The UK Arm of the Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery Trial (TRiCS IV)

An international, multi-centre, randomised controlled trial to assess transfusion thresholds in younger patients undergoing cardiac surgery

Protocol – UK VERSION
Version 2.0, 16 August 2024

Sponsor	St Michael's Hospital (Toronto, Ontario, Canada) Mount Sinai Hospital (Toronto, Ontario, Canada)
Sponsor Reference:	3478
UK Funder:	National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme
Funder Reference:	NIHR150600
UK Coordinating Centre:	University of Leicester Clinical Trials Unit
IRAS ID:	325425
REC Reference:	23/WM/0128
Clinicaltrials.gov Reference:	NCT04754022

Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given. Any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Sponsor:

Signature _____

Print name: _____

Position: _____

Date: _____

Chief Investigator:

Signature: _____

Print name: _____

Date: _____

Principal Investigator:

Signature: _____

Print name: _____

Date: _____

Table of Contents

1. List of abbreviations

A&E	Accident and Emergency
AHRC	Applied Health Research Centre
AKI	Acute Kidney Injury
APR	Annual progress report
Aptt	Activated Partial Thromboplastin Time
BHF	British Heart Foundation
BHF CRC	British Heart Foundation Clinical Research Collaborative
BNF	British National Formulary
CABG	Coronary Artery Bypass Graft Surgery
CAC	Central Adjudication Committee
CAM/CAM-ICU	Confusion Assessment Method (Intensive Care Unit)
CC	Coordination Centre
CCU	Cardiac Care Unit (Intensive care)
CEHR	Centre for Ethnic Health Research
CI	Chief Investigator
CIHR	Canadian Institutes of Health Research
CK-MB	Creatine Kinase - MB
CO	Cardiac Output
CONSORT	Consolidated Standards of Reporting Trials
CPB	Cardiopulmonary Bypass
CRN	Clinical Research Network
EC	Executive Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEG	Electroencephalogram
EQ5D	EuroQol EQ-5D – Quality of Life questionnaire
ER	Emergency Room
FPFV	First participant first visit
DSMB	Data and Safety Monitoring Board
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Hb	Haemoglobin
HCT	Haematocrit
HIF	Hypoxia Inducible Factor
HR	Hazard Ratios
ICDSC	Intensive Care Delirium Screening Checklist
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
INR	International Normalized Ratio
IRAS	Integrated Research Application System
ISF	Investigator Site File
ITT	Intention to Treat
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LCTU	Leicester Clinical Trials Unit
LPLV	Last participant last visit
MI	Myocardial Infarction

mNCA	Model Non-Commercial Agreement
NIHR	National Institute for Health and Care Research (UK)
NHMRC	National Health and Medical Research Council
NHS	National Health Service (UK)
nNOS	Neuronal Nitric Oxide Synthase
ONS	Office for National Statistics
OR	Operating Room
PBM	Patient blood management
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PIS	Participant information sheet
PP	Per-protocol
PPP	Purchasing Power Parity
PPI	Patient and Public Involvement
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality Adjusted Life Year
RBC	Red Blood Cell
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&I	Research and Innovation
rFVIIa	Recombinant factor VIIa
RR	Risk Ratio
SAP	Statistical Analysis Plan
SC	Steering Committee
SIV	Site initiation visit
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TRALI	Transfusion-Related Acute Lung Injury
UKCRC	UK Clinical Research Collaboration
ULN	Upper Limit of Normal
UoL	University of Leicester
WOCBP	Women of Childbearing Potential

2. Key trial contacts

UK Chief Investigator	Prof Gavin Murphy BHF Chair of Cardiac Surgery/Consultant Cardiac Surgeon Department of Cardiovascular Sciences Clinical Sciences Wing Glenfield Hospital Groby Road Leicester LE3 9PQ United Kingdom **Email:** gjm19@leicester.ac.uk **Telephone:** +44 (0)116 256 3054
UK Coordinating Centre	Leicester Clinical Trials Unit College of Life Sciences University of Leicester Maurice Shock Building University Road Leicester LE1 7RH United Kingdom **Email**: tricsiv@leicester.ac.uk
Sponsor(s)	Dr David Mazer St. Michael's Hospital, Unity Health Toronto 30 Bond Street Room 6-510 Donnelly Wing Toronto, Ontario, Canada M5B 1W8 **Email:** David.Mazer@unityhealth.to Dr Nadine Shehata Mount Sinai Hospital 600 University Avenue Room 11-311 Toronto, Ontario, Canada M5G 1X5 **Email:** Nadine.Shehata@sinaihealth.ca
UK Funder	NIHR Health Technology Assessment Programme Evaluations, Trials and Studies Coordinating Centre University of Southampton Enterprise Road Southampton SO16 7NS United Kingdom **Email:** netsmonitoring@nihr.ac.uk

3. Protocol contributors

Name	Position held	Role on trial	Affiliation
Prof Gavin Murphy	Professor of Cardiac Surgery	Lead applicant, UK Chief Investigator	University of Leicester
Dr David Mazer	Professor of Anaesthesia and Physiology	Co-applicant, management of the global trial, governance, data management, analysis and dissemination	St. Michael's Hospital, Toronto
Dr Nadine Shehata	Haematologist, Head of Transfusion Medicine	Co-applicant, management of the global trial, governance, data management, analysis and dissemination	University of Toronto
Prof Andrew Klein	Cardiothoracic Anaesthetist	Co-applicant, support to ensure recruitment to time and target in UK cardiac surgery centres	Royal Papworth Hospital NHS Foundation Trust
Prof Mahmoud Loubani	Consultant Cardiothoracic Surgeon	Co-applicant, support to ensure recruitment to time and target in UK cardiac surgery centres	Hull University Teaching Hospitals NHS Trust
Dr Mohandas Jayarajah	Consultant Cardiothoracic Anaesthetist	Co-applicant, support to ensure recruitment to time and target in UK cardiac surgery centres	University Hospitals Plymouth NHS Trust
Prof Barnaby Reeves	Professor of Health Services Research	Co-applicant, methodological support with respect to protocol development, recruitment, steps to mitigate non-adherence and attrition, and analysis in the UK	University of Bristol
Prof Guiqing Yao	Professor of Health Economics	Co-applicant, health economics expertise	University of Leicester
Dr Marius Roman	Academic Clinical Lecturer in Cardiac Surgery	Co-applicant, supporting UK CI and Head of Trial Management	University of Leicester Department of Cardiovascular Sciences

Name	Position held	Role on trial	Affiliation
Dr Ricky Vaja	Clinical Research Fellow, Associate Surgical Specialty Lead, Cardiothoracic Surgery	Co-applicant, Cardiothoracic Interdisciplinary Research Network lead	Imperial College London
Mr Luke Rogers	Cardiothoracic Surgery SpR	Co-applicant, Cardiothoracic Interdisciplinary Research Network lead	University Hospitals Bristol and Weston NHS Foundation
Dr Seema Agarwal	Consultant in Anaesthesia	Co-applicant, support to ensure recruitment to time and target in UK cardiac surgery centres	Central Manchester University Hospitals NHS Foundation Trust
Mr Anthony Locke	Patient and Public Involvement (PPI) member	Patient co-applicant, oversight for all PPI activities	University of Leicester Cardiac Surgery PPI Group
Ms Niamh Quann	Senior Trial Manager	Development of UK documents and ethics application	University of Leicester
Ms Hannah Gilbert	Trial Manager	Contributions to UK documents and ethics application	University of Leicester
Mrs Carla Richardson	Head of Trial Management	UK trial management and trial governance oversight	University of Leicester

4. Protocol summary

Trial title	An international, multi-centre, randomised controlled trial to assess transfusion thresholds in younger patients undergoing cardiac surgery.
Short title	**TRICS IV: T**ransfusion **R**equirements **i**n Younger Patients Undergoing **C**ardiac **S**urgery.
Hypothesis	A higher haemoglobin (Hb) concentration for red blood cell (RBC) transfusion (liberal transfusion strategy) will be superior to a restrictive strategy in terms of vital organ function (heart, brain and kidney) and mortality 6 months after cardiac surgery.
Primary endpoint	Composite score of any one of the following events occurring 6 months after cardiac surger y: (1) all-cause mortality; (2) myocardial infarction; (3) new onset renal failure requiring dialysis; or (4) new focal neurological deficit (stroke).
Secondary endpoints	1. Incidence of each individual component of the primary outcome: all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) within 6 months. 2. Composite and individual all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) with index hospitalisation or after 28 days postoperatively, whichever comes first. 3. Length of stay in the Intensive Care Unit (ICU) and hospital (index hospitalisation). 4. Prolonged low output state defined as the need for two or more inotropes for 24 hours or more, intra-aortic balloon pump or ventricular assist device postoperatively (index hospitalisation). 5. Duration of mechanical ventilation (index hospitalisation). 6. Infection: defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two out of three of the following criteria: fever, leukocytosis, and positive sputum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement (index hospitalisation). 7. Acute kidney injury (AKI), defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline - a 50% increase in serum creatinine within 1 week or a 26.5 µmol/L increase within 48 hours (index hospitalisation). 8. Delirium, based on one of the following criteria: Confusion Assessment Method (CAM) or CAM-ICU (even on 1 occasion), or Intensive Care Delirium Screening Checklist (ICDSC) >3, or 3DCAM, or 4AT ≥4, or more than one dose of haloperidol or similar antipsychotic drug, or documented delirium by neurologist or neurosurgeon or psychiatrist consultation (index hospitalisation). 9. Gut infarction confirmed by imaging (e.g. angiography), autopsy, or through surgical means (index hospitalisation).

	10. Hospital visits (hospitalisation and/or emergency visits and coronary revascularisation at 6 months). 11. The proportion of patients transfused and the number of blood products utilised (RBCs, plasma, platelets) (index hospitalisation). 12. Seizures, defined as generalised or focal tonic-clonic movements consistent with seizure; or electroencephalogram (EEG) demonstrating epileptiform discharges; or diagnosis of seizures by neurologist or neurosurgeon consultation (index hospitalisation). 13. Encephalopathy, defined as unexpected delayed awakening or severely altered mental status (unconscious despite no sedative medication for more than 5 days), or encephalopathy documented by neurologist or neurosurgeon.
Trial population	Patients at moderate to high risk of death (EuroSCORE I ≥ 6) that are 65 years of age or younger undergoing cardiac surgery on cardiopulmonary bypass (CPB).
Trial design	Multi-centre, open-label, randomised controlled trial of a restrictive versus liberal transfusion strategy in higher risk patients ≤65 years of age having cardiac surgery on cardiopulmonary bypass, using a superiority trial design. A health economic analysis is embedded in the UK arm of the trial. In the UK, an internal pilot including progression criteria has been built in, to assess whether the target number of UK centres within 9 months of green light, and recruitment rate of one participant per site per month, can be achieved.
International sample size	1760 randomised participants in ~72 international sites.
UK sample size	320 participants (160 per group) in 22 UK cardiac centres.
Randomisation	Randomisation will have a 1:1 ratio, will be based on random permuted blocks of varying sizes, and will be stratified by centre and age.
Trial intervention	• **Group 1: Restrictive transfusion strategy:** patients will receive a RBC transfusion if their Hb concentration is <75 g/L (<7.5 g/dL; <4.7 mmol/L) intraoperatively and/or postoperatively. • **Group 2: Liberal transfusion strategy:** patients will receive a RBC transfusion if their Hb concentration is <95 g/L (<9.5 g/dL; <5.9 mmol/L) intraoperatively, or postoperatively in the ICU; and/or <85 g/L (< 8.5 g/dL; <5.3 mmol/L) on the ward.
Accrual period	24 months recruitment + 6 months follow up.
Trial duration	01 February 2023 – 31 January 2026 (36 months).
Assessments	Both investigational arms will be followed during their index hospitalisation or to postoperative day 28, whichever comes first; thereafter for 6 months postoperatively to assess clinical outcomes and mortality. Routinely collected healthcare data (Office for National Statistics, ONS) will be used to ascertain mortality at 6 months in UK participants.

5. Scientific abstract

Research question: Is a higher haemoglobin threshold (< 95 g/L) for red cell transfusion superior to a lower threshold (<75 g/L), in high-risk cardiac surgery patients <65 years of age, as measured by a composite outcome of severe organ injury or death at 6 months postoperatively?

Background: Sub-group analyses of previous large trials suggest that organ injury and death may be reduced by more liberal haemoglobin transfusion thresholds in younger people (≤65 years) undergoing cardiac surgery. Current treatment guidelines recommend more restrictive thresholds. There is wide variability in care. The international Transfusion Requirements in Cardiac Surgery (TRICS) IV trial will address this uncertainty. The UK arm of the trial aims to enrol 320 participants in 22 cardiac centres.

Design: International, multi-centre, open-label, pragmatic RCT with an embedded health economic analysis.

Setting: At least 72 international sites, including 22 UK cardiac centres.

Target population: Adults ≤65 years of age undergoing open chest cardiac surgery with additive European System for Cardiac Operative Risk Evaluation (EuroSCORE I) of ≥6 will be included. People who refuse transfusion or who are undergoing transplant or ventricular assist device insertion will be excluded.

Randomisation: Participants will be randomised with allocation concealment in a 1:1 ratio stratified by centre and age.

Health technology to be assessed: Participants will be allocated to one of two transfusion strategies that will be continued until hospital discharge or 28 days post-surgery:

- **Group 1: Liberal threshold:** Participants will receive red blood cell transfusion if their Hb is < 95 g/L intraoperatively or, postoperatively < 95 g/L in the ICU or <85 g/L on the ward.

- **Group 2: Restrictive threshold:** Participants allocated to a restrictive group will receive red cell transfusion if their Hb is <75 g/L intraoperatively or postoperatively. The Hb triggers reflects the range of transfusion thresholds in contemporary practice.

Outcomes: The primary outcome is a composite of any of the following events within 6 months of the initial surgery: 1. All-cause mortality or 2. Myocardial infarction as defined by the 4th universal definition of myocardial infarction or 3. New onset renal failure with dialysis or 4. New focal neurological deficit (stroke). Secondary outcomes will include costs, quality of life, cost-effectiveness, and safety. Process and adherence will be monitored.

Internal Pilot: Planned site set-up and recruitment targets (1 participant/ site/ month), as well as methods for collection of healthcare resource use, will be tested in a 9 month internal pilot with pre-specified Stop/ Go criteria.

Sample Size: The trial is powered to detect a Risk Ratio of 0.70 between groups at six-months. To achieve 90% power with α =0.05, and with adjustment for an expected attrition rate of 4.5% and a single interim analysis, 1,802 participants (901 per group) are required.

Analysis: will follow a pre-specified statistical analysis plan in the intention to treat population. A cost utility analysis will be performed.

Project timetable: Start date: 1st February 2023. Months 1-7 set-up, months 8-30 recruitment, months 30 to 35 follow-up, months 34 to 36 data cleaning, site closedown.

Dissemination: We use the Knowledge Framework to focus on knowledge creation and dissemination to key stakeholders, including participants, clinicians, service users and commissioners.

6. Lay summary of the research

Aim(s) of the research

The TRICS IV trial is testing whether it is better for younger people (less than 65 years old, 40% of all patients or ~12,000 people per year in the UK) having open heart surgery to have blood transfusion at higher blood counts than those currently recommended by clinical guidelines which recommend transfusion only at very low blood counts (severe anaemia).

Background to the research

Low blood count affects up to 75% of people undergoing heart surgery and can be harmful if the levels are very low (severe anaemia). Low blood count is treated by blood (red cell) transfusion in this setting, although transfusion itself can have risks. Knowing the point at which low blood count needs to be treated by transfusion to prevent harm, whilst minimising the risks from unnecessary transfusion is therefore an important consideration in the care of most people who require heart surgery. Previous large clinical trials undertaken by these researchers have suggested that the low blood count tolerated by most people is approximately 75g/L to 80 g/L (the concentration of haemoglobin in the blood), and it is standard care to transfuse people at this level as a result. However, younger patients in these trials did not tolerate these low levels as well as older people. The numbers of younger people in the previous trials was too small to be sure whether this effect was real or just due to chance. This means that we are unsure as to the correct level for transfusion in younger people, who may be exposed to low blood counts that are harmful if they are treated according to the current standard of care.

Design and methods used

The TRICS IV randomised trial will ask the question: In people 65 years old and younger undergoing heart surgery, does transfusion at a blood count level of 95g/L result in better clinical outcomes when compared to transfusion at 75g/L. To answer this 1802 people who consent to take part will be allocated by chance into groups who will be transfused at the 'low' or 'high' thresholds. The trial will assess which strategy results in the fewest major complications that include heart attacks, stokes, kidney failure, or death. The UK arm of the trial aims to enrol 320 participants in 22 UK cardiac centres.

Patient and public involvement

The proposal has been developed in partnership with the National Cardiac Surgery PPI Group and the National Cardiac Surgery Clinical Trials Initiative Organ Protection Clinical Trial Group. The PPI lead has over a decade in senior PPI roles and is a member of the National Cardiac Surgery PPI Group. He will oversee Patient Researcher who will develop recruitment and dissemination materials that aim to improve equality, diversity and inclusivity in the trial.

Dissemination

Publication in peer-reviewed medical journals, seminars at national and international meetings, presentation of results at conferences and dissemination meetings to be part of the dissemination strategy. By collaborating with international centres, participating international key opinion leaders will present results at various regional and national forums ensuring a widespread audience. In addition, a national workshop will be hosted in the UK to share the knowledge from the trial with relevant stakeholders, including healthcare commissioners, members of the public, clinicians and academics.

7. Introduction, background and scientific rationale

7.1 Background and rationale

Cardiac surgery is one of the most frequent surgical procedures, with approximately 35,000-40,000 procedures conducted in Canada each year.[1] Fifty percent of patients undergoing cardiac surgery are <65 years.[2] Anaemia in these patients is common due to underlying conditions and haemodilution during cardiopulmonary bypass (CPB). Perioperative anaemia has been associated with a significant increase in cardiac (myocardial infarction) and non-cardiac (renal failure and stroke) adverse events and mortality[3,4]. Patients undergoing cardiac surgery receive a high proportion of RBCs to decrease the risks associated with anaemia (approximately 14% to 20% of the blood supply is consumed by cardiac surgical patients[5-7]); although there are potential benefits to transfusion, transfusion is costly, often in short supply and may also lead to considerable mortality and morbidity. Restrictive transfusion triggers have been suggested to be preferred by RCTs in many patient populations including critically ill patients[8], patients undergoing hip fracture surgery[9], and with acute upper gastrointestinal bleeding[10].

Recently, we completed a multi-centred multi-national RCT, Transfusion Requirements in Cardiac Surgery III (TRICS III) funded by CIHR, the National Health and Medical Research Council of Australia, and the Health Research Council of New Zealand comparing a restrictive transfusion threshold to a liberal threshold in 5243 patients undergoing high risk cardiac surgery. The trial was completed ahead of schedule, within budget, and with approximately 30% more patients than initially anticipated. The TRICS III trial outcomes were published in the New England Journal of Medicine[11,12]. Overall, TRICS III demonstrated that a restrictive transfusion strategy was not inferior to a liberal strategy with respect to a composite outcome of death, myocardial infarction (MI), stroke, or new-onset renal failure to day 28, and at 6 months after surgery[11,12]. Predefined subgroup analysis, however, showed a highly significant interaction between the transfusion threshold and age12. Whereas restrictive transfusion was favoured in elderly patients, the odds ratios for the primary composite outcome showed an incremental rise in risk with each decade <65 years of age[12]. There is thus an urgent need to settle the question of whether restrictive transfusion practices in younger patients expose them to significant unnecessary harm.

Transfusion Requirements in Younger Patients Undergoing Cardiac Surgery IV (TRICS IV) is the fourth RCT conducted by an experienced and dedicated group of international investigators to determine whether a liberal transfusion strategy is superior to a restrictive strategy in patients ≤65 years.

TRICS IV is an extension of our experience to understand the mechanisms of anaemia induced organ dysfunction and our clinical studies to determine optimal transfusion thresholds in cardiac surgery. The problem we wish to answer is whether a high haemoglobin concentration (Hb) trigger for transfusion (liberal strategy) is superior to a low trigger (restrictive strategy) in higher risk patients (EuroSCORE I ≥ 6) undergoing cardiac surgery who are ≤65 years. Currently, it is not known the extent to which anaemia in younger patients is a risk factor for adverse outcomes and whether RBC transfusion is required to maintain vital organ function and reduce adverse outcome.

This trial will bring together the TRICS III research team in Canada with the TITRe2 team in the UK. Both of these trials were published in the New England Journal of Medicine and are widely cited in treatment guidelines. The TRICS IV trial aims to recruit 1760 participants from 72 units in 18 countries and is of sufficient size to definitively answer the research question. Inclusion of a large UK cohort will build on the experiences of the TITRE 2 and TRICS III researchers to increase generalisability of the trial results to NHS patients.

If the trial demonstrates that a liberal strategy is superior, the risks and costs of organ injury related to untreated severe anaemia will be reduced. If the liberal strategy is not superior, the risks and costs attributable to unnecessary transfusions will be reduced. The trial will thus provide high-quality generalisable data to guide transfusion practice worldwide, regardless of its eventual results.

7.2 Physiological Effects of Anaemia

Acute severe anaemia has been associated with increased mortality likely due to impaired oxygen delivery and tissue hypoxia13. Since Hb contributes to more than 99% of blood oxygen content, severe anaemia leads to inadequate tissue oxygen delivery, resulting in tissue hypoxia, organ failure, and death. As defined by studies in animals and humans, acute reduction in Hb is sensed at the cellular level and leads to adaptive cardiovascular responses to optimize tissue oxygen delivery. These responses include 1) a characteristic increase in cardiac output (CO) that is proportional to the degree of anaemia; 2) a reduction in systemic vascular resistance with organ-specific vasodilation to facilitate preferential perfusion of vital organs, including the heart and brain; and 3) an increase in tissue oxygen extraction. In addition, anaemia results in the activation of hypoxic cellular mechanisms, including neuronal nitric oxide synthase (nNOS) and hypoxia inducible factor (HIF), with the purpose of maintaining oxygen homeostasis and sustaining organism survival[13].

Acute haemodilution that occurs during CPB has been shown to reduce oxygenation in the brain, heart, kidney, intestine, and muscle14-16. The heart, under normal conditions extracts 60 to 70% of oxygen delivered17. Other organs can increase oxygen extraction to compensate for reduced oxygen delivery; however, increasing myocardial blood flow by coronary vasodilatation is the only compensatory method available for the heart. This increased susceptibility to adversities secondary to anaemia18-20 is particularly problematic when there is a limited capacity to increase blood flow such as in patients who have stenosed coronary arteries, in the presence of myocardial hypertrophy, aortic valve disease, or other circulatory abnormalities[21,22].

7.3 What is the Evidence that the Optimal Haemoglobin Threshold for Transfusion Differs According to the Age of the Patient?

Younger aged patients are susceptible to anaemia. Isovolemic removal of blood to reduce the Hb concentration to 50 g/L in 21 healthy subjects aged 19-33 years resulted in inadequate systemic oxygen in two female subjects who developed transient ST segment changes that were asymptomatic (at a Hb of 62 g/L and 46 to 53 g/L)[23]. Isovolemic removal of blood to reduce the Hb to 50 to 60 g/L in nine other healthy subjects (mean age 29 ± 5 years) also resulted in mild cognitive impairment demonstrating inadequacy of cerebral perfusion[24].

Anaemia may be a physiological response to aging. A systematic review found that the prevalence of anaemia increased with age in both men and women[25]. The prevalence of anaemia observed in individuals more than 85 years was at least 2-3-fold greater than younger individuals. In one trial of community dwelling individuals, anaemia occurred in 43% of men 70-74 years to 60% of men >85 years. In a RCT comparing liberal vs. restrictive transfusion strategies following cardiac surgery, transfused patients were generally older than non-transfused patients, suggesting that they reach Hb triggers earlier because of age[26]. With age, systemic metabolic requirements are reduced[27]. Heart failure occurs more frequently in the elderly - one trial suggested that 50% of heart failure occurs in patients >70 years[28,29]; these patients may not tolerate the volume of RBCs and thus restrictive strategies may then be associated with better outcomes. In TRICS III, the subgroup analysis demonstrated a significant interaction with age (p=0.004) for the primary composite outcome after 6 months. The unadjusted odds ratio for the primary outcome for age 65-74 years was 1.18 (95% CI 0.91–1.54), for 55-64 years 1.47 (95% CI 0.89–2.44), for 45-54 years, 1.79 (95% CI 0.88– 3.67) and for

patients <45 years, 2.37 (95% 0.87–6.43)[12]. Since the majority of patients in TRICS III were over 65 years of age, the signal for harm may have been further diluted in younger patients. In TITRe2, the age interaction was directionally similar to TRICS III with the odds ratio for the primary outcome showing a trend favouring liberal transfusion in patients <75 years: 1.3 (95% CI 0.91-1.84) for the restrictive strategy[30]. The mean age of the 502 patients in the TRACS trial, another RCT comparing liberal and restrictive transfusion strategies was 60 years and a trend for harm was also apparent with restrictive strategies: hazard ratio for mortality, 1.28 (95% CI, 0.60-2.73) and the incidence of cardiogenic shock was 5% in the liberal group (95% CI, 2%-7%) vs 9% in the restrictive group (95% CI, 5%-12%)[2].

7.4 What are the Adverse Events Associated with Transfusion?

There are a number of complications related to transfusion that are associated with considerable morbidity and mortality. Non-infectious risks from transfusion such as transfusion related acute lung injury (TRALI), which tends to occur more frequently in patients having cardiac surgery[31], perhaps because of increased systematic and pulmonary inflammation with cardiac surgery[32,33], has a high case fatality rate, 5 to 13%[34,35]. Additionally, administrative errors resulting in hemolytic transfusion reactions can be life-threatening[36]. Pulmonary edema, due to the volume of RBCs occurs more frequently in patients with critical illness and cardiovascular disease transfused at a Hb of 100 g/L compared to a Hb of 70 g/L8. Although the risk of acquiring transfusion transmitted viruses is low[37], new emerging pathogens constantly threaten the blood supply. Unnecessary transfusions also have an impact on the care of patients. Optimum utilisation of blood components is essential as there is a continuous strain on blood systems because of increased blood utilisation. Additionally, increased transfusion results in increased resource utilisation[38,39] and the cost of blood is increasing40. In an era where there are new emerging pathogens and blood shortages, it is essential for patients to be transfused appropriately.

7.5 What Systemic Reviews Have Been Conducted in Cardiac Patients?

Our recently published meta-analysis of 13 RCTs comparing restrictive and liberal transfusion strategies in patients undergoing cardiac surgery demonstrated that restrictive transfusion strategies did not result in an overall increased risk of anaemia-induced, tissue hypoxia-associated events[41]. The risk ratio (RR) of mortality from 4545 patients assigned to a restrictive transfusion strategy and 4547 transfused according to a liberal strategy was 0.96 (95% CI 0.8, 1.2), myocardial infarction RR 1.0 (95% CI 0.8, 1.3), renal failure RR 0.96 (95% CI 0.8, 1.2), stroke 0.93 (95% CI 0.7, 1.3), or infection RR 1.1 (95% CI 0.98, 1.3). We are unaware of any meta-analyses specifically evaluating the effect of age and transfusion strategies. However, in our meta-analysis, the risk ratios for mortality, stroke and infection were all numerically higher with restrictive transfusion in paediatric studies[41].

The lack of well conducted randomised controlled trials evaluating the effect of age as well as the suggestion of increased risk associated with restrictive transfusion strategies in younger patients further substantiates the need for this RCT.

7.6 What Randomised Controlled Trials are being Conducted Addressing Haemoglobin Thresholds in Cardiac Surgery According to Age?

TRICS III[11] and TITRe2[30] were recently completed and compared restrictive and liberal transfusion strategies. TITRe2, a superiority trial, randomised 2003 cardiac surgical patients with a postoperative Hb <90 g/L to receive RBC transfusions to maintain a Hb of >75 g/L or >90 g/L. A statistically significant difference was not apparent in the primary composite outcome of infection and ischemic events three months after surgery (35.1% in the restrictive group and 33.0% in the liberal group odds ratio, 1.1 (95% CI 0.9, 1.3)); but there was a 1.6% absolute difference in the secondary outcome of 90-day

mortality favouring the liberal strategy. Subgroup analysis according to decades of age was not conducted30.

Although TRICS III established non-inferiority of the restrictive transfusion strategy in the 4860 patients analysed (Hb <75 g/L intraoperatively and postoperatively, or a liberal strategy of RBC transfusion for Hb <95 g/L intraoperatively and postoperatively while in an intensive care unit (ICU), and <85 g/L on a non-ICU ward), a trend of poorer outcomes with a restrictive strategy in younger patients was demonstrated as described above[11].

No other trials assessing the effect of age on transfusion thresholds in cardiac surgery are listed on clinicaltrials.gov.

7.7 Why is a Trial Needed Now?

If restrictive transfusion strategies in younger cardiac surgery patients are associated with harm, a trial is needed to ensure that these patients are transfused according to the appropriate threshold. If younger patients are not experiencing harm from restrictive transfusion strategies, they should not be exposed to the morbidity and mortality of transfusions if transfused unnecessarily.

7.8 Hypothesis

A higher Hb concentration for RBC transfusion (liberal transfusion strategy) will be superior to a restrictive strategy in terms of vital organ function (heart, brain and kidney) and mortality 6 months after cardiac surgery.

8. Trial objectives

8.1 Primary Objective

The primary objective is to determine whether a liberal RBC transfusion strategy is superior to a restrictive strategy in terms of vital organ function (heart, brain and kidney) and all-cause mortality 6 months after surgery.

8.2 Secondary Objectives

The secondary objectives are to determine whether the liberal strategy is superior to a restrictive strategy in terms of:

1. Incidence of each individual component of the primary outcome: all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) within 6 months
2. Composite and individual all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) with index hospitalisation or after 28 days postoperatively, whichever comes first
3. Length of stay in the Intensive Care Unit (ICU) and hospital (index hospitalisation)
4. Prolonged low output state defined as the need for two or more inotropes for 24 hours or more, intra-aortic balloon pump or ventricular assist device postoperatively (index hospitalisation)
5. Duration of mechanical ventilation (index hospitalisation)
6. Infection: defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two out of three of the following criteria: fever, leukocytosis, and positive sputum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement (index hospitalisation)

7. Acute kidney injury (AKI), defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline[46] - a 50% increase in serum creatinine within 1 week or a 26.5 µmol/L increase within 48 hours (index hospitalisation)
8. Delirium, based on one of the following criteria: Confusion Assessment Method (CAM) or CAM-ICU (even on 1 occasion), or Intensive Care Delirium Screening Checklist (ICDSC) > 3, or 3D-CAM, or 4AT ≥4, or more than one dose of haloperidol or similar antipsychotic drug, or documented delirium by neurologist or neurosurgeon or psychiatrist consultation (index hospitalisation)
9. Gut infarction confirmed by imaging (e.g. angiography), autopsy, or through surgical means (index hospitalisation)
10. Hospital visits (hospitalisation and/or emergency visits and coronary revascularisation at 6 months)
11. The proportion of patients transfused and the number of blood products utilised (RBCs, plasma, platelets) (index hospitalisation)
12. Seizures, defined as generalised or focal tonic-clonic movements consistent with seizure; or electroencephalogram demonstrating epileptiform discharges; or diagnosis of seizures by neurologist or neurosurgeon consultation (index hospitalisation)
13. Encephalopathy, defined as unexpected delayed awakening or severely altered mental status (unconscious despite no sedative medication for more than 5 days), or encephalopathy documented by neurologist or neurosurgeon or psychiatrist consultation (index hospitalisation)

9. Trial population

9.1 Inclusion Criteria

1. ≥18 and ≤65 years of age
2. Planned cardiac surgery using cardiopulmonary bypass
3. Informed consent obtained
4. Preoperative European System for Cardiac Operative Risk Evaluation (EuroSCORE I) of 6 or more (using the standard additive EuroSCORE I available at www.euroscore.org/calcold.html or refer to the trial Manual of Operations)*

** The EuroSCORE criteria must be met **prior to randomisation**. If the EuroSCORE changes prior to randomisation due to a decision to change the type of procedure, then the patient should not be randomised. If the EuroSCORE changes after randomisation due to a decision to change the type of procedure (e.g. while in the OR), then the patient will continue to follow the protocol and will not be excluded.*

9.2 Exclusion Criteria

1. Patients who refuse participation
2. Patients who are unable to receive or who refuse blood products
3. Patients who are involved in a preoperative autologous pre-donation program
4. Patients who are having a heart transplant or having surgery solely for an insertion of a ventricular assist device
5. Pregnancy or lactation (a negative pregnancy test must be obtained prior to randomisation for women of childbearing potential)

10. Trial design

10.1 Trial Overview

TRICS IV is an international, multi-centre, open-label, randomised controlled trial of two commonly used RBC transfusion strategies in higher risk patients ≤65 years of age having cardiac surgery, using a superiority trial design.

10.2 Internal pilot

To assess whether the target number of UK centres; 18 within 9 months of green light, and recruitment rate 1 participant/site/month, will be achieved we will undertake a **9 month** internal pilot. Using the range of 0.74 to 1 participant/site/month, and 2 new sites set up per month as described above, we can specify two progression criteria (see table below). Targets for both criteria need to be met to achieve the following traffic light system:

- **Green:** Proceed;
- **Amber:** Amend, consult;
- **Red:** Discuss with funder.

The Trial Steering Committee in consultation with the funder will determine progression. The internal pilot will also be used to refine and amend recruitment strategies where needed, to ensure the sample is representative of the diversity of the UK population, and to test and refine the resource use questionnaire and frequency in collecting such data for the health economic analyses.

Progression criteria	Red	Amber	Green
Recruitment rate (n/site/month)	<0.74	0.74-1	>1.0
Number of sites opened	<14	14 - 18	>18
If met will result in the following:			
Total number of participants recruited (9m pilot)	<66	66-89	>89
No. months (total) to reach UK target (n=320)	>28	22-28	22
Threshold (% of target participants recruited in pilot)	<74%	74-100%	100%

10.3 Randomisation Procedure

Randomisation will be performed by the delegated research nurse/enroling physician using a centralised web-based system (REDCap) generated by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute of St. Michael's Hospital, Unity Health Toronto. UK sites will use this system to enter relevant data to enable randomisation of participants in the UK. Access to the randomisation system will be managed by the AHRC following completion of necessary training.

Randomisation will have a 1:1 ratio, will be based on random permuted blocks of varying sizes, and will be stratified by centre and age. We will use web-based electronic case report forms (eCRFs), which can be accessed by each site, to randomly allocate participants to interventions. Each participant will be assigned a unique participant ID at enrolment. This unique participant ID will be used to identify the individual participant throughout the trial and will not be reassigned to any other participant.

Whenever feasible, randomisation will occur no more than **24 hours** prior to the scheduled surgery to minimise the risk of losing randomised patients due to unplanned surgery cancellations. This timeline is only a guideline and it is not considered a protocol deviation to randomise > 24 hours before surgery.

10.4 Blinding

The trial allocations cannot feasibly be blinded, and therefore this is designed as an open label trial. Adjudication of postoperative myocardial infarction, cerebrovascular accident, infectious and renal outcomes will be blinded, nonetheless.

10.5 Participants lost to follow-up (6 month follow-up)

Site staff should make all reasonable effort to contact participants for the 6 month follow-up visit. In the event that a participant is lost to follow-up, this information will be recorded in the participant research chart and this should be captured in the eCRF in either the 'Hospital Summary' form or the '6 Month Follow-Up' form.

10.6 Premature Discontinuation

Participants have the right to discontinue from the trial or trial transfusion strategy for any reason, at any time, without compromising the medical care they will receive in relation to the trial. All participants who are randomised and undergo surgery will be followed-up for the remainder of the trial up to the 6-month outcome, unless the participant withdraws consent for follow-up.

Any participant who is randomised but for any reason does not undergo surgery will not be followed-up and data will not be collected longitudinally. In this situation, the participant will be replaced to achieve the required sample size.

In both these instances, any data collected until this point will be retained, analysed and used in the final analysis, but no further data will be collected. In addition, the investigator may discontinue a participant from the trial at any time if the investigator considers it necessary, where the above in relation to data collection will also apply.

Sites will be required to complete the 'Hospital Summary' e-CRF with 'did not complete study' for the patient status field. The AHRC Data Coordinating Centre will query as required.

10.7 Participant death

All participant deaths must be reported in the eCRF, including the cause of the death.

If a participant dies while in hospital prior to postoperative day 28, all data up to the time of death will be collected in the eCRF, and the clinical event will be reported in both the "Clinical Events" form and the 'Hospital Summary' form. In this case, the 6 month follow-up visit forms will not need to be completed.

10.8 Concomitant Treatment

There are no other trial related restrictions on concomitant medications, treatments or procedures.

11. Trial intervention

11.1 Description of the Trial Intervention/Transfusion Strategies

Trial participants will be randomised to one of the following transfusion strategies in a 1:1 manner:

- **Group 1: Restrictive transfusion strategy:** patients will receive a RBC transfusion if their Hb concentration is <75 g/L (<7.5 g/dL; <4.7 mmol/L) intraoperatively and/or postoperatively.

- **Group 2: Liberal transfusion strategy:** patients will receive a RBC transfusion if their Hb concentration is <95 g/L (<9.5 g/dL; <5.9 mmol/L) intraoperatively, or postoperatively in the ICU; or <85 g/L (<8.5 g/dL; <5.3 mmol/L) on the ward.

The trial period for intervention will commence on induction of anaesthesia for the index cardiac surgery. When the appropriate Hb trigger is reached, patients in each group will have one unit of RBCs administered followed by repeat determination of the Hb concentration. Each group will be transfused only if their Hb concentration falls below the transfusion threshold. The Hb should be checked before each unit of blood.

The RBC transfusion must take place within the following time frame after the time that the trigger Hb was measured: 2 hours (for patients in the operating room (OR)), 18 hours (in the ICU/Cardiac Care Unit (CCU) or other intensive care environment, including step-down units), or 40 hours (on the hospital ward).

If the investigator decides to perform another intervention, for example re-measuring the Hb or haemoconcentration, and a second Hb value is measured above the trigger within the protocol defined time period (2, 18 or 40 hours, as above), then a transfusion is not required and this would still be considered an adherent "trigger event" (see section 11.5).

Although it is desirable to adhere to the standard triggers, the assigned Hb trigger can be increased to 80 g/L (8.0 g/dL; 5.0 mmol/L) in the restrictive transfusion group or 100 g/L [(10.0 g/dL; 6.2 mmol/L) intraoperative/ICU] / 90 g/L [(9.0 g/dL; 5.6 mmol/L) on the ward] in the liberal transfusion group during an episode of any of the following severe physiologic derangements:

- Mixed/central venous or cerebral oxygen saturation <50%
- Lactate > 4 mmol/L in the absence of the use of epinephrine
- Definitive clinical evidence of active myocardial ischemia as defined by the 4th Universal Definition[42]
- Severe organ dysfunction or failure (heart, kidney, or brain) despite use of two or more inotropic agents or a mechanical circulatory assist device (examples include refractory heart failure or cardiogenic shock, anuria or impending dialysis, or severe neurologic dysfunction requiring acute intervention).

The Hb trigger can be increased due to physiologic derangements above for a maximum of 48 hours or until the physiologic derangement improves, whichever occurs first. After 48 hours, the originally assigned trigger will be resumed and all RBC transfusion administered outside of the assigned strategy will be considered non-adherent.

11.2 Protocol deviations

Adherence to the transfusion triggers will be tracked in the eCRF.

- **Minor protocol deviations** (i.e., out-of-window visit for the 6-month follow-up, labs not performed) or **major protocol deviations** (i.e., improper consent procedure, serious or systematic errors in applying the transfusion triggers) should be documented appropriately on the Protocol Deviation Log and reported to the DCC via TRICSIV@unityhealth.to (with tricsiv@leicester.ac.uk copied in) within 24 hours.

11.3 Duration of Intervention

The assigned transfusion strategy will be applied starting from the time the patient enters the OR for the index cardiac surgical procedure, and will be continued until hospital discharge (based on the index cardiac surgery).

Patients who return to the ICU or the OR after being transferred to the ward in the liberal strategy group will be transfused according to the transfusion strategy for those settings (i.e.<95 g/L; <9.5 g/dL; <5.9 mmol/L).

11.4 Measurement of Haemoglobin

While central laboratory measurement of Hb is preferred, any validated method for determining Hb (using co-oximetry, spectrophotometry) may be used for the purpose of determining transfusion triggers and measuring post-transfusion Hb values (e.g., central laboratory, blood gas machine, approved point-of-care.) Sites may check with the coordination centre (CC) if there is any uncertainty about approved point-of-care testing.

11.5 Adherence to Transfusion Strategy and "Trigger Events"

A **"trigger event"** is defined as follows: an occurrence which starts when a Hb value is measured below the assigned trigger for the first time since any previous event, and ending either (1) when a RBC transfusion is administered, or (2) a Hb value is recorded above the assigned threshold, or (3) after the protocol-defined time period of 2 hours (in the OR), 18 hours (in the ICU/CCU), or 40 hours (on the ward), whichever comes first.

All "trigger events" will be recorded in the eCRF.

11.5.1 Adherent events

At the trigger event level, adherence will be considered to have occurred if

1) a RBC transfusion is started within the protocol-defined time period, or
2) a Hb value above the threshold is measured within the protocol-defined period.

11.5.2 Non-adherent events

Non-adherence will be considered to have occurred if:

1) a RBC transfusion is given without a protocol-defined Hb trigger being met, or
2) a RBC transfusion is <u>not</u> given subsequent to a "trigger event", and the Hb remains below the threshold at the end of the protocol-defined period (or a repeated Hb value was not performed during the protocol-defined time period).

In the event that two (or more) units of RBCs are administered in parallel or immediately consecutively, without measuring the Hb value between units, and if the first Hb value measured after the RBC transfusion of these multiple units is still lower than the transfusion trigger, then the administration of each unit will be considered adherent. If the first Hb value after the transfusion of these multiple RBC units is above the trigger, then the initial RBC transfusion would be considered adherent, and any additional units given after the initial unit (and before any subsequent Hb measurements) would be considered non-adherent.

Adherence to transfusion strategies will be closely monitored throughout the trial, and it is expected that sites will maintain an acceptable adherence rate.

11.6 Temporary Protocol Suspensions

Patients who have rapid blood loss, or are hemodynamically unstable (e.g., a systolic blood pressure <80 mmHg or the need of two or more inotropes) due to blood loss, can be transfused RBCs at the discretion of the attending physician, and the protocol may be temporarily suspended. These patients will not be withdrawn from the trial. The protocol will be resumed immediately after such an event and RBC transfusions administered during this time will not be considered a breach of protocol or non-adherent (although all transfusions will be recorded in the eCRF). The RBC transfusion protocol can be suspended for acute bleeding for a maximum of 24 hours or until surgical haemostasis, whichever occurs first. After 24 hours, the protocol will be resumed and all RBC transfusion administered outside of the assigned strategy will be considered non-adherent.

11.7 Other (non-red-cell) Transfusions

Other blood products may be administered based on institutional protocols but should require the presence of ongoing bleeding and/or documented measurement of abnormal coagulation. The non-RBC product transfusions should be targeted toward the haemostatic abnormality in accordance with published guidelines and generally accepted practice. Plasma (15 ml/kg) or Prothrombin Complex Concentrate should be considered in the presence of haemorrhage with an international normalized ratio (INR) >1.5 if there is ongoing bleeding. Cryoprecipitate or fibrinogen concentrate is suggested in the presence of bleeding and a fibrinogen concentration <1.5 g/L. Platelet transfusion should be considered when there is bleeding with a platelet count less than 80,000 x 109/L or in the presence of documented abnormalities of platelet function. Information about non red-cell and haemostatic factor concentrate transfusions will be collected in the eCRF (e.g., platelets, rFVIIa, fibrinogen concentrate, prothrombin complex concentrates).

11.8 Patient blood management

Patient blood management (PBM) describes the application of personalised, evidence-based, care bundles of interventions that reduce bleeding and transfusion in people undergoing cardiac surgery, with the intention of improving clinical outcomes. PBM is recommended by current guidelines but implementation is variable. A network meta-analysis of 393 RCTs failed to demonstrate an interaction between transfusion thresholds and 4 other PBM interventions; pre-surgery iron therapy, cell salvage and autotransfusion, tranexamic acid, and point-of-care viscoelastic testing, with respect to transfusion, organ injury or death. A post-hoc analyses of TRICS III data also failed to demonstrate an interaction between countries where PBM is/ is not considered the standard of care on transfusion rates or outcomes. For example, in Germany where PBM is considered the standard of care, transfusion rates and outcomes were similar to the results for the TRICS III trial overall (D Mazer, personal communication). For this reason, and given the wide range of healthcare resources across the countries recruiting to TRICS IV, we have not mandated a PBM protocol beyond best local care, although the nature of these interventions will be recorded. This will provide information on the generalisability of the trial findings in both richer/poorer and PBM intensive/ less intensive healthcare settings. The threshold for red cell transfusion is also integral to any PBM care bundle, and the results of TRICS IV will inform evidence based PBM strategies.

12. Screening and eligibility

12.1 Screening and eligibility

All local regulations should be followed as they pertain to screening activities. Potential participants will generally be identified from the cardiac surgical schedule, or in the preoperative anaesthesia or cardiac surgery clinics or ward at each hospital where informed consent will be obtained. Initial eligibility may be assessed through a review of the medical chart or discussion with the patient and if

the patient appears to meet the eligibility criteria, the consent process may be initiated. No trial assessments (including a pregnancy test done for trial eligibility purposes only) may be carried out prior to obtaining informed consent.

Co-enrolment into other observational (non-interventional) studies is generally acceptable as long as this is approved by the local ethics committee.

Co-enrolment into other interventional research studies should be discussed in advance with and approved by the DCC/Sponsor.

12.2 Screening log

A screening log template will be provided by the DCC prior to site activation, and this should be maintained at each site. The screening log will capture information about every patient actively screened for the trial and will collect (a) the reason for ineligibility; or (b) if eligible, whether randomised or not (and if not randomised, why not). Sites should also record **the total number of cardiac surgeries done, on bypass, every month.**

All patients recorded on the screening log will be assigned a screening ID (i.e. S-01, S-02, S-03, etc.), however only patients who are fully eligible, have signed the ICF, and are ready to be randomised should be entered in the eCRF and assigned a participant ID.

Each site is requested to submit the cumulative screening log, along with the data corresponding to the total number of cardiac surgeries performed, on bypass, to the DCC via TRICSIV@unityhealth.to (with tricsiv@leicester.ac.uk copied in) by the first weekday of each month. The DCC may request the screening log more frequently if necessary to review screening activities.

13. Conduct of the trial

After eligibility is confirmed and informed consent is obtained, the following assessments will occur. See 'Schedule of Events' in the appendix.

13.1 Screening (-90 days to 0 days before the index surgical event)

- Written informed consent
- Eligibility criteria including EuroSCORE I and pregnancy test (dipstick or beta HCG) for women of childbearing potential

13.2 Preoperative/baseline assessments (-30 days to 0 days before the index surgical event)

- Recheck eligibility if >30 days since initial screening
- EuroSCORE I
- EQ-5D-3L
- Standard 12-lead Electrocardiogram (ECG)
- Demographics
- Medical/Cardiac History
- Height and Weight measurements
- Concomitant Medications
- Preoperative laboratory values (preoperative value closest to the index surgical date, no more than 30 days prior to the surgery date)

- Randomisation through the eCRF; *whenever feasible, randomisation will occur no more than 24 hours prior to the scheduled surgery to minimise the risk of losing randomised patients due to unplanned surgery cancellations*

13.3 Index Cardiac Surgery (Day 0)

- Surgical/procedure details
- Perioperative medications (anti-fibrinolytics, vasoactive medications) and intravenous (IV) fluids
- Reporting of all protocol-defined "trigger events" (see section 11.5) and transfusions
- Clinical events (see section 14.12)
- Intraoperative laboratory values

13.4 Postoperative period (Day of surgery until hospital discharge or postoperative day 28, whichever comes first)

- Reporting of all protocol-defined "trigger events" (see section 11.5) and transfusions
- Clinical events (see section 14.12.1)
- EQ-5D-3L
- Standard 12-lead ECGs will be performed on the day after surgery and on day 4-6 postoperatively or at hospital discharge, whichever comes first
- Postoperative laboratory values

13.5 3 month Follow-up

- EQ-5D-3L
- Health Economics questionnaire

13.6 6 month Follow-up

- Clinical events (see section 14.12.2)
- Emergency room (ER) visits and hospital admissions since discharge from the index hospitalisation
- EQ-5D-3L
- Obtain the last available standard 12-lead ECG done for clinical purposes
- Concomitant Medications

14. Clinical procedures and safety evaluations

14.1 Informed Consent

Once deemed an appropriate candidate for the trial, the patient will be informed of the possibility of trial participation. Eligible patients will be provided with a written version of the participant information sheet (PIS). The benefits and risks of participating in the trial will be explained to the patient, and the patient will be provided an opportunity to read the PIS and ask any questions he/she may have. Prior to conducting any trial-related procedures, the patient must provide consent to participate by signing* the Research Ethics Committee (REC) approved consent form.

The participant will be given sufficient time to consider the information, and afforded the opportunity to ask questions of the Investigator, their GP or other independent parties to decide whether they will participate in the trial. There will be no requirement that a patient must have the

PIS for a minimum duration prior to consent considering the often emergency/urgent requirements in cardiac surgery. This will apply in urgent cases only and not elective/planned surgery. However, every effort should be made to maximise the amount of time the patient has for consideration of trial enrolment, ensuring they feel that their questions have been addressed and they are happy to take part. Patients and carers may attend once or more times, or have subsequent telephone or video calls, to carefully consider their participation.

Informed consent will be taken by the Principal Investigator (PI) at site or an appropriately qualified individual to whom this task has been delegated, prior to undertaking any trial-related procedures. This will include research nurses and practitioners if compatible with local policy. All participants will be asked for consent to access to their medical records.

Where appropriate and as per local NHS Trust policy guidelines, consent will be obtained either over the telephone or by video call between the participant and the clinician/researcher. The Video/Telephone Consent Form will be completed by the researcher or delegated site person performing consent, confirming that the participant has understood the information and consent process. A copy of the Video/Telephone Consent Form will be given to the participant at the next available opportunity or sent via post, if local trust policy allows, and a copy will be filed in the participants medical records.

*This includes consent obtained by telephone or video call.

14.2 Demography

This includes date of birth, sex and ethnicity.

14.3 Medical/Cardiac History

Data will be collected from patients at baseline consisting of demographics, previous cardiac investigations, and previous cardiac and non-cardiac history.

14.4 Pregnancy test

A negative pregnancy test (dipstick or beta HCG) is required to be obtained prior to randomisation for women of childbearing potential.

14.5 Standard 12-lead ECG

A 12-lead ECG will be performed preoperatively, on the day after surgery and on day 4-6 postoperatively or at hospital discharge (whichever comes first). We will also collect the last ECG performed for clinical purposes up to the 6 month follow-up visit.

14.6 Body weight and height

Body weight and height will be recorded at baseline.

14.7 EuroSCORE I

The preoperative EuroSCORE I will be collected in the eCRF.

14.8 Surgical details

Details about the type of surgical procedure, interventions, duration and complications will be recorded including type of cardioplegia, blood loss, use of hemofiltration, duration of

cardiopulmonary bypass and aortic cross-clamp, presence of arrhythmias, and the use of intraaortic balloon pump/ventricular assist device. In addition, the type and volume of IV fluids administered in the first 24 hours after induction of anaesthesia will be collected in the eCRF.

14.9 Medications

Anti-fibrinolytic agents, vasoactive medications and type and volume of IV fluid administered will be recorded in the eCRF for the intraoperative and postoperative periods.

14.10 Laboratory tests

The following laboratory values are standard of care at most clinical institutions, and the laboratory data will be captured in the eCRF as follows:

14.10.1 Preoperative laboratory values

Hb, hematocrit (HCT), platelets, red cell distribution width, INR, activated partial thromboplastin time (aPTT), fibrinogen, creatinine, and creatine kinase–MB (CKMB) or troponin (preferred)

14.10.2 Intraoperative laboratory values

Lowest Hb (pre/during CPB and chest closure), lowest HCT (pre/during CPB and chest closure), lowest arterial and mixed venous pO2 (pre/during CPB and chest closure), lowest arterial and mixed venous O2 saturation (pre/during CPB and chest closure), lowest cardiac index (pre-CPB and chest closure) if measured, minimum pump flow (during-CPB)

14.10.3 Postoperative laboratory values

- Hb is required to be assessed on postoperative days 1, 2, 5 ±2, and 11 ±3 while in hospital. Hb measurements that are done for clinical purposes will be collected, if more than one Hb is measured on a particular day, the lowest value for that day will be recorded in the eCRF. Any patient who is transfused, is required to have a pre- and post-transfusion Hb measurement.
- CK-MB or troponin (preferred) is required to be assessed on the first postoperative day, approximately 24 hours after the end of surgery.
- Creatinine is required to be measured on postoperative days 1, 2, 3 and 5, and otherwise as clinically indicated.
- Other laboratory values will be performed as clinically indicated or as per local guidelines and collected in the eCRF up to hospital discharge/postoperative day 28: HCT, platelets (within 2 hours of chest closure), INR, aPTT and fibrinogen (within 2 hours of chest closure), CK-MB or troponin (preferred), arterial and mixed venous O2 saturation, arterial and mixed venous pO2.

14.11 Transfusions and “Trigger Events”

All protocol defined “trigger events” (per section 6.4) and all RBC transfusions will be recorded in the eCRF from the start of the index surgical procedure until hospital discharge, as well as the pre- and post-event/transfusion Hb times and values.

All non-RBC transfusions administered during the index hospitalisation period will be reported in the eCRF.

14.12 Clinical Events

14.12.1 Clinical events from the start of surgery until hospital discharge or post-operative day 28, whichever comes first

The following clinical events will be assessed through review of the patient medical records/chart, and reported in the eCRF from the start of the index cardiac surgery until discharge or postoperative day 28, whichever comes first. All definitions are standard definitions.[42-46]

- All-cause mortality
- Myocardial infarction which will be defined in accordance with the 4th Universal Definition of Myocardial Infarction[42]

a) **Early perioperative MI** (intraoperatively or within 48 hours after surgery): Detection of cardiac troponin (preferred) or CK-MB values more than 10 times the 99th percentile of the upper limit from a normal baseline* (i.e. the 99th percentile or less of the upper limit of normal) during the first 48 hours following surgery, and at least one of the following:
   - development of new pathological Q waves on the ECG
   - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - identification of a coronary dissection, new intracoronary thrombus of the new graft or native coronary artery(ies) by angiography or autopsy
   - Although a new left bundle branch block is not part of the 4th Universal Definition, we will include the collection of left bundle branch block to permit comparison to data collected in TRICS III that complied with the 3rd Universal Definition, which included left bundle branch block

*or, if preoperative cardiac enzymes are elevated, the postoperative enzymes are increased by more than 10 times the upper limit of normal (ULN) from the baseline value (i.e. greater than baseline plus 10 x the ULN).

b) **Late perioperative MI** (more than 48 hours after surgery): Detection of a rise and/or fall of cardiac troponin (preferred) or CK-MB values, with at least one value above the upper limit of normal, and with at least one of the following:
   - symptoms of ischemia, as long as the symptoms/signs are not explained by another proven clinical condition (pulmonary embolism, myocarditis, etc.)
   - new, or presumed new, significant ST-T wave changes or new left bundle branch block
   - development of new Q waves on the ECG
   - imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
   - identification of a new intracoronary thrombus of the new graft or native coronary artery(ies) by angiography or autopsy

Percutaneous coronary intervention (PCI) related MI is included in the late MI group, and is arbitrarily defined by elevation of troponin values more than 5 times the 99th percentile of the upper limit from a normal baseline, or a rise of troponin values more than 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

- **New onset renal failure requiring dialysis** (excluding dialysis during CPB)

- **New focal neurological deficit (stroke)** lasting more than 24 hours confirmed by clinical assessment and brain imaging
- **Infection:** infection will be defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two of the following three criteria: fever, leukocytosis, and positive sputum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement44
- **Acute kidney injury:** defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline46 - a 50% increase in serum creatinine within 1 week or a 26.5 µmol/L increase within 48 hours
- **Delirium:** based on one of the following criteria: CAM/CAM-ICU (even on 1 occasion), or ICDSC > 3, or 3D-CAM, or 4AT ≥4, or more than one dose of haloperidol or similar antipsychotic drug, or documented delirium by neurologist or neurosurgeon or psychiatrist consultation
- **Gut infarction:** confirmed by imaging (e.g. angiography), autopsy, or through surgical means
- **Seizures:** defined as generalised or focal tonic-clonic movements consistent with seizure; or EEG demonstrating epileptiform discharges; or diagnosis of seizures by neurologist or neurosurgeon consultation
- **Encephalopathy:** defined as unexpected delayed awakening or severely altered mental status (unconscious despite no sedative medication for more than 5 days), or encephalopathy documented by neurologist or neurosurgeon or psychiatrist consultation

14.12.2 Clinical events at 6 month follow-up visit

At 6 months, an in-person follow-up visit (or telephone, if in-person is not possible) will occur to capture any new hospitalisations or emergency department visits, as well as the following clinical outcomes. A telephone script has been created to facilitate collection of this data, in case an in-person visit is not possible.

- All-cause mortality
- MI
- New onset renal failure requiring dialysis
- Stroke
- Surgical or non-surgical coronary revascularisation
- COVID-19 test result (if done for clinical purposes)

The following will also be collected in the eCRF at the 6 month follow-up visit:

- Details for any **ECG(s) done for any incidence of MI** that occurs up to the 6 month visit, if applicable. Sites will be requested to send de-identified copy(ies) of the ECG(s) to the DCC.
- Details for the **last ECG performed for clinical purposes**. Sites will be requested to send a deidentified copy of the ECG for adjudication to the DCC via TRICSIV@unityhealth.to.
- A **list of all medications** that the patient is taking at the 6 month follow-up visit.

Routinely collected healthcare data via Office for National Statistics (ONS) will be used to ascertain mortality at 6 months in UK participants. A telephone contact to participants who have not died (identified from NHS SPINE data) will occur at 6 months postoperatively to assess clinical outcomes. Laboratory parameters will be determined preoperatively, intraoperatively, daily for the first three days postoperatively then every second day until day 11 and thereafter as clinically indicated while in hospital, as in TRICS III.

15. Evaluation of trial results

15.1 Primary Endpoints

The primary outcome is primary composite endpoint of all-cause mortality, myocardial infarction defined in accordance with the 4th Universal Definition of Myocardial Infarction, new-onset renal failure with dialysis, or new focal neurological deficit (stroke) lasting more than 24 hours confirmed by clinical and/or computed tomographic scan, occurring within 6 months of the initial surgery.

15.2 Secondary Endpoints

The secondary endpoints are as follows; see section 8.12 for definitions and details:

1. Incidence of each individual component of the primary outcome: all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) within 6 months
2. Composite and individual all-cause mortality, myocardial infarction, new onset renal failure requiring dialysis, and new focal neurological deficit (stroke) with index hospitalisation or after 28 days postoperatively, whichever comes first Length of stay in the Intensive Care Unit (ICU) and hospital (index hospitalisation)
3. Prolonged low output state defined as the need for two or more inotropes for 24 hours or more, intra-aortic balloon pump or ventricular assist device postoperatively (index hospitalisation)
4. Duration of mechanical ventilation (index hospitalisation)
5. Infection: defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two out of three of the following criteria: fever, leukocytosis, and positive sputum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement (index hospitalisation)
6. Acute kidney injury (AKI), defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline46 - a 50% increase in serum creatinine within 1 week or a 26.5 µmol/L increase within 48 hours (index hospitalisation)
7. Delirium, based on one of the following criteria: Confusion Assessment Method (CAM) or CAM-ICU (even on 1 occasion), or Intensive Care Delirium Screening Checklist (ICDSC) > 3, or 3D-CAM, or 4AT ≥4, or more than one dose of haloperidol or similar antipsychotic drug, or documented delirium by neurologist or neurosurgeon or psychiatrist consultation (index hospitalisation)
8. Gut infarction confirmed by imaging (e.g. angiography), autopsy, or through surgical means (index hospitalisation)
9. Hospital visits (hospitalisation and/or emergency visits and coronary revascularisation at 6 months)
10. The proportion of patients transfused and the number of blood products utilised (RBCs, plasma, platelets) (index hospitalisation)
11. Seizures, defined as generalised or focal tonic-clonic movements consistent with seizure; or electroencephalogram demonstrating epileptiform discharges; or diagnosis of seizures by neurologist or neurosurgeon consultation (index hospitalisation)
12. Encephalopathy, defined as unexpected delayed awakening or severely altered mental status (unconscious despite no sedative medication for more than 5 days), or encephalopathy documented by neurologist or neurosurgeon or psychiatrist consultation (index hospitalisation)

16. Statistical methods

Trial statistical analyses will be performed by researchers at the Li Ka Shing Knowledge Institute at the University of Toronto.

16.1 Sample Size Estimation

TRICS IV is a superiority trial powered for the primary composite endpoint of all-cause mortality, myocardial infarction, new-onset renal failure with dialysis, or new focal neurological deficit (stroke), within 6 months after the initial surgery. A RR of 0.70, with an incidence rate for the primary endpoint of 14% in the liberal and 20% in the restrictive transfusion arm was used for the sample size calculation, which is in line with observed rates in the modified intention-to-treat (ITT) analysis of TRICS III in individuals younger than 69 years old[12]. As observed in TRICS III, we assumed that 1.5% of the patients would be lost to follow-up by 6 months. With a 1:1 allocation ratio and a two-sided α=0.05, we found that enrolment of a total of 1,440 patients (720 per group) would provide 85% power to detect a RR of 0.70 for the liberal as compared with the restrictive transfusion strategy while accounting for a 1.5% attrition rate and one interim analysis of the primary outcome. To ensure that the main analysis of the primary outcome has at least 80% power, we will conduct a conditional power analysis after 50% of the recruited participants have their primary outcome data available. If the conditional power is ≥60% but <80%, we will re-estimate the sample size needed so that the main analysis of the primary outcome has 80% power, and recruitment of participants will continue until the re-estimated sample size is reached. For all other values of conditional power, we will continue recruitment until the originally planned target sample size of 1,440 patients is reached.

We may include the first 100 randomised participants in an internal pilot assessment of the adherence to Hb triggers that utilize physiological changes for initiation of RBC transfusion.

16.2 Analysis population

The ITT population consists of all patients who underwent randomisation and subsequent cardiac surgery with available outcome data.

The per-protocol (PP) population consists of all participants who underwent randomisation and subsequent cardiac surgery with cardiopulmonary bypass with available outcome data, except for patients who had a protocol adherence of less than 90%, patients who were withdrawn from the trial by the treating physician at any time, and patients who withdrew consent.

16.3 Baseline characteristics

The baseline characteristics of the patients will be summarised by group. Continuous variables will be summarised using mean and standard deviation, or median and inter-quartile range if data do not have a symmetric distribution. Categorical variables will be summarised with counts and percentages. No statistical comparisons of participant characteristics at baseline will be performed between groups.

16.4 Primary Outcome Analyses

The primary analysis of the primary outcome will be based on a chi-squared test. Superiority of liberal over restrictive transfusion will be declared with a p-value<0.05. A secondary analysis of the primary outcome will be based on a Cox regression model to derive hazard ratios (HR) with 95% confidence intervals, with the time to event presented per group using Kaplan Meier curves.

16.5 Secondary and Tertiary Outcomes and Safety Analyses

Separate analysis plans will be prepared for the renal outcomes and health economic outcomes. A separate plan will also be prepared to examine alternative ways to analyse adherence to the transfusion strategies, as well as any future exploratory analyses. For the secondary outcomes, the treatment effect and two-sided 95% CI for each outcome will be estimated by unadjusted analyses using the same variables as for the primary outcome unless otherwise stated, as appropriate. Both PP and ITT analyses of the secondary outcomes will be performed.

For dichotomous outcomes, risk differences and odds ratios along with 95% confidence intervals will be reported for the unadjusted analyses while the odds ratio will be used for adjusted analyses employing logistic regression. For continuous outcomes, mean differences and adjusted mean differences (from linear regression models) will be reported along with 95% confidence intervals. Other outcomes such as length of hospital and ICU stay, and duration of mechanical ventilation may be inappropriate for standard linear regression models, in which case a transformation (e.g. logarithm) or alternate model (e.g. time-to-event) will be considered. Adjusted analyses will be performed using the appropriate regression framework. Time to death at 6 months will be summarised by Kaplan-Meier curves.
Adherence will be summarised by group; we will also describe the distribution of the location of the non-adherent events (operating room, ICU, ward). The mean haemoglobin value (a) prior to non-adherent RBC transfusion events and (b) for non-adherent trigger events will be reported, by group.

16.6 Interim Analyses

One interim analysis will be undertaken after 50% of patients have reached determination of the primary outcome. A group sequential design has been employed that applies a one-sided boundary. The boundary is based on a Hwang-Shih-DeCani spending function for efficacy. If the boundary is crossed, there will be a non-binding recommendation to stop the trial for benefit. We will only conduct additional safety reviews if otherwise directed by the Data and Safety Monitoring Board (DSMB). The following table shows the Z-statistics for the non-binding recommendation to stop the trial due to benefit.

Analysis	Z-statistic
Interim	2.75
Final	1.98

16.7 Planned Subgroup Analyses

We will conduct subgroup analyses of the primary outcome to determine if the effect of the transfusion strategy varies according to the subgroups below. These analyses will be exploratory only. Subgroup analyses will be accompanied by a test for a treatment by subgroup interaction. Additionally, subgroup specific treatment effects and treatment by subgroup interactions will be estimated with an adjusted model using all of the covariates listed below and a single term for interaction between treatment and sub group defined by each covariate of interest. This procedure will be repeated for each covariate to model adjusted subgroup specific estimates. Tests for trend across ordered subgroups of left ventricular function will be derived in an analogous manner. P values, effect estimates and 95% confidence intervals will be reported as estimated from crude and adjusted models.

Subgroup analyses will be performed based on the following criteria:

1. Age

2. Sex
3. Diabetes (with and without insulin)
4. Baseline creatinine >200 (as collected for baseline EuroSCORE I)
5. Baseline preoperative haemoglobin
6. Pre-existing pulmonary disease (as collected for baseline EuroSCORE I)
7. Type of surgery: Coronary artery bypass graft (CABG) only, CABG with another procedure, other procedure only (non-CABG)
8. Left ventricular function (Good, Moderate, Poor, Very Poor)

16.8 Sensitivity Analysis

We will fit a random-effects model that accounts for the variation between sites in the between group difference of the primary composite outcome. We will also conduct an analysis of the primary composite outcome adjusted for variables that have a clinically significant difference between groups at baseline. In additional sensitivity analyses, we will determine whether analyses of specific patient subsets, as defined below, yield similar results for the primary outcome:

1. Excluding patients with any non-adherence to the assigned transfusion strategy
2. Excluding patients whose haemoglobin was never measured below 95g/L from the time of randomisation to the end of the index hospitalisation period
3. Excluding patients who did not receive any RBC transfusions from the time of randomisation to the end of the index hospitalisation period
4. Excluding patients who had at least one protocol suspension from the time of randomisation to the end of the index hospitalisation period
5. Excluding patients randomised according to physiologic triggers
6. Including only patients of the PP population

16.9 Missing Values

While we anticipate that the primary outcome will be available in >95% of patients, if the primary outcome is missing in more than 5% of patients, we will perform analyses to mitigate the effect of missing data as follows: we will develop a missing data model and perform a multiple imputation analysis. We will also carry out inverse-probability weighting. This is a two-stage model where a logistic regression model is first used to estimate the probability of not being missing. Then the analysis of the outcome proceeds on complete cases through a weighted analysis where the inverse probability of "completeness" forms the weights. The inference of the imputed model and inverseprobability weighting will be compared to that of the model with missing data.

16.10 Health Economic Evaluation

The Health Economic analyses will be performed by researchers at the University of Leicester. We will adopt a partially pooled approach. Our base case analyses will be taken from the UK NHS and Personal Social Services (PSS) perspective. We will collect itemised resource usage data from all trial sites and cost them in the UK prices using published sources; British National Formulary (BNF), National Reference Costs, and the Personal Social Services Research Unit (PSSRU). For sensitivity analyses, we will cost resource usages from individual country health care provider perspectives and use Purchasing Power Parity (PPP) to exchange all prices into a common currency. Outcome data will be presented as incremental cost per quality-adjusted life years (QALYs) and per composite outcome avoided over 12 month time horizon. Quality of life will be measured by EQ5D-3L and will be collected at start of the trial, at discharge, and every 3 months thereafter.

The EQ5D-3L questionnaire will be translated into utility scores by using the UK tariff for (baseline analyses and using each individual country tariffs in sensitivity analyses). Resources usage will be collected during the trial including length of hospital and ICU stay, medication, units of blood cell transfusion through case report form and hospital electronic record systems. Post-discharge resources usage will be collected through postal questionnaire at 3 months after discharge including medication, primary care consultations, Accident and Emergency (A&E) visits, outpatient attendances, and hospital re-admissions. Hospital stay information will be extracted from electronic recorded data at the end of the trial. The rest will be collected using a tailed version of CSI at 6th months. The resource usage questionnaire will be redefined after the pilot stage. All itemised resource usage data will be costed using published national data (BNF, National reference cost, and PSSRU) at base case analyses. For sensitivity analyses, we will cost those based on individual participant countries' price and use purchasing power parity to translate those into a common currency.

Cost and QALYs will generated using area under the curve approaches. Generalised linear model will be used to compare differences in costs and QALYs. Bootstrapping methods will be employed to produce incremental cost effectiveness ratio and associated confidence intervals around the estimates. Missing value will be imputed using multiple imputation methods.

17. Trial organisation and oversight

17.1 Trial organisation

The main co-ordination centre (CC) is located in the AHRC, Li Ka Shing Knowledge Institute of St. Michael's Hospital, Unity Health Toronto, at the University of Toronto. The CC will be responsible for developing and programming the electronic eCRFs, data monitoring, data management and analysis, and providing progress and data reports to the Executive Committee (EC), DSMB, and participating sites.

The University of Leicester Clinical Trials Unit (LCTU) has been contracted to undertake trial responsibilities in the UK (i.e., UK trial management, including training, opening and managing participating sites). LCTU will ensure that the trial runs according to the pre-agreed timetable, ethical requirements are complied with, and that all aspects of the trial are performed to the highest quality. Prof Gavin Murphy, British Heart Foundation (BHF) Chair in Cardiac Surgery/ Consultant Cardiac Surgeon, is the Chief Investigator (CI) in the UK.

The international TRICS IV trial was funded by the Canadian Institute for Health Research (CIHR) and commenced recruitment in October 2021. The Australian arm of the trial has been funded by the National Health and Medical Research Council (NHMRC). The UK arm of the trial is funded by National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) programme (ref NIHR150600). Additional support and resources for the trial will be provided by the participating UK NHS Trusts and their corresponding Clinical Research Networks (CRN).

As part of the UK arm, select UK collaborators will be invited to join the existing committees already set-up in Canada. Leicester CTU will assimilate a National Executive Group which will meet regularly to discuss trial management in the UK. These collaborators will report the outcomes of these meetings at the Canadian-led SC and DSMB meetings.

17.2 Data Management and Coordination Centre

The Data Management and Coordination Centre (DCC) is the Applied Health Research Center (AHRC), which is an academic research organisation fully integrated with the Li Ka Shing Knowledge Institute

of St. Michael's Hospital (Unity Health Toronto) and affiliated with the University of Toronto (UofT) in Canada. The DCC is responsible for day-to-day trial operations (e.g., document collection, site activation, data management, payments, etc.). The main trial database will be housed on secure servers at St. Michael's Hospital in Toronto, Canada and accessed by participating sites through the internet.

17.3 Executive Committee

The Executive Committee (EC) will include the Principal Investigators and co-Principal Investigators. The EC will be responsible for providing clinical and methodological guidance, including overall trial design, execution, analysis, and publication of the main trial results. The EC will oversee the management of the clinical trial sites and will also provide guidance around the publication strategy. While the trial is ongoing, the EC will approve any protocol amendment that may become necessary and will be responsible for maintaining the scientific integrity of the trial. The EC will reside in Canada.

17.4 Steering Committee

The trial Steering Committee (SC) will consist of the EC and at least one representative of each of the geographic regions of Investigators (e.g., Canada, Australia, United States, United Kingdom, South America, Europe, Asia, and Africa). The Steering Committee will meet by teleconference regularly throughout the trial period to discuss enrolment rates and non-adherence, and at the completion of the trial to provide operational insight and assist with issue resolution. A list of committee members will be maintained by the CC. The SC will reside in Canada.

17.5 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be assembled to ensure patient safety, receive and review interim analyses, provide feedback to the SC, and ensure the trial follows the highest ethical standards. The DSMB will be provided data on safety regularly throughout the trial period, in accordance with the DSMB Charter. The safety data will include all clinical events. We will only conduct additional safety reviews if otherwise directed by the DSMB.

The DSMB will consider clinical and statistical significance, consistency of data over time, consistency of the direction of risk and benefit-risk ratios if there is consideration for recommendation for early trial discontinuation. The DSMB will have the ability to request additional safety analyses or additional interim analyses, and to convene a full committee meeting and make any further recommendations to the steering committee about the safe conduct of the trial after considering all the available data and any new external data from relevant studies. The DSMB will have access to the randomisation codes, if needed. The DSMB will reside in Canada.

17.6 Clinical Adjudication Committee

The Clinical Adjudication Committee (CAC) consists of at least three members of appropriate clinical background (cardiac surgeons, cardiologists, haematologists, anaesthesiologists, or intensivists) who have been appointed by the EC. The members of the CAC will review and adjudicate clinical outcomes in a blinded manner according to a manual of procedures approved by the CAC and the EC. Sites will be requested to provide de-identified clinical documents for review by the CAC. The CAC will reside in Canada.

17.7 Patient and Public Involvement (PPI)

The UK proposal has been developed in partnership with the National Cardiac Surgery PPI Group and the National Cardiac Surgery Clinical Trials Initiative Organ Protection Clinical Trial Group. Our patient

co-applicant and PPI lead (Anthony Locke) has over a decade of experience in senior PPI roles and is a member of the National Cardiac Surgery PPI Group. He contributed to the drafting of the grant application and will provide oversight for all PPI activities, with operational support provided by LCTU, The Centre for Ethnic Health Research (CEHR), and the National PPI Group.

The trial was reviewed by the Leicester Cardiac Surgery PPI Group. The rationale for the TRICS IV trial and the trial design were presented to seven members of the group. Responses were universally supportive and concluded that this was a reasonable extension to our existing programme of research, that the rationale for the trial in younger patients was reasonable, that the methodology to extend the original TRICS III trial was acceptable as this would likely yield results in a shorter period of time and with greater efficiency, that the transfusion thresholds were justifiable and that the endpoints were important to patients.

We will also use research funds to employ and train a service user to lead our work on equality, diversity and inclusivity. This will include workshops and advisory groups during the set-up period for the trial (months 1-6) in partnership with CEHR . The primary aim of this work will be to develop methods for including underserved groups by implementing public facing materials, as well as development of participation and dissemination strategies that overcome barriers to inclusion. The Patient Researcher will write a report at the end of this work describing their experience. This will be disseminated via the Society of Cardiothoracic Surgeons Quarterly Bulletin, the BHF CRC, the National Cardiac Surgery PPI group, and the University of Leicester and Trial websites. The Patient Researcher will also write a more detailed report describing their experience for dissemination through trials methods journals, social media, INVOLVE and the NIHR website.

18. Ethical and Regulatory Considerations

The UK arm of the TRICS IV trial will be conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004) and the UK Policy Framework for Health and Social Care Research (2017). It will also be conducted according to the International Conference on Harmonisation Good Clinical Practice Guidelines (ICH-GCP), relevant regulations and the SOPs and quality management procedures of the Sponsor, host organisations and LCTU.

Once the initial Sponsor review process is complete and all requested documentation has been received and checked, authorisation from the Sponsor will be issued to book further review of the proposed research. The NHS Research Ethics Committee (REC) and the Health Research Authority (HRA) will then review the UK proposal.

Agreement in principle is subject to the research receiving all relevant UK regulatory permissions and full execution of the relevant contracts. The application for UK regulatory approvals will be submitted via the Integrated Research Application System (IRAS).

Recruitment at participating UK sites will commence once REC favourable opinion, HRA approval and local NHS Trust confirmation of capability (C&C) are in place before potential participants are approached. Participating clinical sites will be activated by the DCC after the following conditions are met:

- The site contract has been fully executed;
- The DCC has received a copy of all essential documentation;
- After training activities are completed for every trial member listed on the delegation log.

Activation will be confirmed via an email from the DCC to the lead site Investigator and site staff, and a copy of the activation email should be stored in the ISF.

For any required amendments to the trial, the CI, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. Amendments will be implemented upon receiving approval from the sponsor. Amendments to the protocol, if necessary, will be reviewed and approved by the EC with input from the SC.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. If the trial is ended prematurely, the UK CI will notify the REC, including the reasons for the premature termination. Otherwise, the CI (or delegate) will notify the REC when the trial has ended by completing the end of trial notification form and will submit a final report of the results within one year after notifying the REC.

A UK Trial Master File (TMF) will be maintained by LCTU for the duration of the trial. Each participating UK site will maintain an Investigator Site File (ISF). Both will be stored for a minimum of 7 years after the trial has ended and archived in accordance with the relevant SOPs.

18.1 Assessment and management of risk

18.1.1 Potential risks and hazards communicated to eligible patients

Similar to TRICS III, patients allocated to the liberal strategy may receive a transfusion that they otherwise may not have been given and which may result in a reaction. The other potential harm is that patients may not receive a transfusion when it may otherwise have been administered if they are allocated to the restrictive strategy. These patients may experience an adverse event secondary to anaemia or tissue hypoxia. The transfusion levels selected for this trial, however, are levels that we have used in TRICS III and TITRE2. They were acceptable to the centres participating in TRICS and TITRE 2 as supported by the high adherence (90.9%) to transfusion strategies. The potential harms of either transfusion strategy can still occur outside this trial since with routine care, these transfusion thresholds are commonly used. The Data Safety Monitoring Board (DSMB) will review safety reports biannually and data from the interim analysis. The DSMB will have the ability to request additional safety analyses and make recommendations about the conduct of the trial.

18.1.2 Steps to minimise bias

- **Randomisation and allocation concealment:** The centralised, web-based randomisation system will ensure allocation concealment. In case of rare service interruptions that occur during non- business hours, each site will be provided with a back-up randomisation method. There were no such unanticipated service interruptions in TRICS III.

- **Managing potential bias due to the unblinded nature of the trial:** Blinding or masking of treatment allocation is not possible for the medical team administering transfusions. Knowledge of the Hb is essential for detecting early haemorrhage or for the use of blood conservation strategies as part of routine postoperative care. To address this key source of bias we aim to mitigate detection, procedural, and post randomisation bias using techniques that were effective in TRICS III and TITRE 2 such as
  - Masking clinical outcomes through a blinded adjudication
  - Masking the statistician and the DSMB when the data are presented for the interim

  - Choosing objective outcomes with source data verification. Of the 3683 events that were adjudicated in TRICS III, only 156 (4%) required a third adjudicator. All discrepancies were easily resolved.
  - Careful documentation of protocol non-adherence as per TRICS III including the application of pre-specified definitions of minor and major protocol deviations.

- **Adherence and attrition:** Patients have the right to discontinue from the trial or trial transfusion strategy for any reason, at any time. All participants who are randomised and undergo surgery will be followed for the remainder of the trial up to the 6-month outcome, unless the participant withdraws consent for follow up. Any participant who is randomised but for any reason does not undergo surgery, will not be followed and data will not be collected longitudinally. In this situation, the participant will be replaced to achieve the required sample size. Strategies to optimise adherence and reduce attrition developed in TRICS III and TITRE 2 will be applied. In both TRICS III and TITRE 2 severe non-adherence occurred in 9% of participants. Loss to follow-up for the primary outcomes of the TITRe2 trial and TRICS III trial were 4.8% at 90 days and 4.5 % at 180 days respectively.

- **Reporting Bias:** The trial protocol is registered on clinicaltrials.gov (NCT04754022), and will be published prospectively. A statistical analysis plan will be published prior to data lock. The trial will be reported as per the CONSORT statement.

18.1.3 Steps to address potential inequity of sampling across the population

Participation in the UK arm of the trial will aim to reflect the diversity of the UK population, and the team will develop tools that anticipate how health inequalities interact to create barriers to inclusion among underserved groups. A dedicated Patient Researcher will deliver this component of the research plan in partnership withCEHR, which has expertise in engagement with underserved communities, developing competencies in research staff, and mitigating the effects of health inequalities on research participation. To ensure effective engagement, the Patient Researcher will be employed by University of Leicester Cardiovascular Sciences and work alongside the UK trial management team.

18.2 Insurance and indemnity

LCTU will ensure that each mNCA with each participating site obliges the participating site to effect and maintain appropriate insurance cover for the conduct of the trial, taking into account the nature of the research activities contemplated.

If a participant is harmed due to negligence, this will be covered by the local NHS Trust(s) indemnity arrangements for all participants in clinical trials. If a trial participant wishes to make a complaint about any aspects of the way they have been treated or approached during the research project, the standard NHS complaint system will be available to them. Details of this are made available to participants the PIS.

18.3 Informed Consent and Patient Protection

It is an obligation of the site Investigator to obtain informed consent from every trial participant by means of a dated and signed informed consent form before any trial related procedure is performed. 'Informed consent' also implies individual discussion with the participant about the nature of trial interventions to be conducted in a language that is easy to comprehend. The participant should fully understand that their refusal to participate in the trial will not affect the quality of medical care received. In addition, the patient must be informed that, without disclosing their name, relevant

medical data will be disclosed to the CC and that their medical records may be inspected during on-site monitoring. The trial participant should also be informed in writing about the possibility of audits by authorised representatives of the CC or the Sponsor or a designee in which case a review of those parts of the hospital records relevant to the trial may be required.

The participant should be informed in writing that their medical data relevant to this trial will be stored and analysed while maintaining confidentiality in accordance with local data protection laws. All data transferred to the eCRF and any process derived from the eCRF will be de-identified.

18.4 Trial Protocol Adherence and Modifications

Site Investigators must read, understand and follow the trial protocol. The same applies to instructions given in the eCRF and to any additional instructions issued through the CC. Changes to the protocol should only be made by the EC in the form of protocol amendments. Leicester CTU is responsible for the distribution of any protocol amendments to site Investigators and staff involved in the trial in the UK.

18.5 Trial Network Registration

TRICS IV is registered on clinicaltrials.gov (NCT04754022).

19. Data collection and management

19.1 Data Collection and Documentation

For every patient, the hospital or clinic file must clearly indicate that the patient has given informed consent and participated in the trial. Copies of the participant consent form and information sheet will be provided to the participant and placed in the hospital notes of all participants and the original will be stored in the ISF. A sticker will be placed on the cover of the notes (or inside cover) for participants taking part in the trial detailing the trial title, PI contact details and retention period. A similar electronic method will be implemented within any corresponding electronic data health records.

All entries in the eCRFs must be backed up by source data. Source data must be made available if requested by the EC or CC. The eCRFs must be completed in a timely manner. All trial records should be kept in accordance with applicable national laws and regulations.

Participating sites will provide information on data storage to the UK central coordinating centre at LCTU.

19.2 Electronic data capture system

Electronic data capture (REDCap™) will be used for this trial, meaning that all trial data will be entered in eCRFs at the investigational site. Data collection will be completed by authorised trial site personnel designated by the site Investigator. Appropriate training and security measures will be completed with the site Investigator and all authorised trial site personnel prior to the trial being initiated and any data being entered into the system for any trial participants. The trial data will be housed on a secure in-house server at St. Michael's Hospital in Toronto throughout the duration of trial, and up to 7 years after the trial is complete.

19.3 Data Collection and Cleaning

All eCRF corrections are to be made by an Investigator or other authorised trial site personnel. Prior to database lock, the site Investigator/co-Investigator must confirm that they have reviewed the data, and that the data are complete and accurate. Data validation procedures will be described in detail in the Data Management Plan.

19.4 Routine Data Linkage

In the UK, participants will be asked to consent to have their personal information linked with routinely collected healthcare data, after the last participant last visit. This will include access to ONS data for ascertainment of mortality at part of the primary outcome at 6 months post-surgery. To facilitate this, UK participants' NHS numbers will be kept at recruiting sites. These data will then be used to submit an ONS data access request by LCTU after last participant/last visit in the UK arm. Resource usage data will be collected using a bespoke patient completed questionnaire, which will be recorded in a UK developed and managed REDCap database. This will cover medication, primary care consultation, outpatients attendance and hospital admission. A postal questionnaire will be administered 3 months after discharge to collect information on medication, primary care consultation, outpatient attendances and hospital admission. Quality of life data will be collected every three months after discharge by post.

19.5 Measurement of costs and outcomes

1. **Mortality** will be ascertained in UK participants through an ONS data access request, as described above.
2. **Myocardial infarction**, which will be defined in accordance with the 4th Universal Definition of Myocardial Infarction.

a) **Early perioperative MI** (intraoperatively or within 48 hours after surgery): Detection of cardiac troponin (preferred) or CK-MB values more than 10 times the 99th percentile of the upper limit from a normal baseline* (i.e. the 99th percentile or less of the upper limit of normal) during the first 48 hours following surgery, and at least one of the following:
   - Development of new pathological Q waves on the ECG.
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
   - Identification of a coronary dissection, new intracoronary thrombus of the new graft or native coronary artery(ies) by angiography or autopsy.

b) **Late perioperative MI** (more than 48 hours after surgery): Detection of a rise and/or fall of cardiac troponin (preferred) or CK-MB values, with at least one value above the upper limit of normal, and with at least one of the following:

- Symptoms of ischemia, as long as the symptoms/signs are not explained by another proven clinical condition (pulmonary embolism, myocarditis, etc.). new, or presumed new, significant ST-T wave changes or new left bundle branch block.
- Development of new Q waves on the ECG.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Identification of a new intracoronary thrombus of the new graft or native coronary artery(ies) by angiography or autopsy.

c) **Percutaneous coronary intervention (PCI) related MI** is included in the late MI group, and is

- Arbitrarily defined by elevation of troponin values more than 5 times the 99th percentile of the upper limit from a normal baseline, or a rise of troponin values more than 20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia, or (ii) new ischemic ECG changes, or (iii) angiographic

findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.

3. **Prolonged low output state** defined as the need for two or more inotropes for 24 hours or more, intra-aortic balloon pump or ventricular assist device postoperatively.
4. **New onset renal failure** requiring renal replacement therapy (excluding dialysis during CPB).
5. **New focal neurological deficit (stroke)** lasting more than 24 hours confirmed by clinical assessment and brain imaging.
6. **Infection:** infection will be defined as septic shock with positive blood cultures; pneumonia defined as autopsy diagnosis or roentgenographic infiltrate and at least two of the following three criteria: fever, leukocytosis, and positive sputum culture; and/or deep sternal or leg wound infection requiring intravenous antibiotics and/or surgical debridement.
7. **Acute kidney injury:** defined by the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline (40) - a 50% increase in serum creatinine within 1 week or a 26.5 µmol/L increase within 48 hours.
8. **Delirium:** based on one of the following criteria: CAM/CAM-ICU (42) (even on 1 occasion), or ICDSC > 3, or 3D-CAM, or 4AT ≥4, or more than one dose of haloperidol or similar antipsychotic drug, or documented delirium by neurologist or neurosurgeon or psychiatrist consultation.
9. **Gut infarction:** confirmed by imaging (e.g. angiography), autopsy, or through surgical means.
10. **Seizures:** defined as generalised or focal tonic-clonic movements consistent with seizure; or EEG demonstrating epileptiform discharges; or diagnosis of seizures by neurologist.
11. **Encephalopathy:** defined as unexpected delayed awakening or severely altered mental status (unconscious despite no sedative medication for more than 5 days), or encephalopathy documented by neurologist or neurosurgeon or psychiatrist consultation.
12. **Duration of mechanical ventilation** (during index hospitalisation).
13. **Length of stay** in the Intensive Care Unit including readmissions (ICU) and hospital (time to discharge from acute care after index hospitalisation; this includes time to discharge from satellite acute care units) and Days Alive and Out of Hospital at 6 months.
14. **Healthcare resource use:** We will collect information on length of stay, time on ICU, units of red blood transfusion, procedures, laboratory tests, examination and medication during hospital stay using case report forms and electronic record systems. A resource usage questionnaire will be designed to collect resource usage information after discharge covering medication, primary care consultation, outpatients attendances, A&E visits and hospital re-admission
15. **Quality of Life:** We will measure QoL using the EuroQol-5D-3L (EQ-5D-3L). The EQ-5D-3L includes five dimensions: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression, each scored on three levels. We will apply the individual country's tariff and scoring algorithm to translate EQ-5D-3L scores to utility scores. This will be used to generate Quality Adjusted Life Year (QALY) profiles for the cost-effectiveness analysis.
16. **Clinical events:** The number and type of clinical events (more commonly referred to as 'adverse events' in the UK arm) will be recorded on the eCRF and reviewed by a Central Adjudication Committee (refer to section 17.6).

19.6 Data protection and participant confidentiality

Participants' personal data included the REDCap system shall be treated in confidence and in compliance with local data protection laws. The UK data collected as part of the health economics and quality of life questionnaires shall be treated in compliance with ICH-GCP the UK Policy Framework for Health and Social Care and the EU General Data Protection Regulation (GDPR). When processing or archiving personal data, the Sponsor or its representative shall take all appropriate measures to

safeguard and prevent access to this data by any unauthorised third party. Pseudonymised data may be shared with the study investigators or sponsor and used as part of the dissemination.

Each participant will be assigned a unique identification number upon enrolment. All personalised information for participants will be kept confidentially at the recruiting site unless there is specific consent and HRA approval for transfer of this to another site for trial-related purposes.

All electronic patient identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Each person (both the field-based data collectors and at AHRC) will be assigned access to only the portions of the database they need. All data are encrypted and data transfers into the system are one-way (data is not transferred out of the system).

Paper documentation will be stored in a locked filing cabinet in the relevant research office. Neither hard copies nor electronic files containing personal information will be removed from the research office or stored in a non-secure manner electronically. The trial research team will comply with local NHS Trust data protection policies. Direct access to source data/documents may be required for trial-related monitoring. All paper and electronic data will be retained for at least 7 years after completion of the trial in accordance with Sponsor SOPs. UK data will be stored at a University of Leicester approved archiving facility which will ensure that it is stored securely and accessed only by authorised individuals.

19.7 Direct Access to Source Data/Documents

The site Investigator shall supply the EC, CC or delegate on request with any required background data from the trial documentation or clinic records.

19.8 Data access and storage

All trial documentation will be retained in a secure location during the conduct of the trial. Personal identifiable data will be retained by each participating site for a maximum of 12 months following the end of the trial, after which it will be destroyed, unless participants have expressed an interest in receiving a copy of the trial results. In these circumstances, personal identifiable details such as names and contact details will be retained on a password protected database until required, and then destroyed.

All electronic data will be stored on secure network systems, to which only the relevant trial personnel will have access.

For the purposes of this trial:

- St Michael's Hospital, Unity Health Toronto, Canada, will act as the Data Controller for data held on REDCap;
- The University of Leicester will act as the Data Controller for:
  - the UK data collected as part of the health economics and quality of life questionnaires;
  - the data collected as part of routine data linkage in the UK, in joint status with the Office for National Statistics (ONS).

19.9 Records Retention

The site Investigator must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. The ISF will contain the protocol/amendments, REC/HRA approval with correspondence, sample informed consent form, staff

curriculum vitae and GCP certificates, and other appropriate documents/correspondence, etc. Should the site Investigator wish to assign the trial records to another party or move them to another location, the CC must be notified in advance. Trial records at each site should be stored as per local requirements or for 7 years after publication of the trial, whichever is longer.

19.10 Monitoring

Routine on-site monitoring is not planned for this trial. However, ad-hoc on-site visits may be requested in order to review local procedures and/or local source documentation as needed and therefore the patient informed consent form must inform patients of this possibility. Additionally, "remote monitoring" may be performed, in which copies of de-identified source documents would be requested for review by the DCC.

20. End of trial

This trial will end when the specified number of participants have been recruited, all participants have completed their last follow up-visit, data validation has taken place, the database is locked, statistical analysis is complete and the final results published.

21. Dissemination and publication policy

TRICS IV will be published in peer-reviewed medical journals, seminars at national and international meetings, presentation of results at conferences and dissemination meetings to be part of the dissemination strategy. By collaborating with international centres, participating international key opinion leaders will present results at various regional and national forums ensuring a widespread audience. In addition, a national workshop will be hosted in the UK to share the knowledge from the trial with relevant stakeholders, including healthcare commissioners, members of the public, clinicians and academics.

Led by our PPI co-applicant, the Patient Researcher, and other PPI collaborators we will develop a social media presence with a web page, Instagram and Twitter feed. These will track both the progress of the trial and eventual results and will allow people with an interest in transfusion and perioperative care to have access to our findings in a contemporary and user-friendly way.

Through the University and British Heart Foundation communications teams (Prof Gavin Murphy is a BHF Chair of Cardiac Surgery) and the NIHR, we will use press releases to alert the popular press and broadcasters to the trial, and publish discussion articles in journals such as Anaesthesia, the British Journal of Anaesthesia and the European Journal of Cardiothoracic Surgery to accompany publication of the main trial report. Trial investigators will be informed of the trial results at an investigators meeting.

TRICS IV will have broad generalisability due to its pragmatic nature, large sample size, broad eligibility criteria, and the diversity of the patient cohort across multiple types of cardiac centre (University/ Non-University) and countries. We expect the results to inform practice and influence treatment guidelines worldwide. We have planned for the knowledge framework to be used at the end of this trial. The knowledge framework will focus on knowledge creation (i.e., dissemination).

We will also work with the Knowledge Translation Consultation Service at St. Michael's Hospital (led by Dr Sharon Strauss) and the University of Toronto to assist with translating research to policymakers, physicians, patients and the public.

22. COVID and Feasibility Risk Assessment

A significant uncontrolled factor is the uncertainty as to the impact of the COVID-19 pandemic on recruitment. Proposed mitigating factors are outlined below.

22.1 Participating Sites

We have consulted with all 22 UK units who have expressed an interest in participating in the TRICS IV trial. All of these sites saw surgical activity return to near normal within 3 months of cessation of the March 2021 lockdown. However, all 22 units (28 principal investigators replied to our request for information) indicated their continued willingness to collaborate, that they did not envisage significant barriers to the trial, that there would be capability and capacity to deliver the trial, and that they were implementing routine COVID-19 screening <72 hours of surgery, as per current best practice. The trial is undertaken as part of normal clinical care and therefore no additional research space or resources are required. The trial will be managed by the Leicester Clinical Trials Unit, which is currently working at full capacity and will be in a position to manage the trial. The non-UK arms of the TRICS IV trial are funded separately. The lead Canadian arm of the trial, funded by the Canadian Institutes of Health Research started recruitment in October 2021.

22.2 Effect of the COVID-19 pandemic on participants

It is impossible to quantify what effect, if any, the fear of COVID-19 infection will have on recruitment. On the one hand, the success of the RECOVERY trial will have enhanced the potential benefits of clinical trials to the health of the country as a whole. On the other, any hospitalisation will be associated with increased anxiety that may affect recruitment. The fact that both arms of the trial represent standard care in different UK centres will also mitigate anxiety and should promote recruitment. Participation in the trial does not involve hospital visits, tests, or procedures, beyond normal care. For people waiting in hospital, risks of transmission from research staff will be mitigated by adherence to safe practices as per local hospital guidance.

22.3 COVID-19 risk to participants and staff

As per guidance from the Society for Cardiothoracic Surgery in the United Kingdom and Ireland, it is now the standard of care that all people referred for cardiac surgery in UK centres have self-isolated for at least 14 days AND have a negative COVID-19 PCR test within 72 hours of surgery. In urgent patients where the clinical need mandates surgery within the 72 hour PCR testing window, a CT scan to look for evidence of subclinical pneumonitis is required. These steps mean that it is extremely unlikely that anyone with a subclinical COVID-19 infection will be recruited to the trial. Furthermore, there will be no increased exposures to participants or staff due to the proposed follow-up schedule. We do not envisage that the risk of COVID-19 infection will influence the ability to complete participant follow-up as per protocol.

23. References

1. Number of cardiovascular surgeries in Canada from 2007-2014. Available at https://www.statista.com/statistics/647978/cardiovascular-surgery-numbers-canada. Accessed Feb 2019.
2. Hajjar LA, Vincent JL, Galas FR, Nakamura RE, Silva CM, Santos MH, Fukushima J, Kalil Filho R, Sierra DB, Lopes NH, Mauad T, Roquim AC, Sundin MR, Leão WC, Almeida JP, Pomerantzeff PM, Dallan LO, Jatene FB, Stolf NA, Auler JO Jr. Transfusion requirements after cardiac surgery: the TRACS randomised controlled trial. *JAMA.* 2010 Oct 13;304(14):1559-67.
3. Neal B, Chapman N, Patel A. Managing the global burden of cardiovascular disease *European Heart Journal Supplements*. 2002: 4 (Supplement F); F2–F6.
4. Karkouti K, Wijeysundera DN, Beattie S for Reducing Bleeding in Cardiac Surgery (RBC) Investigators. Risk Associated With Preoperative Anaemia in Cardiac Surgery A Multicenter Cohort Study. *Circulation* 2008; 117: 478-484.
5. Covin R, O'Brien M, Grunwald G, Brimhall B, Sethi G, Walczak S, Reiquam W, Rajagopalan C, Shroyer AL. Factors affecting transfusion of fresh frozen plasma, *platelets, and red blood cells during elective coronary artery bypass graft gurgery. Arch Pathol Lab Med* 2003; 127: 415-23.
6. Chiavetta JA, Herst R, Freedman J, Axcell TJ, Wall AJ, van Roy SC. A survey of red cell use in 45 hospitals in Central Ontario, Canada. *Transfusion*, 1996; 36: 699-706.
7. Josephson CD, Glynn SA, Kleinman SH, Blajchman MA; State-of-the Science Symposium Transfusion Medicine Committee. A multidisciplinary "think tank": the top 10 clinical trial opportunities in transfusion medicine from the National Heart, Lung, and Blood Institute-sponsored 2009 state-of-the-science symposium. Transfusion 2011 Apr;51(4):828-41Hebert PC, Hu LQ, Biro GP. Review of physiologic mechanisms in response to anaemia. *Can Med Assoc J* 1997; 156(suppl):S27-S40.
8. Hebert PC, Wells G, Blajchman MA et al. A multicenter, randomised controlled clinical trial of transfusion requirements in critical care. *New Engl J Med* 1999; 340: 409-17.
9. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators. Liberal or restrictive transfusion in high-risk patients after hip surgery. *N Engl J Med*. 2011 Dec 29;365(26):2453-62.
10. Villanueva C1, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med. 2013 Jan 3;368(1):11-21.
11. Mazer CD, Whitlock RP, Fergusson DA, Hall J, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, McGuinness S, Royse A, Carrier FM, Young PJ, Villar JC, Grocott HP, Seeberger MD, Fremes S, Lellouche F, Syed S, Byrne K, Bagshaw SM, Hwang NC, Mehta C, Painter TW, Royse C, Verma S, Hare GMT, Cohen A, Thorpe KE, Jüni P, Shehata N; TRICS Investigators and Perioperative Anaesthesia Clinical Trials Group. Restrictive or Liberal Red-Cell Transfusion for Cardiac Surgery. N Engl J Med 2017 Nov 30;377(22):2133-2144.

12. Mazer CD, Whitlock RP, Fergusson DA, Belley-Cote E, Connolly K, Khanykin B, Gregory AJ, de Médicis É, Carrier FM, McGuinness S, Young PJ, Byrne K, Villar JC, Royse A, Grocott HP, Seeberger MD, Mehta C, Lellouche F, Hare GMT, Painter TW, Fremes S, Syed S, Bagshaw SM, Hwang NC, Royse C, Hall J, Dai D, Mistry N, Thorpe K, Verma S, Jüni P, Shehata N; TRICS Investigators and Perioperative Anaesthesia Clinical Trials Group. Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery. N Engl J Med. 2018 Sep 27;379(13):1224-1233.

13. Hare GMT, Freedman J, Mazer CD. Risks of anaemia and related management strategies: can perioperative blood management improve patient safety? *Canadian Journal of Anaesthesia* . 2013 Feb;60(2):168-75.

14. Karkouti K, Beattie WS, Wijeysundera DN, Rao V, Chan C, Dattilo KM, Djaiani G, Ivanov J, Karski J, David TE. Haemodilution during cardiopulmonary bypass is an independent risk factor for acute renal failure in adult cardiac surgery. *J Thorac Cardiovasc Surg* 2005 Feb;129(2):391-400.

15. Karkouti K, Djaiani G, Borger MA, Beattie WS, Fedorko L, Wijeysundera D, Ivanov J, Karski J. Low hematocrit during cardiopulmonary bypass is associated with increased risk of perioperative stroke in cardiac surgery. *Ann Thorac Surg* 2005 Oct;80(4):1381-7.

16. Kulier A, Levin J, Moser R, Rumpold-Seitlinger G, Tudor IC, Snyder-Ramos SA, Moehnle P, Mangano DT; Investigators of the Multicenter Study of Perioperative Ischemia Research Group; Ischemia Research and Education Foundation. Impact of preoperative anaemia on outcome in patients undergoing coronary artery bypass graft surgery. *Circulation* 2007 Jul 31;116(5):471-9.

17. Tsui AK, Dattani ND, Marsden PA, El-Beheiry MH, Grocott HP, Liu E, Biro GP, Mazer CD, Hare GM. Reassessing the risk of haemodilutional anaemia: Some new pieces to an old puzzle. *Canadian J Anaesthesia* 2010 Aug;57(8):779-91.

18. Hagl S, Heimisch W, Meisner H, Erben R, Baum M, Mendler N. The effect of haemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol.* 1977 Jul-Aug;72(4):344-64.

19. Wilkerson DK, Rosen AL, Sehgal LR, Gould SA, Sehgal HL, Moss GS. Limits of cardiac compensation in anemic baboons. *Surgery* 1988 Jun;103(6):665-70.

20. Jan KM, Chien S. Effect of hematocrit variations on coronary hemodynamics and oxygen utilisation. *Am J Physiol* 1977 Jul;233(1):H106-13.

21. Geha AS, Baue AE. Graded coronary stenosis and coronary flow during acute normovolemic anaemia. *World J Surgery* 1978 Sep;2(5):645-51.

22. Kobayashi H, Smith CE, Fouad-Tarazi FM, Wicker P, Estafanous GF. Circulatory effects of acute normovolaemic haemodilution in rats with healed myocardial infarction. *Cardiovasc Res*. 1989 Oct;23(10):842-51.

23. Weiskopf RB, Viele MK, Feiner J, Kelley S, Lieberman J, Noorani M *et al*. Human cardiovascular and metabolic response to acute severe isovolemic anaemia. *JAMA* 1998; 279: 217-221.

24. Weiskopf RB1, Kramer JH, Viele M, Neumann M, Feiner JR, Watson JJ, Hopf HW, Toy P. Acute severe isovolemic anaemia impairs cognitive function and memory in humans. Anesthesiology. 2000 Jun;92(6):1646-52.

25. Beghé C, Wilson A, Ershler WB. Prevalence and outcomes of anaemia in geriatrics: a systematic review of the literature. Am J Med. 2004 Apr 5;116 Suppl 7A:3S-10S.

26. Reeves BC, Pike K, Rogers CA, Brierley RC, Stokes EA, Wordsworth S, Nash RL, Miles A, Mumford AD, Cohen A, Angelini GD, Murphy GJ. 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 Aug;20(60):1-260.

27. Wijeysundera, D.N., et al., Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. Lancet, 2018. 391(10140): 2631-2640.

28. Strait, J.B. and E.G. Lakatta, Aging-associated cardiovascular changes and their relationship to heart failure. Heart Fail Clin, 2012. 8(1): 143-64.

29. McKee, P.A., et al., The natural history of congestive heart failure: the Framingham study. N Engl J Med, 1971. 285(26): 1441-6.

30. Reeves BC, Pike K, Rogers CA, Brierley RC, Stokes EA, Wordsworth S, Nash RL, Miles A, Mumford AD, Cohen A, Angelini GD, Murphy GJ. Liberal or restrictive transfusion after cardiac surgery. N Engl J Med. 2015 Mar 12;372(11):997-1008.

31. Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. *Blood.* 2005 Mar 15;105(6):2266-73.

32. Tuinman PR, Vlaar AP, Cornet AD, Hofstra JJ, Levi M, Meijers JC, Beishuizen A, Schultz MJ, Groeneveld AJ, Juffermans NP. Blood transfusion during cardiac surgery is associated with inflammation and coagulation in the lung: a case control study *Crit Care.* 2011;15(1):R59.

33. Vlaar AP, Hofstra JJ, Determann RM, Veelo DP, Paulus F, Levi M, Zeerleder S, Vroom MB, Schultz MJ, Juffermans NP. Transfusion-related acute lung injury in cardiac surgery patients is characterized by pulmonary inflammation and coagulopathy: a prospective nested case-control study. *Crit Care Med.* 2012 Oct;40(10):2813-20.

34. Vlaar AP, Hofstra JJ, Determann RM, Veelo DP, Paulus F, Kulik W, Korevaar J, de Mol BA, Koopman MM, Porcelijn L, Binnekade JM, Vroom MB, Schultz MJ, Juffermans NP. The incidence, risk factors, and outcome of transfusion-related acute lung injury in a cohort of cardiac surgery patients: a prospective nested case-control study. *Blood.* 2011 Apr 21;117(16):4218-25.

35. Vamvakas EC, Blajchman MA. Transfusion-related mortality: the ongoing risks of allogeneic blood transfusion and the available strategies for their prevention. *Blood* 2009;113(15):3406-17.

36. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activitybased costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010 Apr;50(4):753-65.

37. O'Brien SF, Yi QL, Fan W, Scalia V, Goldman M, Fearon MA. Residual risk of HIV, HCV and HBV in Canada. Transfus Apher Sci. 2017 Jun;56(3):389-391.

38. Goodnough LT, Soegiarso RW, Birkmeyer JD, Welch HG. Economic impact of inappropriate blood transfusions in coronary artery bypass graft surgery. *Am J Med* 1993; 94: 509-514.

39. Shander A, Hofmann A, Ozawa S, Theusinger OM, Gombotz H, Spahn DR. Activitybased costs of blood transfusions in surgical patients at four hospitals. *Transfusion* 2010 Apr;50(4):753-65.

40. Amin M, Fergusson F, Wilson K, Tinmouth A, Aziz A, Coyle D, Hébert P. The societal unit cost of allogenic red blood cells and red blood cell transfusion in Canada. *Transfusion* 2004; 44: 1479,1486.

41. Shehata N, Mistry N, da Costa BR, Pereira TV, Whitlock R, Curley GF, Scott DA, Hare GMT, Jüni P, Mazer CD. Restrictive compared with liberal red cell transfusion strategies in cardiac surgery: a meta-analysis. Eur Heart J. 2018 Aug 10. doi: 10.1093/eurheartj

42. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018 Oct 30;72(18):2231-2264.

43. Tuman KJ, McCarthy RJ, March RJ, Najafi H, Ivankovich AD. Morbidity and duration of ICU stay after cardiac surgery. A model for preoperative risk assessment. *Chest* 1992 Jul;102(1):36-44.

44. Higgins TL, Estafanous FG, Loop FD, Beck GJ, Blum JM, Paranandi L. Stratification of morbidity and mortality outcome by preoperative risk factors in coronary artery bypass patients. A clinical severity score. *JAMA* 1992 May 6;267(17):2344-8.

45. Petaja L, Salmenpera M, Pulkki K, Pettila V. Biochemical injury markers and mortality after coronary artery bypass grafting: a systematic review. *Ann Thorac Surg* 2009;87(6):1981-1992.

46. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International Supplement*. 2012; March Vol 2. Supplement 1.

24. Appendices

24.1 Schedule of events

Assessment	Screening	Pre-operative	Index Cardiac Surgery	Post-operative (ICU, Ward)	3 months	6 months	After LPLV (UK arm of the trial)
Trial Day/Month	-90 to 0	-30 to 0	Day 0	Postoperative period: day of surgery until hospital discharge or postoperative day 28	3 months +/- 21 days after Day 0	6 months +/- 21 days after Day 0	
Observation/ Procedure							
Inclusion/exclusion	X						
Informed consent	X						
Pregnancy test[1]	X[1]						
Demographics		X					
Medical/cardiac history		X					
Height and weight		X					
EuroSCORE I	X	X					
Randomisation		X					
Surgical details			X				
Intervention (transfusion strategy) applied[2]			XXXXXXXXXXXXXXXX[2]				
Trigger event & transfusion details collected[2]			XXXXXXXXXXXXXXXX[2]				
Preoperative laboratory values[3]		X[3]					
Intraoperative laboratory values[4]			X[4]				
Postoperative laboratory values[5]				X[5]			
ECG[6]		X[6]		X[6]		X[6]	
Concomitant medications		X				X	
Clinical events			XXXXXXXXXXXXXX[8]			X[7]	
EQ-5D-3L		X		X	X	X	
Health economics questionnaire					X		
Routine data linkage							X

[1]*Women of childbearing potential.*

[2]*All protocol defined "trigger events" and all red cell transfusions will be recorded in the eCRF from the start of the index surgical procedure until hospital discharge, as well as the pre- and post-event/transfusion Hb, times, and values. All nonred cell transfusions administered during the index hospitalisation period will be reported in the eCRF.*

[3]*Hb, haematocrit, platelets, INR, aPTT, fibrinogen, creatinine, and CK-MB or troponin (preferred).*

[4]*Lowest Hb (pre/during CPB and chest closure), lowest HCT (pre/during CPB and chest closure), lowest arterial and mixed venous pO2 (pre/during CPB and chest closure), lowest arterial and mixed venous O2 saturation (pre/during CPB and chest closure), lowest cardiac index (pre-CPB and chest closure) if measured, minimum pump flow (during-CPB).*

[5]*Hb will be assessed on postoperative days 1, 2, 5±2, and 11±3 while in hospital. Hb measurements that are done for clinical purposes will be collected, if more than one Hb is measured on a particular day, the lowest value for that day will be recorded in the eCRF. Any patient who is transfused is required to have a pre- and post- transfusion Hb measurement. CK-MB or troponin (preferred) is required to be assessed on the first postoperative day, 24 hours after the end of surgery. Serum creatinine is required to be measured on postoperative days 1, 2, 3 and 5 and otherwise as clinically indicated. Other laboratory values will be performed as clinically indicated or as per local guidelines and collected in the eCRF up to hospital discharge/postoperative day 28: HCT, platelets (within 2 hours of chest closure), INR, aPTT and fibrinogen (within 2 hours of chest closure), CK-MB or troponin (preferred), arterial and mixed venous O2 saturation, arterial and mixed venous pO2.*

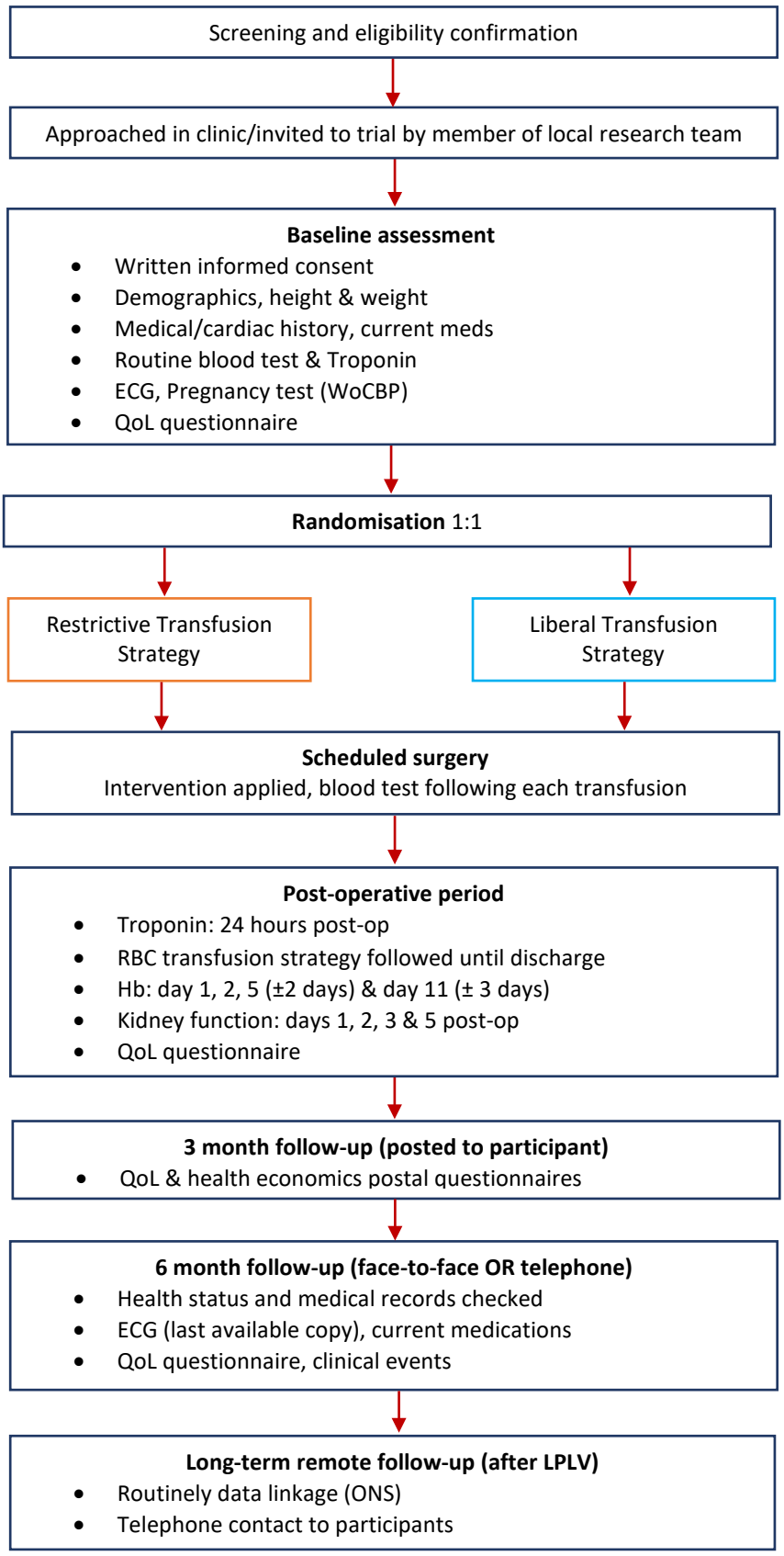
[6]*A 12-lead ECG will be performed preoperatively, on the day after surgery and on day 4-6 postoperatively or at hospital discharge, whichever comes first. We will also collect the last ECG performed for clinical purposes up to the 6 month follow-up visit.*

[7]*Includes routine oral medication at baseline and follow-up, anti-fibrinolytic agents, vasoactive medications and type and volume of IV fluid administered for the intraoperative and postoperative periods.*

[8]*Clinical events from the start of surgery until hospital discharge or postoperative day 28, whichever comes first. The following clinical events will be assessed through review of the patient medical records/chart, and reported in the eCRF from the start of the index cardiac surgery until discharge or postoperative day 28, whichever comes first. All definitions are standard definitions. (36, 40, 41) At 6 months, the following clinical outcomes will be collected based on a follow-up visit or access to ONS data: All-cause mortality, MI, new onset renal failure requiring dialysis, stroke, surgical or nonsurgical coronary revascularisation, COVID-19 test result (if done for clinical purposes).*

[9]*Includes ER visits and hospital re-admissions.*

24.2 Trial flow chart



24.3 Amendment History

Amendment no.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	2.0	16 August 2024	Claire Smith	Amendment to the progression criteria (section 10.2); for NIHR progression trials it is more common for the amber criteria to be 75% of the green criteria. Amendment to Informed Consent (section 14.1), to state no minimum time required to consider the PIS prior to consent in view of the often emergency/urgent requirements in cardiac surgery. Introduction of video/telephone consent, (section 14.1), which may also be obtained where necessary and as per local trust policy, for which the new document Video/Telephone Consent Form will be completed by the clinician/researcher and the participant. Typo correction to the schedule of events table (section 24.1); clinical events now include the superscript to match the description below the table. Minor amendment to the ICF with the addition of 2 boxes to the participant ID allowing adequate space.