g/dL or Hct below 27%).
- Patient consented and met the post-consent inclusion criteria (i.e. Hb dropped below 9g/dL or Hct dropped below 27%) but was not randomised.

The frequency of each type of protocol deviation will be described.

3.5.2 Non-compliance with transfusion protocol

The following types of protocol deviation will be described:

- Patient received a RBC transfusion outside of protocol.
- Patient was not given a RBC transfusion that, according to the protocol, should have been given.

Such compliance will be assessed for the period from randomisation to hospital discharge. If patients withdraw or have their treatment discontinued, compliance after the time of withdrawal/discontinuation will not be assessed. For both of the above types of non-compliance, instances will be classified into mild, moderate or severe dependent on the likely influence on transfusion rates, and therefore possible influence on study outcomes:

	Transfusion outside of protocol	Transfusion according to protocol withheld
Mild	N/A	A transfusion took place, but more than 24 hours after the relevant breach of the transfusion threshold
Moderate	Patient transfused outside of protocol, but patient did breach the threshold for transfusion at some point post-operatively	Patient was not transfused following a breach, but the patient had previously had at least one post-randomisation transfusion
Severe	Patient transfused outside of protocol, and patient did not breach the threshold for transfusion at any point post-operatively	Patient was not transfused following a breach, and patient had no post-randomisation transfusions

Note it may be possible for patients to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation.

Additional analyses will be carried out looking at non-compliance with the transfusion protocol in further detail:

- The following characteristics of different non-compliance will be described by treatment group:
  - Reasons for deviations
  - Number of deviations per patient
  - Hb/Hct levels at deviation
  - Day of week
  - Time of day (weekday, evening or weekend)
  - Time of year (split as Feb-Apr, May-Jul, Aug-Oct and Nov-Jan, to reflect the time of year when changes to junior medical staff are made)

  For withheld transfusions only:
  - Number of previous breaches of transfusion threshold for withheld transfusions
  - Time from first breach of transfusion threshold to transfusion
- Descriptive analyses will be carried out to investigate any differences in patient baseline and operative characteristics between those with and without non-compliance. This will be done separately for any non-compliance and any severe non-compliance, with patient characteristics compared within randomised group.
- The rates of non-compliance with the transfusion protocol across the sites will be described graphically. These will compare the proportions of patients with a) any non-compliance and b) any severe non-compliance with the transfusion protocol.

- Finally, at the beginning of the trial sites were asked to give feedback on standard transfusion protocols to gauge how the trial protocol differed from standard procedures. At the end of the study this exercise will be repeated, with sites being asked additional information on how and when protocols have changed. This information will be summarised as part of the trial reporting.

3.6 Analysis population

The analysis will consist of all randomised patients, excluding:

- Patients marked as "randomised in error": this is a small number of patients (<10) for whom it is realised shortly after randomisation and prior to any intervention that are not eligible
- Patients withdrawn who were unhappy for data collected to be used.

All study analyses will be performed on a modified ITT basis.

3.7 Safety population

Safety data will be analysed on an ITT basis, and will therefore be the same as the analysis population. Note that often safety data are analysed as the treatment received rather than on an ITT basis, however in this study that will not be feasible as protocol deviations do not constitute a "cross-over" between groups. In addition, as the primary outcome is a measure of risk and is analysed on an ITT basis, it will be consistent to also analyse safety data on an ITT basis.

4 DERIVATIONS

4.1 Primary outcome

The primary outcome is defined as follows:

Component event	***Within index admission***	***After hospital discharge***
Sepsis[1]	**YES**, if on CRF C5 there is at least one antibiotic course with: - Date/time antibiotic course started≥date/time of randomisation, AND - *SIRS total*[2]≥2 **NO**, if: - Patient was not given any antibiotics in their post-operative stay (excluding prophylaxis), OR - For all courses of antibiotics, either: o Date/time course started<date/time of	**YES**, if a readmission form (X1) has been completed with: - Infective complication=Yes, AND - Date of admission is within 3 months of operation **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise

	randomisation, OR ○ *SIRS total*=0 and *SIRS missing*[2]≤1 ○ *SIRS total*=1 and *SIRS missing*=0 **MISSING**, otherwise	
Wound infection[3]	**YES**, If at least one wound with in-hospital asepsis score >20 **NO**, if all scored wounds have in-hospital asepsis score ≤ 20, and no wounds have missing in-hospital asepsis scores **MISSING**, otherwise	**YES**, if at least one wound with post-discharge asepsis score >20 **NO**, if all scored wounds have post-discharge asepsis score ≤ 20, and no wounds have missing post-discharge asepsis scores **MISSING**, otherwise
Permanent stroke[1]	**YES**, if on CRF C6: – Stroke=Yes, AND – Date/time of stroke≥date/time of randomisation, AND – Verified by CT=Yes or verified by MRI=Yes, or verification criteria missing **NO**, if: – Stroke=No, OR – Stroke=Yes and date/time of stroke<date/time of randomisation, OR – Stroke=Yes and verified by CT=No and verified by MRI=No **MISSING**, otherwise	**YES**, if a readmission form (X1) has been completed with: – Stroke=Yes, AND – Date of admission is within 3 months of operation, AND – Verified by CT=Yes or verified by MRI=Yes, or verification criteria missing **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise
MI	**YES**, if on CRF C6: – Suspected MI=Yes, AND – Date/time of MI≥date/time of randomisation, AND – At least 2 out of 3 adjudication committee members agree that an MI has occurred **NO**, if: – Suspected MI=No, OR – Suspected MI=Yes and date/time of MI<date/time of randomisation, OR – Suspected MI=Yes and at least 2 out of 3 adjudication committee members agree that an MI has not occurred **MISSING**, otherwise	**YES**, if a readmission form (X1) has been completed with: – Suspected MI=Yes, AND – Date of admission is within 3 months of operation, AND – At least 2/3 adjudication committee members agree that an MI has occurred **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise
AKI[1]	**YES**, if on CRF C6: – AKI=Yes, AND – Date/time of AKI≥date/time of randomisation, AND – Acute Kidney Injury Network (AKIN) criteria stage 1, 2 or 3=Yes or missing	**YES**, if a readmission form (X1) has been completed with: – AKI=Yes, AND – Date of admission is within 3 months of operation, AND

	NO, if: – AKI=No, OR – AKI=Yes and date/time of AKI<date/time of randomisation, OR – AKI=Yes and AKIN criteria stage 1, 2 or 3=No **MISSING**, otherwise	– AKIN criteria stage 1, 2 or 3=Yes or missing **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise
Gut infarction[1]	**YES**, if on CRF C6: – Gut infarction=Yes, AND – Date/time of gut infarction≥date/time of randomisation, AND – Verified by laparotomy=Yes or verified by post mortem=Yes, or verification criteria missing **NO**, if: – Gut infarction=No, OR – Gut infarction =Yes and date/time of gut infarction <date/time of randomisation, OR – Gut infarction =Yes and verified by laparotomy=No and verified by post mortem=No **MISSING**, otherwise	**YES**, if a readmission form (X1) has been completed with: – Gut infarction=Yes, AND – Date of admission is within 3 months of operation, AND – Verified by laparotomy=Yes or verified by post mortem=Yes, or verification criteria missing **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise

Notes:

[1] For sepsis, stroke, AKI and gut infarction the event will default to NO if the documentary evidence does not support that the event occurred.

[2] SIRS elements are defined as:

- *Temperature: YES if >38°C or <36°C, NO if 36-38°C, MISSING otherwise*
- *Heart rate: YES if >90 beats/minute, NO if ≤90 beats/minute, MISSING otherwise*
- *Respiration: YES if respiratory rate >20 breaths/min OR $PaCO_2$ <32 mm Hg or <4.3 kPa, NO if respiratory rate ≤20 breaths/min, MISSING otherwise*
- *White blood cell (WBC): YES if >12,000/mm^3 or <4,000/mm^3, NO if 4,000-12,000/mm^3, MISSING otherwise*

***SIRS total** = total of (temperature, heart rate, respiration, WBC), with YES=1, NO=0*

***SIRS missing** = number of missing elements of (temperature, heart rate, respiration, WBC)*

[3] For details of how to derive in-hospital and post-discharge asepsis scores see Supplementary Material.

Separately for pre- and post-discharge, the composite primary outcome is defined as:

- If any of the component events occurred, the composite primary outcome is classified as occurring.
- If all of the component events did not occur (with no missing components), the composite primary outcome is classified as not occurring.

- Otherwise (i.e. there is missing data for at least one of the component events, and all non-missing component events did not occur), the composite primary outcome is classified as missing.

Overall (at any time), the composite primary outcome is defined as:

- If the composite outcome occurred pre-hospital discharge and/or post-discharge, the overall composite outcome is classified as occurring.
- If the composite outcome did not occur either pre- or post-discharge, the overall composite outcome is classified as not occurring.
- Otherwise (i.e. the outcome is missing either pre- and/or post-discharge, and, if applicable, did not occur at the other time point), the composite outcome is classified as missing.

The time to primary outcome occurring is defined as follows:

Situation	Time to primary outcome defined as
One or more of the components occur within the index admission	Time (in hours) from randomisation to the onset of the first event (note: the timing of asepsis is assumed to be either: a) the date of sepsis if sepsis is also reported, or b) the halfway point of the participant's post-randomisation stay (i.e. halfway between the randomisation date and the date of discharge from the cardiac surgery unit)
No components occur in the index admission, but one or more occur after discharge	Time (in days) from randomisation to the hospital admission where the event was reported (note: the timing of asepsis will be defined as either a) the date of sepsis if sepsis is also reported, or b) the halfway point between discharge date and 6 weeks post-operatively)
No components occur, patient completed 3 month follow-up	Censored as the time (in days) between randomisation and follow-up
No components occur, patient did not complete 3 month follow-up	Censored as the time (in days) between randomisation and hospital discharge (or death if the patient died prior to 3 month follow-up)

4.2 Secondary outcomes

The following secondary outcomes require derivations to be made:

Secondary outcome	Rules
Infectious events	**YES**, if sepsis=Yes, OR wound infection=Yes
	NO, if sepsis=No AND wound infection=No
	MISSING, otherwise
Ischaemic events	**YES**, if stroke=Yes, OR MI=Yes, OR AKI=Yes, OR gut infarction=Yes
	NO, if stroke=No, AND MI=No, AND AKI=No, AND gut infarction=No
	MISSING, otherwise

Secondary outcome	Rules
RBC units transfused intra-operatively	Total number of units listed on CRF B2 with reason for transfusion=A[2] (intra-operative)
RBC units transfused during pre-randomisation re-operation	Total number of units listed on CRF B2 with reason for transfusion=B (re-operation) and date/time < date/time of randomisation
RBC units transfused during post-randomisation re-operation	Total number of units listed on CRF B2 with reason for transfusion=B (re-operation) and date/time ≥ date/time of randomisation
RBC units transfused after treatment according to protocol discontinued	Total number of units listed on CRF B2 with reason for transfusion=C (treatment according to protocol discontinued)
RBC units transfused post-operative but pre-randomisation	Total number of units listed on CRF B2 with reason for transfusion=D (pre-randomisation)
RBC units transfused in breach of protocol	Total number of units listed on CRF B2 with reason for transfusion=E (in breach of protocol)
RBC units transfused per protocol	Total number of units listed on CRF B2 with reason for transfusion=F (per protocol)
Total RBC units transfused	Total number of RBC units listed on CRF B2
Total duration of post randomisation ICU/HDU stay (hours)	Calculated as the sum of the following components: – Duration of initial cardiac intensive care unit (CICU)/HDU stay = Earliest of (ward admission date/time, general ICU date/time, discharge date) – Latest of (Randomisation date/time, CICU/HDU admission date/time) * 24 – Duration of initial general ICU stay (if applicable) = (Date/time of next admission following general ICU admission) – Latest of (Randomisation date/time, Date/time of general ICU admission) * 24 – Duration of any readmissions to CICU/HDU/general ICU: (Date/time of next admission following relevant readmission) – Latest of (Randomisation date/time, Date/time of CICU/HDU/general ICU readmission) * 24
ICU/HDU censor variable	**YES** if patient died during ICU/HDU stay **NO** otherwise
Duration of post randomisation hospital stay	(Date of discharge from cardiac surgery unit or date of death) – (Randomisation date)
Postoperative hospital stay censor variable	**YES** if patient died during hospital stay **NO** otherwise

[2] Note: for early versions of the study CRFs, reasons for transfusions were not recorded and therefore will be derived from dates/times of transfusions, operation, re-operation, treatment discontinuation, randomisation and Hb/Hct levels at transfusions.

Secondary outcome	Rules
All-cause mortality	**YES**, if either: – Patient recorded as dead at discharge from hospital on CRF B1 and/or D1 – A SAE form (CRF F1) has been completed with either: reason for reporting SAE=patient died, OR outcome of SAE=death AND date of death is within 3 months of operation date – NHS mortality tracing shows the patient died with a date of death within 3 months of operation date **NO**, otherwise
Time to death (days)	(Date of death – Randomisation date)
Significant pulmonary morbidity	**YES**, if: EITHER, on CRF C7 any of the following are true: – Initiation of mask CPAP=Yes AND date/time ≥date/time of randomisation, OR – Re-intubation/ventilation=Yes AND date/time ≥date/time of randomisation, OR – Tracheostomy=Yes AND date/time is after date/time of randomisation OR, a readmission form (X1) has been completed with date of admission within 3 months of operation and any of the following are true: – Initiation of mask CPAP=Yes, OR – Re-intubation/ventilation=Yes, OR – Tracheostomy=Yes **NO**, if: On CRF C7: – Initiation of mask CPAP=No OR (Initiation of mask CPAP=Yes AND date/time <date/time of randomisation), AND – Reintubation/ventilation=No OR (Reintubation/ventilation=Yes AND date/time <date/time of randomisation), AND – Tracheostomy=No OR (Tracheostomy =Yes AND date/time <date/time of randomisation) AND, patient completed 3 month follow-up/died and there is not a readmission form completed for initiation of mask CPAP, reintubation/ventilation or tracheostomy **MISSING**, otherwise
EQ5D single summary index score	Five digit 'state' score is derived as: 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score. Each state score is then assigned a single summary index score according to reference scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health.

4.3 Protocol compliance

New variable	Rules
Did not meet pre-consent	**YES**, if consent=Yes but one or more of the eligibility criteria are not met

New variable	Rules
eligibility criteria but was consented	**NO**, otherwise
Did not meet post-consent eligibility criteria but was randomised	**YES**, if randomisation date non-missing but Hb ≥9g/dL (Hct ≥27%) on all days post-operatively **NO**, otherwise
Randomised >24 hrs after meeting post-con sent eligibility criteria	**YES**, if either: – First day that Hb <9g/dL (or Hct <27%) is 2 or more days before date of randomisation, OR – (Randomisation date/time – Date/time threshold first breached) >1 day **NO**, otherwise
Consented and met post-consent eligibility criteria but not randomised	**YES**, if randomisation date missing but there is at least one day postoperatively when Hb <9g/dL (or Hct <27%), and patient is not withdrawn/treatment discontinued at time Hb <9g/dL **NO**, otherwise
Any transfusion outside of protocol	Transfusions listed on CRF B2 prior to treatment discontinuation/patient withdrawal where one of the following is true: – Reason for transfusion=E (outside of protocol) – Reason for transfusion=F (per protocol) or missing and: o CRF E1 (reason for giving transfusion outside of protocol) has been completed, OR o Recorded Hb/Hct is above the relevant (treatment group specific) threshold, OR o Transfusion is within 2 hours of a previous transfusion that had the same Hb/Hct (or missing). These are two units of blood given together without rechecking Hb/Hct
Moderate transfusion outside of protocol	Transfusion outside of protocol (i.e. identified from above) whereby patient breached relevant threshold for transfusion at some point post-randomisation
Severe transfusion outside of protocol	Transfusion outside of protocol (i.e. identified from above) whereby patient did not breach the relevant threshold for transfusion at any point post-randomisation
Mild withheld transfusion	Any instances that are more than 24 hours before the next per protocol transfusion whereby: – A CRF E2 (withheld transfusion) was completed – According to CRF B1 the patient breached the relevant threshold on a day that was prior to the breach date for the next per-protocol transfusion, and no CRF E2 was completed or other type of transfusion given on that day – According to CRF B2 the "number of breaches prior to trigger breach" is greater than 0, and these breaches have not been accounted for in the previous two steps – According to CRF B2 the "number of breaches prior to trigger breach" is 0, no CRF E2s have been completed and the answer to the question "Was RBC prescribed within 24h of breach" is No

New variable	Rules
Moderate withheld transfusion	Any instances between the last per protocol transfusion received and discharge whereby the patient breached the relevant threshold for transfusion (identified either via a completed CRF E2 or via a breach on CRF B1).
Severe withheld transfusion	For patients who did not have any post-randomisation transfusions (including post withdrawal, in breach of protocol and per-protocol), any instances post-randomisation whereby the patient breached the relevant threshold for transfusion (identified either via a completed CRF E2 or via a breach on CRF B1).
Any withheld transfusion	**YES**, if mild withheld transfusion=Yes, OR moderate withheld transfusion=Yes, OR severe withheld transfusion=Yes **NO**, otherwise
Any severe protocol deviation (transfusion protocol)	**YES**, if severe extra transfusion=Yes, OR severe withheld transfusion=Yes **NO**, otherwise
Any protocol deviation (transfusion protocol)	**YES**, if any extra transfusion=Yes, OR any withheld transfusion=Yes **NO**, otherwise
Threshold breaches that do not constitute a protocol deviation	Any instances where a CRF E2 has been completed that are within the 24 hour period prior to a per-protocol transfusion

4.4 Other variables

New variable	Rules
Reason for exclusion from study	Exclusion group defined as: - PIL not sent: PIL sent=No, Approach is not Yes, Consent is not Yes - Not approached: PIL sent=Yes, Approach=No, Consent is not Yes - Ineligible: Eligible=No, Consent is not Yes - Eligible but did not consent: Eligible=Yes, Consent=No
Age at randomisation	(Randomisation date – date of birth (DOB))/365.25
Body mass index (BMI)	Weight (kg) / Height $(cm)^2$ * 10,000
EuroSCORE	For all patients start with Euroscore of zero and add points according to the following rules: - Age: <60=0, 60-64=1, 65-69=2, 70-74=3, 75-79=4, 80-84=5, 85-90=6, >90=7 - Sex: Male=0, Female=1 - Chronic pulmonary disease: add 1 - Extracardiac arteriopathy, neurological dysfunction, Creatinine >200 µmol/l, unstable angina, pulmonary hypertension, recent MI, surgery other than isolated CABG: add 2 for each - Previous cardiac surgery, active endocarditis, critical preoperative state, surgery on thoracic aorta: add 3 for each

New variable	Rules
	– Postinfarct septal rupture: add 4 – LV function: Good (>50%)=0, Mod (30-50%)=1, Poor (<30%)=3
Day of randomisation (days post-op)	(Randomisation date – Operation date)
Time between surgery and randomisation (hours)	(Randomisation date/time - Operation date/time) * 24
Day of withdrawal post-op for pre-randomisation withdrawals	(Withdrawal date – Operation date)
Day of withdrawal post-randomisation for post-randomisation withdrawals	(Withdrawal date – Randomisation date)
Day of treatment discontinuation (days post-randomisation)	(Treatment discontinuation date – Randomisation date)
Duration of operation (hours)	(Operation end time – Operation start time) * 24
Complication (on C7) occurred pre-randomisation	**YES** if complication (C7) occurred and date/time of onset<date/time of randomisation **NO** otherwise
Complication (on C7) occurred post-randomisation	**YES** if complication (C7) occurred and date/time of onset≥date/time of randomisation **NO** otherwise
Ventilation time (hours)	Calculated as the sum of the following components: – (Extubation date/time – Randomisation date/time) * 24 – (Re-extubation date/time) – Latest of (Randomisation date/time, re-intubation date/time) * 24 (if applicable)
Duration of ward stay (hours)	Calculated as the sum of the following components: – Duration of initial ward stay = Earliest of (Date/time of next admission following ward admission) – Latest of (Randomisation date/time, Ward admission date/time) * 24 – Duration of any readmissions to ward: (Date/time of next admission following ward readmission) – Latest of (Randomisation date/time, Date/time of ward readmission) * 24
Ward censor variable	**YES** if patient died during ward stay **NO** otherwise
Timing of unexpected SAE	Pre-discharge if SAE start date ≤ discharge date Post-discharge if SAE start date > discharge date
Maximum intensity of unexpected SAE	Maximum of intensity variable on initial SAE form and all follow-up SAE forms
Final outcome of unexpected SAE	Outcome (resolved without sequelae, resolved with sequelae, ongoing, died) according to last SAE form completed (may be initial report or follow-up)

New variable	Rules
Percentage decline in Hb	(Pre-operative Hb (CRF A2) – minimum Hb post-operatively (B1)) / Pre-operative Hb * 100
eGFR	([140–age] * Weight (A2) * [0.85 if female]) / (Pre-op creatinine (mg/dl) * 72)

5 STATISTICAL ANALYSES

5.1 Descriptive data

Baseline (i.e. patient demography and past history) and intra-operative characteristics will be described by treatment group for patients in the analysis population. In addition post-operative outcomes that are not study outcomes or AEs will be described by treatment group.

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous studies. However, if distributional assumptions are not valid, changes will be made.

Any imbalances in the characteristics of the patients will be described but statistical tests for imbalance will not be carried out.

5.2 Primary and secondary outcome data

All outcomes listed in the study protocol will be presented as follows:

5.2.1 Primary outcome

The primary outcome will be summarised as follows:

- The numbers and percentages of patients experiencing at least one element of the primary outcome at any time post-randomisation will be presented by treatment group. This outcome will be analysed as a binary outcome, see section 5.3.2.
- In addition, the numbers and percentages of patients experiencing: a) any infectious event, b) any ischaemic event and c) each of the individual primary outcome components will be given by treatment group.
- The frequency of each combination of component events will be described by deriving a 6-digit variable where each digit relates to one of the components, and takes the value "1" if the patient experienced the outcome, "0" if they did not and "." if the component

is missing. The numbers of patients with each value of this variable will be described by treatment group.

- The time from randomisation to the first occurrence of the primary outcome will also be analysed as a time to event outcome as a secondary analysis (see section 5.3.2). Patients that don't experience the primary outcome will be censored at either:
  - Date of 3 month follow-up, for patients with 3 month follow-up completed
  - Date of death, for patients who die prior to 3 month follow-up.
  - Date of discharge from hospital, for patients who survive 3 months post-operatively but do not complete the follow-up questionnaire.
- Various sensitivity analyses will also be undertaken (see **Section 5.5**).

5.2.2 Secondary outcome: units of RBCs and other blood components transfused during a participant's hospital stay

RBC transfusions

All RBCs transfused post-randomisation will be summarised by the median and IQR (or mean and SD if the data is not skewed, which is unlikely) number of units transfused in each treatment group. This outcome will be analysed as a continuous outcome (see section 5.3.2).

In addition, a more detailed breakdown of the numbers of units transfused will be presented, and the above summary statistics will also be presented split into the four types of transfusion (re-operation transfusions, transfusions after treatment according to protocol has been discontinued, transfusions in breach of protocol, per protocol transfusions). However, no further comparisons between the groups will be made. The total RBC units transfused (both pre- and post-randomisation) will also be given, but no formal comparison made.

Fresh frozen plasma (FFP), platelets and cryoprecipitate transfusions

FFP, platelets and cryoprecipitate transfusions will be summarised by the median and IQR number of units transfused during a participant's hospital stay for each group. All three outcomes will be analysed as continuous outcomes (see section 5.3.2). Note it is not possible to spilt such transfusions into pre- and post-randomisation due to how the data was collected. The numbers of units of RBC, FFP, platelets and cryoprecipate transfused will also be described graphically.

Use of Activated Factor VII and Beriplex

Activated Factor VII and Beriplex use will be summarised by the numbers and percentages of patients in each group for whom the blood product was used. Both outcomes will be

analysed as binary outcomes (see section 5.3.2). Note it is not possible to spilt such product use into pre- and post-randomisation due to how the data was collected.

Hb/Hct levels

The average nadir daily Hb and Hct levels in each group at each day post-randomisation will be described graphically by the mean and SD (or median and IQR if distributions are skewed) in each treatment group. Although no formal comparisons will be made, the Hb/Hct levels at day three post-randomisation (chosen because at this point the differing transfusions regimens will be likely to have had an effect on Hb/Hct levels, and most patients will still be in hospital and have readings available for comparison) in each group will be used as an overall summary measure.

5.2.3 Secondary outcome: proportion of patients experiencing an infectious/ischaemic event

The presentation of the proportion of patients experiencing infectious/ischaemic events is covered within the primary outcome table. Both outcomes will be analysed separately as binary outcomes (see section 5.3.2).

5.2.4 Secondary outcomes: other clinical outcomes

For the presentation of other clinical outcomes (duration of post-operative ICU/HDU and hospital stay, all-cause mortality and significant pulmonary morbidity).

The duration of post-randomisation ICU/HDU and hospital stay, and the time to death (all-cause mortality) will be summarised by the median and IQR in each treatment group. All outcomes will be analysed as time to event outcomes (see section 5.3.2), with censor variables as defined below:

Outcome	Censor variable
Duration of post-randomisation ICU/HDU stay	Time of death in ICU/HDU
Duration of post-operative hospital stay	Time of death in hospital
All-cause mortality	Time of last follow-up (usually 3 months post-operation)

Significant pulmonary morbidity will be summarised as the numbers and percentages of patients in each treatment group experiencing the event. The outcome will be analysed as a binary outcome (see section 5.3.2).

5.2.5 Secondary outcome: EQ5D

The responses to each of the five EQ5D questions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) will be summarised as the numbers and percentages of patients in each treatment group choosing each response, at each time-point

(pre-operative, 6 weeks post-operative and 3 months post-operative). No formal statistical comparisons between the groups will be made.

The two continuous EQ5D outcomes (single summary index and visual analogue scale) will be summarised as means and SDs (or medians and IQRs if distributions are skewed) at each time point, in each treatment group. Both outcomes will be analysed as continuous longitudinal outcomes, see section 5.3.2.

Note that a summary figure will be produced summarising all the results from sections 5.2.4 and 5.2.5.

5.3 Analysis models

5.3.1 Adjustment in models

The intention is to adjust all models for factors included in the cohort minimisation: operation type (coronary artery bypass graft (CABG) only, Valve only, CABG and valve, Other – with CABG only as the reference group) as a fixed effect and centre as a random effect (or a shared frailty term in time to event models). Occasionally operation type differs between the study database and the randomisation system as it has been entered incorrectly into the randomisation system. In this case the value from the study database will be used, as the operation type recorded on the database has been confirmed to be correct in such instances.

5.3.2 Models for different data types

General methods of assessing treatment effects are outlined below. For all treatment comparisons the liberal group will be the reference group. Details specific to each outcome are described as appropriate.

- **Binary outcomes** (primary outcome, proportions of infectious/ischaemic events, use of Activated Factor VII/Beriplex and significant pulmonary morbidity) will be compared between treatment groups using logistic regression. Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group). Treatment comparison estimates will be presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI).
- **Continuous outcomes** (units of RBCs, FFP, platelets and cryoprecipitate transfused) will be compared using linear regression. For untransformed data treatment comparisons will be presented as adjusted differences in means with 95% CI, and for logarithmically transformed data as adjusted ratios of geometric means with 95% CI. If

a logarithmic transformation is not satisfactory other analysis/presentation methods will be sought.

- **Time to event outcomes** (duration of ICU/HDU stay, duration of post-operative hospital stay and all-cause mortality) will be compared using Cox's proportional hazards (PH) models, with treatment comparisons presented as hazard ratios (HR) and 95% CI. Such models require an assumption of PH to be met. If such outcomes consist of more than one distinct time periods (e.g. the patient had two separate admission periods in ICU, or the patient was admitted to ICU after they were randomised) time periods may be "split" (e.g. by using the "stsplit" command in Stata) to account for this. Any patients with a time of zero will be included in analyses by assuming a time of half of the smallest non-zero time to event.
- **Continuous longitudinal outcomes** (EQ5D single summary index and visual analogue scale scores) will be compared using linear mixed effects methodology with the treatment group and study design variables (see section 5.3.2) fitted as fixed effects, and patient terms as random effects. Separate parameter estimates will be incorporated into models for 1) the mean baseline response across both treatment groups and 2) at each post-intervention time point for each treatment (i.e. saturated model with time fitted as a categorical variable). This approach of "jointly" modelling the baseline and post-intervention measurements avoids the necessity to either exclude cases with missing baseline measures or to impute missing baseline values. If the time x treatment interaction (post-intervention) is not statistically significant at the 10% level an overall treatment effect will be reported. If the interaction is statistically significant the changes in treatment effect with time will be described. Different variance/covariance structures will be explored, and the structure that provides the best fit in terms of information criteria such as AIC, BIC and likelihood ratio tests will be used. Treatment comparisons will be presented as adjusted differences in means with 95% CI.

5.3.3 Statistical significance

For hypothesis tests two-tailed p-values<0.05 are considered statistically significant. Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing.

5.3.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g. residual plots, tests for PH, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and

comments made in footnotes. Sensitivity analyses may be performed to examine the effect on the study's conclusions of excluding outlying observations.

If there are any boundary problems for either of the EQ5D continuous scales (i.e. if there are an inflated number of patients scoring "perfect health") then alternative analysis methods will be sought. Examples include: creating a binary endpoint from the continuous outcome and analysing using the methods outlined above.

5.3.5 Multiple testing

No formal adjustment will be made for multiple testing. However, the following measures to try and avoid problems with over-interpretation will be taken: 1) formal statistical comparisons will not be made for outcomes with low event rates, and 2) only pre-specified subgroup analyses will be performed (see section 5.4), and a significance level of 5% will be used for the tests for interaction for subgroup analyses despite being low powered tests. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

5.4 Subgroup analyses

There are seven pre-specified subgroup analyses stated in the study protocol:

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

Each subgroup analysis will be performed by adding a relevant interaction term to the primary outcome logistic regression model (e.g. for sex, a sex*treatment interaction term will be added to the model). The hypothesis for all subgroup analyses is that there will be no interaction. Results of the subgroup analyses will be presented in forest plots, (one for subgroup analyses with statistically significant tests for interaction, and one for those without significant interactions), with ORs and 95% CIs within each subgroup displayed alongside p-values from results of tests for interactions. P-values for treatment estimates within each subgroup will not be given.

Note that for each of the subgroup analyses the first group listed in each set of brackets above will be the reference group (e.g. for age it will be the <75 years group). Also, for the

operation type subgroup analysis, operation type as a four-level variable will not be adjusted for as a fixed effect (see section 5.3.1). No further subgroup analyses will be performed.

5.5 Sensitivity analyses

The following sensitivity analyses have been identified, note these were not pre-specified in the study protocol:

- *Examining treatment estimates for the primary outcome by site, ordering sites by rates of severe non-compliance with the transfusion protocol.* This will be implemented by producing a forest plot of treatment estimates for each site, with the sites ordered by their rates of severe non-compliance with the transfusion protocol. The hypothesis is that the treatment effect should tend towards the null with increasing non-compliance. Any sites with no patients that experienced the primary outcome will be excluded from this analysis, although a footnote will be added indicating the severe non-compliance rates for such sites.
- *Assessing the effect of the timing of randomisation and transfusions on the primary outcome.* This will be implemented by two sensitivity analyses that re-analyse the primary outcome:
  - Excluding all events that occurred in the first 24 hours after randomisation. The justification for doing this is that such events occurring in the first 24 hours after randomisation are less likely to be attributable to the treatment regimen.
  - Excluding patients who were transfused prior to randomisation (either: intra-operative, post-operative but pre-randomisation or during pre-randomisation re-operations). The justification is that it may be these transfusions that lead to the primary outcome rather than any post-randomisation transfusions.
- *Assessing the effect of AKI.* In collecting AKI data, it was unfortunately overlooked that the creatinine rise required to trigger AKI should occur in a 48 hour period. However highest daily creatinine levels have been recorded separately, so the following sensitivity analyses have been planned that re-analyse the primary outcome:
  - Excluding patients identified with AKI who do not have an increase in creatinine over a 48 hour period or less, according to the daily highest creatinine levels collected (accepting that these patients may have triggered AKI anyway due to urine output or renal replacement therapy).

- Including patients that have not been identified as having AKI, but according to their daily highest creatinine levels have a rise in creatinine that would meet the criteria (and were not having haemofiltration or dialysis pre-operatively).

– *Serious primary outcome events.* The interim analysis showed that the majority of the primary outcome events are either sepsis or AKI. Therefore the primary outcome will be re-analysed including only the more "serious" events. This will mean the following changes to the definitions of the primary outcome:

- All MIs, gut infarctions and strokes will be included
- Only AKI stage 3 events will be included
- All asepsis events will be excluded (the more serious wound infections will be identified via serious sepsis events)
- For pre-discharge sepsis events: serious events will be identified via presence of sepsis plus organ failure (defined as: MI, stroke, AKI, laparotomy for gut infarction and one or more of reintubation, ARDS, low cardiac output and/or tracheostomy; for these latter events the event must meet the criteria of an SAE).
- Post-discharge sepsis events will be included (as they require hospitalisation)

5.6 Pre-specified observational analyses

There are three pre-specified observational analyses in the study protocol:

1. Estimating the relationship between the number of RBC units transfused, and the risk of mortality and morbidity, stratified by trial arm.
2. Investigating the relationship between percentage decline in Hb from the preoperative level and the risk of primary and secondary outcomes, taking into account the number of RBC units transfused.
3. Investigating whether RBC age is associated with the risk of primary and secondary outcomes.

Planned tables and figures for these analyses are not included in this SAP, as they are likely to vary dependent upon the final models used. However, in brief, tables of pre-operative and intra-operative characteristics will be presented by the (categorised) exposure of interest as well as tables reflecting the models fitted and variables adjusted for.

Some preliminary analysis techniques are outlined below; however the final techniques used are likely to change dependent upon the findings of a) exploratory analyses, and b) the analysis of the trial primary and secondary outcomes. This section of the SAP may therefore be reviewed and expanded once the main trial outcomes have been analysed.

5.6.1 Analysis of number of RBC units transfused and percentage decline in Hb (analyses 1 and 2)

Analyses 1 and 2 will be implemented by fitting logistic regression models, with an outcome of the primary outcome and/or all-cause mortality. Three separate models will be fitted to address the hypotheses posed by both analyses, with the following explanatory variables:

- Model 1: total number of RBC units transfused (either pre- or post-randomisation)
- Model 2: percentage decline in Hb
- Model 3: total number of RBC units transfused and percentage decline in Hb

In all of these models the following variables will be adjusted for if found to be potential confounders: randomised allocation, operation type, centre (as a random effect), EuroSCORE, age and sex.

Points of note:

- The total number of RBC units transfused will be fitted as either a continuous variable or an ordinal categorical variable, dependent upon model fit.
- The percentage decline in Hb will be defined as the percentage change from the pre-operative value to the lowest Hb level reached post-operatively and prior to the primary outcome.

5.6.2 Age of blood analysis (analysis 3)

Analysis 3 will be achieved by linking the batch numbers of all RBCs transfused to a blood bank database. The age of each unit transfused will then be determined from the date of donation and date of transfusion. A logistic regression model will be fitted with an outcome of primary outcome and/or all-cause mortality as the outcome variable and the age of blood as the exposure.

For the primary analysis age of blood will be defined as the age of the 'oldest' unit of blood transfused at any time (i.e. including intra-operative, during re-operations, pre-randomisation and post-randomisation). The following variables will be adjusted for if found to be potential confounders: number of RBC units transfused, blood group, EuroSCORE, age and sex.

Points of note:

- The sensitivity of fitting the model using the age of the 'oldest' unit of blood will be explored by refitting the model using other definitions of the exposure variable. This may include: the mean age of all RBC units, the use of any blood more than 14 days old, the number or percentage of RBC units given that are more than 14 days old, the

use of blood that is older than the median age of all RBC units transfused. There are known problems with all of these approaches, e.g.: the age of the 'oldest' unit of blood is likely to be confounded by the number of RBC units transfused, the use of any blood more than 14 days old is likely to be confounded by blood group and many of these methods will need to exclude patients not transfused any RBC units.

5.6.3 Points relevant to all analyses:

- Potential confounders are defined as: variables associated with both the exposure and the outcome that are not an intermediary step on the causal pathway between the exposure and outcome, that significantly contribute to the relevant multivariate model (defined as a likelihood ratio p-value <0.05 or by modifying the effect estimate by greater than 10%).
- It may be sensible to restrict the analyses to only patients who did not receive a proportionately large number of RBC units (e.g. restrict to those who received five or less units).
- The instrumental variable method of controlling for confounding will be explored.
- In all of the analyses (with the exception of decline in Hb) there is a potential problem that some of the RBCs may be transfused after the outcome. Therefore fitting the models described above may not be appropriate due to the timing of the exposure relative to the outcome. If this proves to be the case then alternative approaches will be considered, including:
  - Nested matched case-control study: each patient with the primary outcome (i.e. case) will be matched to a control (by matching on at least centre and randomised allocation, other factors may also be used). For both the case and the control any RBC units transfused after the time that the case first experienced the primary outcome will be excluded from analyses.
  - Time to event analyses with a time varying covariate of RBC units given: this would address the issue of exposure time (for cases the event would be the primary outcome event, and for controls the last follow-up), but would ignore any blood given after the occurrence of an outcome event.

5.7 Meta-analysis combining the results of TITRe2 with other studies

It is intended to perform a meta-analysis combining the primary outcome results from this study with any previous systematic reviews and studies. This analysis will be performed using standard meta-analysis methods for binary outcomes, using a random effects model. Results will be presented in a forest plot.

Previous studies will be included in the meta-analysis if they fulfil the following criteria:

- The patient population was patients undergoing cardiac surgery.
- Restrictive and liberal RBC transfusion strategies are compared, although the actual Hb/Hct thresholds for transfusion can differ between studies.
- The outcomes included in the meta-analysis are post-operative morbidity or mortality – if possible (i.e. there are sufficient numbers of studies) each component of the TITRe2 primary outcome will be analysed separately.

Data from studies will be used individually if possible, i.e. aggregate data from previous systematic reviews/meta-analyses will only be used if individual study level data is not available. Also care will be taken to ensure that data from studies are included only once, i.e. data should not be included as part of a systematic review and then also from the study in its own right.

5.8 Post-hoc analyses

A secondary post-hoc analysis of severe in hospital events will be performed. This will involve refitting the primary outcome model with an outcome of: death, severe sepsis (as defined in section 5.5), ARDS, tracheostomy, low cardiac output, MI, AKI stage 3, gut infarction and/or stroke.

5.9 Missing data

In all tables missing data will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored.

5.9.1 Missing predictor data

There will be no missing data for any of the randomisation factors (by design). All other potential predictors are preoperative measurements of continuous longitudinal outcomes, and due to the joint modelling approach described previously the handling of missing values for such data is considered in the context of missing longitudinal data (see below).

5.9.2 Missing continuous outcome data measured at one time point

- If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e. excluding cases with missing data).
- If the proportion of missing data is between 5% and 15%, marginal mean imputation will be performed, i.e. imputing the overall median or mean for continuous data, or the most common category for binary or categorical data.
- If the proportion of missing data is between 15% and 25% conditional mean imputation methods will be used. This involves predicting the outcome from a regression model

from (linearly related) covariate(s). These covariates will include the design variables, plus other potentially important covariates (e.g. age, gender, additive EuroSCORE).

- If the proportion of missing data is above 25% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g. using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules.

5.9.3 Missing longitudinal continuous outcome data

For continuous data measured at multiple time points preoperative values will be modelled jointly with those measured postoperatively, as described previously, thereby allowing all cases with at least one observation to be included. If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured pre-operatively) then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.

5.9.4 Missing binary or categorical outcome data

No formal imputation techniques will be used for missing binary or categorical outcome data. The following approach will be followed for handling missing data will be used for the primary outcome:

- The amounts of missing data in each treatment group will be described.
- The primary outcome element expected to have the highest amount of missing data is wound infection (asepsis scoring). If in-hospital asepsis scores are missing and the following are true the patient will be assumed to have no wound infection: 1) no antibiotics for suspected wound infection were prescribed in hospital, 2) follow-up is complete and the patient reported no problems with the healing of the wound at follow-up.
- If after the above point has been implemented the level of missing data is greater than 5%, this is likely to be mainly due to missing follow-up data. In this case separate treatment estimates will be made for: 1) primary outcome at hospital discharge, and 2) primary outcome at any time.
- Finally a sensitivity analysis will be carried out reanalysing the primary outcome twice: firstly assuming patients with missing data didn't have the primary outcome and

secondly assuming patients with missing data had the primary outcome. Any impact on treatment difference estimates will be noted.

5.10 Safety data

AEs occurring in the study period for all patients in the safety population will be tabulated. No formal comparisons between treatment groups will be made.

Tables will summarise *expected* AEs listed in the study protocol. Events occurring prior to hospital discharge will be summarised, with events that meet the serious criteria[3] indicated (serious adverse events, SAEs). Such events are captured via the study CRFs. After hospital discharge, only SAEs are collected and will be summarised. Finally the numbers of SAEs occurring at any time will be described (i.e. either pre or post hospital discharge).

Further tables will summarise *unexpected* SAEs, i.e. events that are not listed in the study protocol that meet the serious criteria. Such events are captured via separate SAE report forms and the event type will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System organ class (SOC) terms will be used to group events, with groupings further broken down into preferred terms (PTs) if necessary.

A summary table of expected and unexpected events combined occurring at any time will also be produced.

5.11 Use of Hb/Hct

At most sites, Hct measurements are not used in treatment decisions. However at approximately a quarter of sites both Hb and Hct measurements are used; e.g. a patient in the liberal group would be transfused if their Hb fell below 9g/dL OR their Hct fell below 27%.

In the presentation of the study results, Hb values are presented unless either: a) Hb is missing and Hct non-missing, b) the Hct is lower than the Hb. In either of these cases the Hct is converted to Hb (by dividing by three) and used in its place.

6 BIBLIOGRAPHY

1. Wilson AP, Treasure T, Sturridge MF, Gruneberg RN. A scoring method (ASEPSIS) for postoperative wound infections for use in clinical trials of antibiotic prophylaxis. *Lancet* 1986;**1**:311-3.

[3] An event is classified as serious if it meets one or more of the following criteria: a) resulted in death, b) was life threatening, c) resulted in persistent or significant disability/incapacity, d) prolonged an ongoing hospitalisation or resulted in hospitalisation

2. Wilson AP, Weavill C, Burridge J, Kelsey MC The use of the wound scoring method 'ASEPSIS' in postoperative wound surveillance. *J Hosp Infect* 1990;**16**:297-309.
3. Mehta RL, KellumJA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A. Acute Kidney Injury Network: Report of an Initiative to Improve Outcomes in Acute Kidney Injury. *Critical Care*. 2007; **11**:R31.
4. EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 119-208.

7 AMENDMENTS TO THE SAP

Previous version	Previous date	New version	New date	Brief summary of changes

SUPPLEMENTARY MATERIAL: ASEPSIS SCORES

In-hospital asepsis scores

For each wound used in the operation (a minimum of one – chest – and a maximum of six – chest, left leg, right leg, left arm, right arm, other, per patient) a wound specific in-hospital asepsis score is derived using the following steps:

1. A daily score is derived for each of the days that the wound was scored (ideally scored on three separate occasions), from the following:
   - If both filter questions (wound hot/wound wet) are "No" then the daily score is zero.
   - Otherwise the daily score is derived from summing the points awarded as follows for the four proportions of wound affects answers given on the CRF:

Proportion of wound affected:	0%	<20%	20-39%	40-59%	60-79%	>80%
Serous exudates	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent exudates	0	2	4	6	8	10
Wound separation	0	2	4	6	8	10

   Note: *Any missing scores will be assumed to be 0, unless all four scores are missing and then the daily score will be set to be missing.*

2. Data collection is ideally performed on days 3, 5 and 8 post-operatively. The following rules are used to determine if daily scores are valid:
   - A two day window is allowed either side of the intended day, so for example the day 3 score can be done between day 1 and day 5[4].
   - Any assessments done outside of these windows, after the date of discharge, or in an invalid order (e.g. day 5 done before day 3) are invalid and not used.
   - A minimum of one daily score is required to proceed further. If this is not the case then the in-hospital asepsis score for that wound is missing.
3. Scores for days 1 to 10 are calculated; scores for missing days are either propagated from the nearest score or interpolated between scores. Note that the actual day of assessment is used rather than the intended day. See the following examples:

[4] Note the day 8 score is intended to be performed on day 8 or, if the patient discharged sooner, on the day of discharge. Therefore if the patient is discharged prior to day 8 the allowed window will be within two days of discharge (for example if the patient is discharged on day 6 the window will be day 4 to day 6)

	EXAMPLE 1		EXAMPLE 2	
Day (post-op)	Score	Rule	Score	Rule
1	3	Propagate	6	Propagate
2	3	Observed	6	Propagate
3	2.25	Interpolate	6	Observed
4	1.5	Interpolate	8	Interpolate
5	0.75	Interpolate	10	Observed
6	0	Observed	8	Interpolate
7	0	Propagate	6	Interpolate
8	0	Propagate	4	Interpolate
9	0	Propagate	2	Interpolate
10	0	Propagate	0	Observed

4. Any daily scores after day 7 are then discarded. The remaining scores are summed and then multiplied by 5/7 to give a single score representing five days' worth of daily asepsis scores.
5. The final in-hospital asepsis score for the wound is then calculated from adding points to the score derived from point 4 if any of the following events occurred at any time in the post-operative stay for that wound:
   - Antibiotics given for wound infection: 10 points
   - Isolation of bacteria: 10 points
   - Drainage of pus under local anaesthetic: 5 points
   - Drainage of pus under general anaesthetic: 10 points
   - Length of hospital day >14 days: 5 points

   Note: *any missing elements will be assumed to be 0.*

Post-discharge asepsis scores

Post-discharge asepsis scores are calculated by taking the in-hospital asepsis score for each wound and adding additional points if the patient has answered the questions on the 3-month follow-up questionnaire for that wound as follows:

- Been given antibiotics for wound infection=Yes AND patient did not have antibiotics for wound infection in initial hospital admission: 10 points
- Doctor opened/drained an abscess=Yes AND patient did not have drainage of pus under local anaesthetic in initial hospital admission: 5 points
- Wound been opened and cleaned under general anaesthetic in hospital=Yes AND patient did not have drainage of pus under general anaesthetic in initial hospital admission: 10 points

- Wound discharged pus=Yes AND the purulent exudates question on the in-hospital questionnaire was no/missing at all time points: 5 points
- District nurse had to dress wound=Yes AND patient did not have drainage of pus under local anaesthetic in initial hospital admission: 5 points

Note: *any missing elements will be assumed to be 0.*

EME
HS&DR
HTA
PGfAR
PHR

Part of the NIHR Journals Library
www.journalslibrary.nihr.ac.uk

Published by the NIHR Journals Library