The PASPORT Trial

	NAME	TITLE	SIGNATURE	DATE
Author	Lauren Scott Gemma Clayton	Medical statisticians		
Authoriser	Chris Rogers	Co-head of CTEU		

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List of abbreviations

Acronym	Details
AIC	Akaike information criterion
AKIN	Acute Kidney Injury Network
ARDS	Acute respiratory distress syndrome
AVLT	Auditory Verbal Learning Test
AFT	Accelerated failure time
BIC	Bayesian information criterion
CABG	Coronary artery bypass graft
CI	Confidence interval
COWAT	Controlled Oral Word Association Test
CPB	Cardiopulmonary bypass
CRF	Case report form
CVA	Cerebrovascular accident (stroke)
EQ5D	EuroQol five-dimension scale
FFP	Fresh Frozen Plasma
GHQ	General health questionnaire
GM	Geometric mean
GMR	Geometric mean ratio
HAD	Hospital anxiety and depression scale
HCT	Haematocrit
HDU	High dependency unit
HR	Hazard ratio
ICU	Intensive care unit
IQR	Inter quartile range
ITT	Intention to treat
MAR	Missing at random
MD	Mean difference
NIRS	Near Infra-Red Spectrometry

Acronym	Details
OR	Odds ratio
RBC	Red blood cells
RCT	Randomised controlled trial
SAP	Statistical analysis plan
SD	Standard deviation
SAE	Serious adverse event
SIRS	Systemic inflammatory response syndrome
STEMI	ST-elevation myocardial infarction
TIA	Transient Ischaemic Attack
TITRE2	A multi-centre randomised controlled trial of Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery
WAIS-R	Wechsler Adult Intelligence Scale- Revised

1. INTRODUCTION TO SAP

1.1 Scope

The PASPORT trial aims to recruit 200 patients. This statistical analysis plan (SAP) details information regarding the statistical analysis of the completed PASPORT trial and covers all analyses of trial data outlined in the study protocol, with the exception of the health economic analyses.

1.2 Editorial changes

Any changes made to this SAP after approval must be clearly justified and documented as an amendment at the end of this document. The SAP should then be re-approved.

1.3 SAP document approval

The trial statistician should authorise this document.

1.4 Skeleton tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the study (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in **Appendix A** of this document, and are intended as a guide for trial reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may differ. However the content should be consistent with **Appendix A.**

2. STUDY BACKGROUND AND OBJECTIVES

2.1 Study background

The PASPORT trial is a multi-centre blinded randomised controlled trial (RCT) to compare generic and patient-specific algorithms for optimising tissue oxygenation during CPB in adult cardiac surgery patients. Centres include Bristol, Leicester and Hull.

Compared to the generic algorithm (including a haematocrit transfusion threshold of 23), we hypothesise that the patient-specific, goal-directed algorithm (based on optimising regional cerebral oxygen saturation), combined with a pre-specified "restrictive" haematocrit transfusion threshold of 18, will result in fewer RBC transfusions and will reduce complications arising from unnecessary transfusion and from low oxygen levels during CPB.

2.2 Study objectives

A. To compare the effects of the patient-specific, goal-directed, algorithm versus the generic algorithm in terms of cognitive function and post-operative infectious complications.

B. To compare the effects of the patient-specific, goal-directed algorithm versus the generic algorithm with respect to a range of secondary outcomes.

C. To estimate the cost-effectiveness of the patient-specific, goal-directed algorithm versus the generic algorithm and describe this in terms of cost-effectiveness acceptability curve.

Note objective C is not covered in this SAP.

2.3 Primary outcome

The patient-specific algorithm is designed both to maintain cerebral oxygen delivery better, and to reduce the likelihood of a patient having an unnecessary RBC transfusion, compared to the generic algorithm. Therefore, there are 'co-primary' outcomes designed to measure both hypothesised benefits of the patient-specific algorithm.

We will measure **cognitive function** three months after surgery, and **infectious complications** during the first three months after surgery. These will be measured to determine whether the patient-specific algorithm (designed to optimise cerebral oxygenation and restrict transfusion) will improve cognitive outcomes, and reduce infectious complications (a potential risk of unnecessary transfusion), compared to current practice (where cerebral oxygenation monitoring is not implemented and a generic transfusion threshold is used).

2.3.1 Cognitive function

Cognitive function will be assessed by a qualified examiner blinded to treatment allocation preoperatively, on or between four and seven days post-operatively and again at three months. Recommended cognitive domains will be tested as follows (tests will be performed in a fixed order):

- **Attention:** First trial of the AVLT, Sustained and divided attention: Trail- Making Test parts A and B [1,3]
- **Verbal memory:** Rey Auditory Verbal Learning Test (AVLT) [1,2]
- **Visuo-spatial:** Block Design from the Wechsler Adult Intelligence Scale- Revised (WAIS-R) test [4]
- **Psychomotor speed:** Digit Symbol Test from the Wechsler Adult Intelligence Scale–Revised (WAIS-R) test [4]
- **Executive function/Verbal fluency:** Controlled Oral Word Association Test (COWAT) [5].
- **Motor coordination:** Grooved Pegboard Test, dominant and non-dominant hand [1]

To help interpret the cognitive function data, the following assessments related to the cognitive testing will be carried out for all participants:

- The Wechsler Test of Adult Reading will provide a measure of intellectual ability [6], preoperatively only.
- Documentation of medications known to interfere with neuropsychological functions (including hypnotics, sedatives, neuroleptics, anxiolytics, antidepressants, and β-blockers) preoperatively, 4-7 days post-operatively and three months post-operatively.
- Assessment of patient's current mental health using the General Health Questionnaire (GHQ-30) and Hospital Anxiety and Depression Scale (HAD) [7] preoperatively, 4-7 days post-operatively and three months post-operatively, to take into account the potential interaction between post-operative cognition and mood.

2.3.2 Infectious complications

Serious infectious events will be defined by:

Infectious events	***Definition / method of verification***
Sepsis	Defined by the following two conditions, both of which must be satisfied for sepsis to be documented: (a) Antibiotic treatment for suspected infection, ***and*** (b) The presence of SIRS[1] within 24 hours prior to start of antibiotic treatment
Wound infection	ASEPSIS score >20; sternum, leg and arm (if applicable). Wounds will be assessed at least once during a participant's hospital stay and details of the ASEPSIS assessment added to the study CRF. A questionnaire will be administered at 3 months to identify wound infections arising after discharge.

Sepsis occurring post-discharge will only contribute to the primary outcome if the event results in admission to hospital or death. A cumulative infection score will be calculated by supplementing data on wound infections (the ASEPSIS score that describes signs and symptoms of wound infection on a continuous scale), with data describing the severity of sepsis. We are developing this score with data from our RCT of a "restrictive" versus "standard" generic post-operative transfusion threshold (TITRe2) (see section 2.5).

2.4 Secondary outcomes

Data will also be collected to characterise the following secondary outcomes at three months (unless otherwise stated):

1) Units of RBC and other blood components transfused: the number of units of RBC and other blood components transfused during the operative period and post-operative hospital stay will be recorded

2) Cerebral oxygenation during the operative period: NIRS readings will be recorded for both groups for comparison. Monitoring will start before pre-oxygenation and anaesthetic induction and continue until the patient leaves theatre.

3) Oxygen delivery and utilisation during CPB: serial measurements of oxygen delivery (arterial) and utilisation will be collected from the clinical perfusion record.

[1] SIRS - systemic inflammatory response syndrome. SIRS is central to the diagnosis of infective complications. It will be defined as ≥2 of the following conditions: temperature >38^{o}C or <36^{o}C; heart rate >90 beats/minute; respiratory rate >20 breaths/min or $PaCO_2$ <32 mm Hg or $PaCO_2$ <4.3 kPa; WBC count >12,000/mm^3 or <4,000/mm^3. Blood test results and temperature will be classified using standard reference ranges.

4) EuroQol EQ5D: will be assessed at baseline and at six weeks and three months after surgery.

5) Length of ICU / HDU stay

6) Length of hospital stay

7) Clinical outcomes, defined as:

(a) Stroke (validated by CT scanning); blinded assessment of brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit (defined as deficit in motor, sensory or co-ordination functions);

(b) ST elevation myocardial infarction accompanied by troponin > 5 ng / ml;

(c) Post-operative acute kidney injury (defined as AKIN criteria stage 1, 2 or 3);

(d) Respiratory complications i.e. re-intubation, ventilation > 48 hours, tracheostomy, or acute respiratory distress syndrome (ARDS).

8) Cumulative resource use, cost and cost-effectiveness (not included in this SAP)

9) All-cause mortality within 30 days of surgery

10) Biochemical markers of organ injury:

The following will be measured from venous blood samples taken preoperatively, on return to ITU, and 6 hours, 24, 48 and 96 hours post-operatively. The use of these markers has been described previously:

(a) S100 / 100B (brain);

(b) Troponin I or T (heart);

(c) Creatinine clearance (derived from serum creatinine) (kidney);

(d) Interleukins (systemic inflammation).

The following will be measured from urine collected for over a 3 hour period (one sample taken preoperatively, and three samples taken over the first two post-operative days);

(e) Urinary creatinine and electrolytes, and urinary microalbumin, NGAL, IL18, LFABP, KIM-1 [8,9], alpha- and pi- glutathione-S-transferase (markers of tubular and glomerular renal injury)

11) Compliance with transfusion protocol:

Data will be collected for all patients during surgery to characterise compliance with the randomly assigned transfusion protocols. Haematocrit is measured at regular intervals during surgery and in cardiac ICU and all of these data will be collected. When a transfusion decision is made which is inconsistent with the allocated protocol, the attending doctor will be required to explain the decision and this will be documented on the CRF.

2.5 Changes to the study objectives during the course of the study

It states in the protocol that as part of the primary outcome, an infection score will be derived based on work in the TITRe2 trial. The results from the TITRe2 trial (n=2007) suggest that infection rates will be similar in the two groups and that serious infections will be few [10]. In light of these findings an infection score has not been developed. Additionally, the infection rates are expected to be low, (approx. 20% sepsis and 5% asepsis in TITRe2 trial). Therefore a binary infection indicator will be derived to include patients who experience sepsis and/or asepsis. The number of infections and number of sites infected will also be described as a secondary outcome; the primary outcome will be based on neuro-cognitive outcomes only.

Alpha and pi- glutathione-S-transferase (markers of tubular and glomerular renal injury) have been excluded from the analysis as the ELISA for each of these respectively did not work and the results should be considered meaningless. This was fed back to the manufacturer.

3. STUDY POPULATION

The study population consists of all patients aged 16 years and over undergoing valve or combined CABG and valve surgery at the Bristol Royal Infirmary, Glenfield Hospital or Castle Hill Hospital. For specific exclusion criteria see section 5.2**.**

The trial originally planned to recruit 150 patients. This was increased to 200 patients due to lower correlations between repeated measures of cognitive outcomes than expected, and higher loss to follow up than expected for the three month cognitive assessments in the early stages of the trial.

3.1 Flow of participants

The duration of follow-up in the trial is three months after surgery. After discharge from hospital, follow-up data will be collected as follows:

- Cognitive function and related assessments, and infectious complications will be assessed at a follow-up visit at three months.
- EuroQol EQ5D will be assessed at six weeks (via postal questionnaire) and at three months (at the follow-up visit).

If the distribution of timings is similar for both groups then all data will be included. If the distribution differs significantly ($p<0.05$), then pre-defined windows will be used. The windows will be chosen to make maximal use of the data, excluding extreme outliers. Any observations excluded will be described. Participant flow will be described via a flowchart (**Figure F1**).

3.2 Randomisation

Patients are randomly assigned to the two treatment groups in a 1:1 ratio using stratification to achieve balance across centres and type of surgery (valve or CABG and valve). Random allocations are generated by computer once the relevant baseline data (information to identify the patient and the type of surgery) have been entered into the system).

3.3 Protocol deviations

The following types of protocol deviation will be considered:

3.3.1 Eligibility

- Patient did not meet the study eligibility criteria but was treated in the study.
- Patient did not receive trial intervention.

3.3.2 Transfusion threshold adherence

- Patient in the conventional group received transfusion(s) when HCT is above 23.
- Patient in the conventional group did not receive a transfusion when HCT dropped below 23.
- Patient in the patient-specific group received transfusion(s) when HCT is above 18 and other parts of the Murkin protocol have not been attempted first.
- Patient did not receive a transfusion when HCT dropped below 18 (this applies to both groups).

3.3.3 Other non-adherence

- The Murkin protocol was not followed for patients in the patient-specific group when NIRS reading dropped below 70% of baseline or an absolute value of 50%.
- The Murkin algorithm was followed for a patient in the conventional group (i.e. patient crossed-over between treatment groups)

Note it may be possible for patients to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation (**Table T1**) with full details given in separate listings (**Table T2**)

3.4 Withdrawals

Patients (or clinicians on their behalf) can withdraw from the study at any time post-randomisation (including prior to their surgery). In some cases patients may be happy for data collection to continue, and therefore such patients will be included in the study analyses on an intention to treat (ITT) basis, see **section 3.5**.

Data on all withdrawals is captured on a specific case report form (CRF), and will be tabulated by treatment allocation (**Table T3**).

3.5 Analysis population

The analysis population consists of all randomised patients excluding:

- Patients who died or withdrew after randomisation but prior to surgery, because surgery did not take place.
- Patient withdrawals at any time who were unwilling for data collected to be used

The main trial analyses will be performed on an intention to treat (ITT) basis.

3.6 Safety population

The safety population consists of the same patients as the analysis population with the addition of any patients who died after randomisation but prior to surgery. Safety data will be presented on an ITT basis for consistency, as the study outcomes include safety outcomes (e.g. sepsis/asepsis). Safety outcomes by treatment received (where different from treatment allocated) will be included as footnotes.

4. DERIVATIONS

4.1 Primary outcomes: cognitive function

The primary outcome is neurocognitive data in which six dimensions will be assessed and a summary score for each derived: Attention, verbal memory, psychomotor speed, verbal fluency and visual motor coordination.

COGNITIVE FUNCTION
(assessed pre-operatively, and 5 days and 3 months post-op)
Scaled/standard scores will be used throughout

1. Attention - TRAIL MAKING

The patient draws lines to connect both the numbers and letters in ascending order to form a trail and this is then timed in seconds.

Task B score will be reported – no derivation required.
Interpretation: The lower the score (in seconds), the better a patient's attention.

2. Verbal memory - RAVLT

Trial 6 is the recall trial in which patients must recall as many words as they can from the first 5 learning trials after having an interference trial.

Standard scores (adjusted for age) will be reported. No derivation required – recorded directly on CRF.

Interpretation: The higher the score, the better a patient's verbal memory.

3. Visuo-spatial skills - WAIS III (Wechsler)

Block design: The patient has to copy designs shown on paper using a set of blocks.

Scaled scores (adjusted for age) will be reported. No derivation required.

Interpretation: The higher the score, the better a patient's visuo-spatial skills. Low scores are indicative of brain insult and those with dementia.

4. Psychomotor speed - WAIS III (Wechsler)

Digital symbol coding: Patients had to copy symbols on a piece of paper and had a maximum of 2 minutes.

Scaled scores (adjusted for age) will be reported. No derivation required.

Interpretation: The higher the score, the better a patient's psychomotor speed. Low scores are indicative of brain insult and those with dementia.

5. Verbal fluency - MULTILINGUAL APHASIA (COWAT)

Patients come up with a list of as many words they can think of in a max of 1 minute, not including names/proper nouns.

An overall score, adjusted for years of education and age, will be derived. The appropriate number from the table below will be added to the raw score.

Interpretation: The higher the score, the better a patient's verbal fluency.

6. Visual motor coordination - PEG BOARD

The time it takes to fill up a peg board from left to right. This is done using both a patient's dominant and non-dominant hand.

The dominant hand will be used – no derivation required.

Interpretation: The lower the score (in seconds), the better a patient's visual motor coordination.

Multilingual aphasia (COWAT) adjustment

	Age		
Years in education	25-54	55-59	60-69
<9	8	10	12
9-11	5	7	9
12-15	3	4	6
16+	0	1	3

4.2 Secondary outcomes

The secondary outcome variables will be derived as follows:

	New variable	Rules
1	**Units of RBC and other blood components transfused: the number of units of RBC and other blood components transfused during the operative period and post-operative hospital stay will be recorded.**	
	RBC units transfused intra-op	= Total number of intra-op RBC units listed on CRF C6 if any intra-op transfusions of RBC=yes =0 if any intra-op transfusions of RBC=no Else missing
	RBC units transfused post-op	= Total number of post-op RBC units listed on CRF D10 if 'any post-op transfusions of RBC'=yes =0 if 'any post-op transfusions of RBC'=no Else missing
	Any FFP	**YES** if intra-op FFP≥1 OR post-op FFP≥1 **NO** if intra-op FFP=0 AND post-op FFP=0 Else missing
	Any platelets	**YES** if intra-op platelets≥1 OR post-op platelets ≥1 **NO** if intra-op platelets =0 AND post-op platelets =0 Else missing
	Any cryoprecipitates	**YES** if intra-op cryoprecipitates≥1 OR post-op cryoprecipitates ≥1 **NO** if intra-op cryoprecipitates =0 AND post-op cryoprecipitates =0 Else missing
	Any activated factor VII	**YES** if intra-op activated factor VII =yes OR post-op activated factor VII =yes **NO** if intra-op activated factor VII =no AND post-op activated factor VII =no Else missing
2	**Cerebral oxygenation during the operative period: NIRS readings will be recorded for both groups for comparison. Monitoring will start before pre-oxygenation and anaesthetic induction and continue until the patient leaves theatre.**	
	Cerebral oxygenation during the operative period (NIRS)	Operative period: Time of operation end – start NIRS was applied. Cerebral oxygen:

	New variable	Rules
		Area under the curve (of the average of the left and right oximetry measures) will be used to summarise multiple measurements per patient. The minimum cerebral oxygen during the operative period will be descriptively summarised.
3	**Oxygen delivery and utilisation during CPB: serial measurements of oxygen delivery and utilisation will be collected from the clinical perfusion record.**	
	Oxygen deliver n during CPB	CPB :(End of CPB – start of CPB). Serial measurements of arterial oxygen saturation (CRF C3) measured at five fixed time points (Start of CPB, 20 minutes after start of CPB, 40 minutes after start of CPB, pre-warm and pre-wean). Oxygen delivery: $= CO*CaO_2 * 10$ $= CO*[(Hb*1.39*SaO_2)+(PaO_2*0.003)] * 10$ $= CO*[(Hb*1.39*SaO_2)+(PaO_2*0.003)] * 10$ $= CO*[((Hct*0.333)*1.39*SaO_2)+(PaO_2*0.003)]*10$ $= ml\ O_2/min$ where CO=Cardiac output – pump flow – l/min where SaO_2=arterial oxygen saturation - % where Hb=Hct*0.333
	Oxygen utilisation during CPB	$= CO*(CaO_2 – CVO_2)*10$ $= CO*(Arterial – venous\ O_2\ difference)*10$ $= ml\ O_2/min$ where CVO2= Hb*1.39*SVO2 where Hb=Hct*0.333 where SVO2=venous oxygen saturation - %
4	**EuroQol EQ5D: will be assessed at baseline and at six weeks and three months after surgery.**	
	EQ5D single summary index score	Five digit 'state' score is derived as: 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score. Each state score is then assigned a single summary index score according to reference scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health.
	EQ5Dstate score	= 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score.
	EQ5D single summary utility score	Each five digit state score will be assigned a single summary utility score according to standard scales (this can also be calculated using the eq5d command in Stata). These utility scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health. If any of the five components of the state score is missing, the overall score will be missing.

	New variable	Rules	
5	**Length of ICU / HDU stay**		
	CICU/ HDU length of stay (hours)	Duration of initial cardiac intensive care unit (CICU/HDU) stay: Earliest of (ward admission date/time, discharge date) –(CICU/HDU admission date/time) * 24 If readmitted to CIC/HDU= yes then the readmissions should be calculated and added to the above time as follows: (Date/time of next admission following relevant readmission) –(Date/time of CICU/HDU readmission) * 24 Note. As discharge does not have a time associated, midday will be assumed for discharges and SAE onset time will be used if patient died.	
	CICU/HDU length of stay censoring variable (patient died in CICU)	**YES** if patient died during ICU/HDU stay **NO** otherwise	
	Duration of ward stay (hours)	Calculated as the sum of the following components: Duration of initial ward stay: Earliest of (Date/time of next admission following ward admission, discharge date) – (Ward admission date/time) * 24 Duration of any readmissions to ward: (Date/time of next admission following ward readmission) –Date/time of ward readmission) * 24	
	Ward stay censor variable	**YES** if patient died during ward stay **NO** otherwise	
6	**Length of hospital stay**		
	Total length of stay (days)	Date of discharge – operation date	
	Total length of stay censoring variable (patient died in hospital)	**YES** if patient died during hospital stay **NO** otherwise	
	In hospital death indicator	**YES** if discharge destination= patient died **NO** otherwise	
7	**Clinical outcomes, defined as**		
(a)	**Infection**	In-hospital	3 month follow up
	Sepsis	**YES**, if patient had at least one antibiotic course in hospital with *SIRS total*[1]≥2 **NO**, if: – Patient was not given any antibiotics in their post-operative stay (excluding prophylaxis), OR – For all courses of antibiotics: ➢ *SIRS total*=0 and *SIRS missing*[1]≤1 ➢ *SIRS total*=1 and *SIRS missing*=0 **MISSING**, otherwise	**YES**, if a readmission has been recorded on the three month follow up questionnaire and date of admission is within 3 calendar months of operation date and (either antibiotics for infection=yes or an infection has been reported at follow up) **NO**, if the above conditions are not met and patient completed 3 month follow-up questionnaire/ died **MISSING**, otherwise

	New variable	Rules	
	Asepsis[2]	**YES**, If at least one wound with in-hospital asepsis score >20 **NO**, if all scored wounds have in-hospital asepsis score ≤ 20, and no wounds have missing in-hospital asepsis scores **MISSING**, otherwise	**YES**, if at least one wound with post-discharge asepsis score >20 **NO**, if all scored wounds have post-discharge asepsis score ≤ 20, and no wounds have missing post-discharge asepsis scores **MISSING**, otherwise
	Any infection	**YES:** If sepsis in-hospital=yes OR sepsis at 3 month follow up=yes OR asepsis in-hospital =yes OR asepsis at 3 month follow up =yes; **NO:** If sepsis in-hospital=no AND sepsis at 3 month follow up=no AND asepsis in-hospital =no AND asepsis at 3 month follow up =no; **MISSING**, otherwise	
(b)	Stroke (validated by CT scanning); blinded assessment of brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit (defined as deficit in motor, sensory or co-ordination functions)		
	Stroke	**YES**, if on CRF D8: - Stroke=Yes, AND - Date/time of stroke≥date/time of randomisation, AND - Verified by CT=Yes or verified by MRI=Yes, or verification criteria missing **NO**, if: - Stroke=No, OR - Stroke=Yes and date/time of stroke<date/time of randomisation, OR - Stroke=Yes and verified by CT=No and verified by MRI=No **MISSING**, otherwise **AFTER DISCHARGE: **YES**, if a readmission form (X1) has been completed with: - Stroke=Yes, AND - Date of admission is within 3 months of operation, AND - Verified by CT=Yes or verified by MRI=Yes, or verification criteria missing **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise	
(c)	ST elevation myocardial infarction accompanied by troponin > 300 ng / L		
	STEMI	**YES** if - ST elevation myocardial infarction = Yes AND - (troponin T > 300 ng / l) OR troponin T missing and an ECG has been performed with either new Q's or new ST depression in 2 contiguous leads) AND - Date/time of STEMI ≥date/time of randomisation **NO** if ST elevation myocardial infarction = No OR	

	New variable	Rules
		– Date/time of STEMI <date/time of randomisation OR – (ST elevation myocardial infarction = Yes AND troponin T ≤ 300 ng /l) OR troponin T is missing and an ECG has not been performed OR an ECG has been performed and there are no new Q's or new ST depression in 2 contiguous leads For Leicester Troponin I is measured and the limit defined as >400 ng/l Missing otherwise
(d)	Post-operative acute kidney injury (defined as AKIN criteria stage 1, 2 or 3	
	AKI	**YES**, if on CRF D7: – AKI=Yes, AND – Date/time of AKI ≥date/time of randomisation, AND – Acute Kidney Injury Network (AKIN) criteria stage 1, 2 or 3=Yes or missing **NO**, if: – AKI=No, OR – AKI=Yes and date/time of AKI<date/time of randomisation, OR – AKI=Yes and AKIN criteria stage 1, 2 or 3=No **MISSING**, otherwise **AFTER DISCHARGE: **YES**, if a readmission form (X1) has been completed with: – AKI=Yes, AND – Date of admission is within 3 months of operation, AND – AKIN criteria stage 1, 2 or 3=Yes or missing **NO**, if the above conditions are not met and patient completed 3 month follow-up/died **MISSING**, otherwise
(e)	Respiratory complications i.e. re-intubation, ventilation > 48 hours, tracheostomy, or acute respiratory distress syndrome (ARDS)	
	Respiratory complications	**Total ventilation time (hours):** ([extubation date + extubation time] – [operation end date + operation end time])*24 + ([first re-extubation date + first re-extubation time] – [first re-intubation date + first re-intubation time])*24 + any additional periods of ventilation **Respiratory complications:** **YES** if re-intubation=yes OR ventilation>48 hours OR tracheostomy=yes OR ARDS=yes **NO** if re-intubation=no AND ventilation≤48 hours AND tracheostomy=no AND ARDS=no Otherwise missing
8	**Cumulative resource use, cost and cost-effectiveness (not covered in this SAP)**	
9	**All-cause mortality within 30 days of surgery**	

	New variable	Rules
	Death within 30 days of surgery	**YES** if patient had an SAE AND reason for SAE=resulted in death AND (death date-operation date)≤30 days **NO** if patient didn't have an SAE OR (patient did have SAE(s) but reason for SAE(s) is not resulted in death) OR (patient had an SAE and reason for SAE=resulted in death but (death date-operation date)>30 days)
10	**Biochemical markers of organ injury**	
(c)	Creatinine clearance (derived from serum creatinine) (kidney)	=[(urinary creatinine (mg/dl))/(serum creatinine (mg/dl)]*[(volume of urine (ml)/(collection period (min)] N.B Converison of units is required: 1 mg/dl = µmols/l / 88.4 1 mg/dl=mmol/l * 18.018

Notes:
[1] For stroke, STEMI, AKI and ARDS the event will default to NO if the documentary evidence does not support that the event occurred.

4.3 Protocol deviations

The following protocol deviations require derivations to be made:

New variable	Rules
Murkin protocol is defined as having been actioned if any of the following criteria are met	**YES** if any of the following are acted upon (CRF C5): – CPP<60mmHg and metaraminol was administered – No effect and CPP<80 mmHg and metaraminol was administered – $PaCO_2$<35 mmHg and gas flow reduced – FiO_2<0.6 and FiO_2 was raised – No effect and FiO_2<1.0 and FiO_2 was raised to 1.0 – Decrease in cerebral metabolic rate and increase of propofol or increase in pump flow to maximum tolerated by oxygenator – Target is not met and Hct 18-23 and 1 unit of RBC was transfused **NO** otherwise
Eligibility	
Ineligible but treated	**YES** if eligibility criteria not met and patient treated in the trial **NO** otherwise
Did not receive any trial intervention	**YES** if eligibility criteria met and patient treated in the trial but did receive any trial intervention **NO** otherwise
Transfusion threshold adherence	
Transfused above HCT 23 in conventional group	**YES** (if an RBC transfusion is given in the period when HCT>23) and (patient is in the conventional group) **NO** otherwise
Did not receive a transfusion when HCT dropped below 23 (conventional group)	**YES** if (an RBC transfusion has not been given in a period after HCT<23) and (patient is in the conventional group) **NO** otherwise
Transfused above HCT 18 in patient-specific group without Murkin protocol being followed	**YES** if (an RBC transfusion has been given in the period when HCT>18) and (the Murkin protocol has not been followed) and (patient is in the patient-specific group) **NO** otherwise
Did not receive a transfusion when HCT dropped below 18 (patient-specific and conventional group)	**YES** if (an RBC transfusion has not been given in the period after HCT<18) **NO** otherwise
Other non-adherence	
Murkin protocol not followed when NIRS reading drops below 70% of baseline or absolute value of 50%	**YES** if none of the Murkin protocol has been actioned and NIRS reading drops below 70% of baseline or absolute value of 50% and patient is in the patient-specific group **NO** otherwise

Murkin algorithm followed for patient in conventional group i.e. patient crossed-over between treatment groups	**YES** if any of the Murkin protocol has been actioned and patient is in the conventional group **NO** otherwise

4.4 Other variables

Details for any other variables which are derived for use in any other figures or tables are given below:

New variable	Rules
Reason for exclusion from trial	If any eligibility criteria not met; then = Ineligible If all eligibility criteria met but patient not approached; then = Not approached If all eligibility criteria met, and patient was approached but did not consent; then = Did not consent Otherwise = Other
Age	(Operation date – date of birth)/365.25
BMI	(Weight (kg) / Height (cm)^2) * 10,000
Operation length (hours)	(Operation end time - start time)*24
EuroSCORE	For all patients start with Euroscore of zero and add points according to the following rules: – Age: <60=0, 60-64=1, 65-69=2, 70-74=3, 75-79=4, 80-84=5, 85-90=6, >90=7 – Sex: Male=0, Female=1 – Chronic pulmonary disease: add 1 – Extracardiac arteriopathy, neurological dysfunction, Creatinine >200 µmol/l, unstable angina, pulmonary hypertension, recent MI, surgery other than isolated CABG: add 2 for each – Previous cardiac surgery, active endocarditis, critical preoperative state, surgery on thoracic aorta: add 3 for each – Postinfarct septal rupture: add 4 LV function: Good (>50%)=0, Mod (30-50%)=1, Poor (<30%)=3
Operative duration (minutes)	=Operation end time – operation start time
Cross-clamp time (minutes)	=Time cross-clamp released – time cross-clamp applied
Total ventilation time (hours)	Calculated as the sum of the following components: ([extubation date +extubation time] – [operation end date + operation end time])*24 + ([first re-extubation date + first re-extubation time] – [first re-intubation date + first re-intubation time]) + any additional periods of ventilation
Time between randomisation and previous MI (months)	Calculated as the sum of the following components: (year of operation – year of previous MI)*12 + month of operation – month of previous MI
MI within last 90 days	If previous MI = yes and time between randomisation and previous MI ≤ 3 months; then =Yes Otherwise = No
Time between randomisation and withdrawal (days)	(withdrawal date – randomisation date)
Medications known to interfere with neuropsychological functions	**YES:** if at least one of the medications listed (Hypnotics, Sedatives, Neuroleptics, Anxiolytics, Antidepressants, β-blockers) are yes **NO:** if all of the medications listed are no **MISSING:** otherwise
SAE's	
Serious adverse event maximum intensity	Maximum of intensity variable on initial SAE form and all follow-up SAE forms
SAE relatedness	Maximum (worst case scenario) of relatedness variable on initial SAE form and all follow-up SAE forms
SAE resolution date and time	SAE end date and time on final follow-up SAE form (or initial SAE form if no follow-up forms required)

New variable	Rules

Timing of SAE	If (SAE onset date + SAE onset time) < (operation date + operation start time); then = Pre-surgery
	If (operation date + operation start time) < (SAE onset date + SAE onset time) and SAE onset date ≤ date of discharge; then = Post-surgery but pre-discharge
	If SAE onset date > date of discharge; then = Post-discharge

Cardiac arrest	**YES:** If resuscitation (involving ventricular defibrillation/DC shock) = yes & chest re-opening=yes & external/internal cardiac massage=yes; **NO:** if resuscitation = no; **MISSING:** otherwise
Haemodynamic support	**YES:** If [Inotropes = yes OR Intra-aortic Balloon Pump (IABP) = yes OR Pulmonary artery catheter = yes OR Vasodilator = yes OR Low cardiac output = yes]; **NO:** if [Inotropes = no AND IABP = no AND Pulmonary artery catheter = no AND Vasodilator = no AND Low cardiac output = no]; **MISSING:** otherwise
Arrhythmias	**YES:** If [Supraventricular Tachycardia (SVT)/Atrial Fibrillation (AF) requiring treatment = yes OR Ventricular Fibrillation (VF)/Ventricular Tachycardia (VT) requiring treatment = yes OR New pacing = yes]; **NO:** if [SVT/AF requiring treatment = no AND VF/VT requiring treatment = no AND New pacing = no]; **MISSING:** otherwise
Pulmonary complications	**YES:** If [Re-intubation and ventilation = yes OR Tracheostomy = yes OR Mask Continuous Positive Airway Pressure (CPAP) = yes OR Acute Respiratory Distress Syndrome (ARDS) = yes OR Pneumothorax or effusion requiring drainage = yes]; **NO:** if [Re-intubation and ventilation = no AND Tracheostomy = no AND Mask CPAP = no AND ARDS = no AND Pneumothorax or effusion requiring drainage = no]; **MISSING:** otherwise
Thromboembolic complications	**YES:** if pulmonary embolus=Yes **NO:** if pulmonary embolus=No **MISSING:** otherwise
Renal complications	**YES:** if haemofiltration/dialysis=Yes **NO:** if haemofiltration/dialysis=No **MISSING:** otherwise
Gastrointestinal (GI) complications	**YES:** If [Peptic ulcer/GI bleed/perforation = yes OR Pancreatitis = yes OR Other GI complication = yes]; **NO:** if [Peptic ulcer/GI bleed/perforation = no AND Pancreatitis = no AND Other GI complication = no]; **MISSING:** Otherwise
Neurological complications	**YES:** If [Permanent stroke = yes OR Transient Ischaemic Attack (TIA) = yes]; **NO:** if [Permanent stroke = no AND TIA = no]; **MISSING:** Otherwise
Re-operation	**YES:** If re-operation is due to tamponade, bleeding, mediastinitis, cardiac arrest, low cardiac output or other cause; **NO:** Otherwise
Excess bleeding	**YES:** If bleeding is greater than or equal to 400ml/h for I hour or 200ml/h for 4 hours ; **NO:** Otherwise

New variable	Rules
Wound dehiscence	**YES:** If Wound dehiscence requiring rewiring or treatment = yes; **NO:** if Wound dehiscence requiring rewiring or treatment = no; **MISSING:** Otherwise
GHQ30	Sum of Likert scale scores (0-1-2-3) [11] across 30 questions giving a minimum of 0 and maximum of 90. For missing data, the standard procedure is to count omitted items as low scores (0). A high score represents a more severe condition. A threshold of 72 will be used to dichotomise the outcome into 'severe'/'non-severe' (≥72 = 'severe', <72 = 'non-severe').
HADS	The questionnaire features seven questions for anxiety and seven for depression. Each item is scored from 0-3. The scores from the seven questions are added to give a separate score for anxiety and depression; the maximum score for each is 21. A high score represents more anxiety/depression. A threshold of 8 will be used to dichotomise both scores [12]. For missing data, the score for a single missing item from a subscale is inferred by using the mean of the remaining six items. If more than one item is missing, then the subscale should be judged as invalid and cannot be used.

[1]SIRS elements are defined as:

- *Temperature: YES if >38°C or <36°C, NO if 36-38 °C, MISSING otherwise*
- *Heart rate: YES if >90 beats/minute, NO if ≤90 beats/minute, MISSING otherwise*
- *Respiration: YES if respiratory rate >20 breaths/min OR $PaCO_2$ <32 mm Hg or <4.3 kPa, NO if respiratory rate ≤20 breaths/min, MISSING otherwise*
- *White blood cell (WBC): YES if >12,000/mm^3 or <4,000/mm^3, NO if 4,000-12,000/mm^3, MISSING otherwise*

***SIRS total** = total of (temperature, heart rate, respiration, WBC), with YES=1, NO=0*
***SIRS missing** = number of missing elements of (temperature, heart rate, respiration, WBC)*
[2] For details of how to derive in-hospital and post-discharge asepsis scores see Appendix B.

5. STATISTICAL ANALYSES

5.1 Baseline data

Baseline (i.e. patient demography and past history) characteristics will be described by treatment group for patients in the analysis population. **Tables T4** to **T6** will be used as templates for this.

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given in **Tables T4** to **T6** are those we expect to use based on a-priori knowledge of the clinical measurements gained from previous studies. However, if distributional assumptions are not valid, changes will be made.

Any imbalances in the characteristics of the patients at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

5.2 Primary and secondary outcome data

5.2.1 Adjustment in models

The intention is to adjust all models for both stratification factors (centre and type of surgery) as fixed effects. Occasionally values of these variables may differ between the study database and the randomisation system; in this case inconsistent values will be queried and ultimately values from the study database will be used.

For rare binary outcomes, where the data are insufficient to allow estimation of regression coefficients for these stratification variables, the analyses will be unadjusted.

Analyses of the neurocognitive outcomes will be adjusted for reading ability at recruitment (Wechsler Test of Adult Reading), medication (any medication given vs no medication), GHQ-30 (≥72 vs <72), HADS-Anxiety (≥8 vs <8) and HADS-Depression (≥8 vs <8) measured pre-operatively, in addition to the stratification variables.

GHQ-30, HADs and medication data are also collected at 4-7 days and 3 months. The treatment effect will be estimated with and without the inclusion of these “updated” covariates in the model.

For continuous outcomes that are measured pre-operatively as well as post-operatively, pre-operative and postoperative values will be modelled jointly in preference to the pre-operative value being modelled as a covariate. Joint modelling will avoid the necessity to either exclude cases with missing pre-operative measures or to impute missing pre-operative values.

5.2.2 Descriptive analyses

The distribution of neurocognitive outcomes, for those with and without reading difficulties and with and without mental health issues will be described.

5.2.3 Analysis models

All outcomes listed in the study protocol will be presented as per the template tables **Table T7** to **T14** and **Figure F2 to F6.** General methods of presentation and assessing treatment effects are outlined below. For all treatment comparisons the generic algorithm group will be the reference group. Details specific to each outcome are described as appropriate.

Date type	Outcomes
Binary	RBC blood transfusions
	Clinical outcomes (stroke, STEMI, acute kidney injury and respiratory complications)
Continuous	Cerebral oxygenation during operation (NIRS)
Time to event	Duration of ITU stay
	Duration of hospital stay
	All-cause mortality within 30 days of surgery
Longitudinal	Quality of life (EQ5D)

	Cognitive functions (Primary outcome) Arterial oxygen delivery and utilisation during CPB Biomarkers of organ injury (S100/100B, troponin, creatinine clearance, Interleukins, urinary markers)

- **Binary outcomes** will be presented as numbers and percentages of patients in each treatment group. Outcomes will be compared between treatment groups using logistic regression. Treatment comparison estimates will be presented as adjusted odds ratios (OR) and 95% confidence intervals (95% CI). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome (with at least one event in each treatment group).

  For the presentation of transfusion outcomes see **Table T9** and **Figure F2**. Although the any transfusion vs. no transfusion will be compared, the number of units of RBC transfused will be described in each group (i.e. by the number of patients with 0, 1, 2, 3 and >3 transfusions).

- **Continuous outcomes** will be summarised by the mean and SD in each treatment group, if distributions are approximately normal. If distributions are non-normal, data may be summarised by the median and IQR or geometric mean (GM) if a logarithmic transformation provides an approximately normal distribution. Outcomes will be compared using linear regression. For untransformed data treatment, comparisons will be presented as adjusted differences in means with 95% CI, and for logarithmically transformed data as adjusted ratios of GMs with 95% CI.

- **Time to event outcomes** will be presented as medians and IQRs, estimated from survival modelling, and compared using adjusted Cox proportional hazards models. Therefore treatment comparisons will be presented as hazard ratios (HR) and 95% CI. The validity of the assumption of proportional hazards will be tested and, if this assumption is not met for treatment group, a Cox model with a time-dependent covariate (the interaction term between the treatment and the survival time) will be used. This type of model will allow the difference between the two groups to be estimated within discrete time periods. Models will be stratified by centre to allow for separate baseline hazard functions for each centre. If the proportional hazards assumption is not met, options such as stratification or fitting interaction terms will be explored. Patients who die will be censored at their time of death.

Outcome	Censor variable
Duration of post-randomisation ICU/HDU stay	Time of death in ICU/HDU
Duration of post-operative hospital stay	Time of death in hospital
All-cause mortality	Time of last follow-up (usually 3 months post-operation)

- **Continuous longitudinal outcomes** will be summarised as means and SDs (or medians and IQRs if distributions are skewed) at each time point. Outcomes will be compared using linear mixed effects methodology with the treatment group and study design variables (see **section 5.2.1**) fitted as fixed effects, and patient terms as random effects. Three approaches will be considered:

  a) Fitting time as a categorical variable (i.e. ignoring information on the actual time the measurement was taken) and investigating different variance/covariance structures to best allow for the correlation between measurements taken at different times for the same patient. Variance/covariance structures will be compared using likelihood ratio tests. If a time x treatment interaction term is statistically significant at the 10% level then separate treatment effect estimates at each time point will be presented. If the interaction is not statistically significant an overall treatment effect will be reported.

b) Fitting time as a continuous variable, with random intercepts (patient IDs) and slopes (time), to allow for different trajectories for different patients. This approach takes into account the actual times the measurements were taken. Quadratic time terms (e.g. time^2) will be included if appropriate, i.e. dependent on model diagnostic plots.

c) Fitting time as area under a curve. Adjusting for operation type will allow for individual patient profiles to be compared.

For outcomes assessed at specified time points (e.g. EQ5D) approach a) will be used. For NIRS c) will be used.

For both approaches b) and c) separate parameter estimates will be incorporated into models for: 1) the mean baseline response across both treatment groups and 2) at post-intervention time points for each treatment. This approach avoids the necessity to either exclude cases with missing baseline measures or to impute missing baseline values (see **section 5.2.1**). Treatment comparisons will be presented as adjusted differences in means with 95% CI, and for logarithmically transformed data as adjusted ratios of GMs with 95% CI.

Very low concentrations of biomarkers cannot be detected reliably from the assay (they are below the lower limit of detection, LLD). Therefore, any value less than the LLD will be treated as "<LLD" and not as a genuine reading. Methods of handling values below the LLD will be investigated and alternative methods will be used (e.g. replacing these with a value which is half the LLD, or estimating from a uniform distribution between a fixed lower value and the LLD or fitting a two part model for mixed discrete-continuous outcomes) depending on the number of values below the LLD.

Outcomes may also be presented graphically, if appropriate. For time to event outcomes this will usually consist of Kaplan-Meier survival curves. For continuous outcomes this may consist of graphs depicting estimated means (plus 95% CI or standard error) for each treatment group.

5.2.4 Statistical significance

For hypothesis tests two-tailed p-values<0.05 are considered statistically significant. The only exception to this is tests for interactions where a 10% threshold will be used as such tests have low power. Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing.

The study assesses multiple neurocognitive functions as part of the primary outcome however no adjustment is intended to be made for multiple testing (see Section 5.2.8). When interpreting the primary outcome results against the study hypotheses, if either all six dimensions or four out of six statistically significant at the 5% level we would suggest this gives evidence to support the study hypotheses. Any other combinations will be considered insufficient evidence for the study hypotheses.

5.2.5 Model assumptions

For all methods outlined, underlying assumptions will be checked using standard methods, e.g. residual plots, tests for proportional hazards, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and comments made in footnotes. Sensitivity analyses will be performed to examine the effect on the study's conclusions of excluding outlying observations; any change in the study's conclusions would be reported.

5.2.6 Subgroup analyses

Some laboratory markers (S100, IL6, IL8, NGAL, IL18, LFABP and KIM1) were only measured on a consecutive subgroup of patients. These are the only subgroup analyses planned.

5.2.7 Sensitivity analyses

No sensitivity analyses (other than assessing the impact of outliers, see section 5.2.4) are planned.

5.2.8 Missing data

In all tables missing data will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored.

- Missing predictors:
  - All potential predictors are preoperative measurements of continuous longitudinal outcomes, and due to the joint modelling approach described previously the handling of missing values for such data is considered in the context of missing longitudinal data (see below).
- Missing outcomes measured at one time point:
  - If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e. excluding cases with missing data).
  - If the proportion of missing data is between 5% and 15% conditional mean imputation methods will be used. This involves predicting the outcome from a regression model from (linearly related) covariate(s). These covariates will include the design variables, plus other potentially important covariates (e.g. age, gender, additive EuroSCORE).
  - If the proportion of missing data is above 15% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g. using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules.
- Missing longitudinal data:
  - For continuous data measured at multiple time points preoperative values will be modelled jointly with those measured postoperatively, as described previously, thereby allowing all cases with at least one observation to be included. If appropriate (the level of missingness is >20%) then any variables that are predictive of missingness will be identified, and if there is reason to suggest that an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured pre-operatively) then such variables will be adjusted for in the models of interest. These models can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.

5.2.9 Multiple testing

No formal adjustment will be made for multiple testing (see Section 5.2.3 for discussion in relation to primary outcomes). However as previously described formal statistical comparisons will not be made for outcomes with low event rates and only pre-specified subgroup analyses will be performed. Consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

5.3 Safety data

Adverse events occurring in the study period for all patients in the safety population will be tabulated as per **Table T15**.

Table T15 summarises expected adverse events listed in the study protocol, with events that meet the serious criteria[2] indicated. Such events are captured via the study CRFs. It also summarises

[2] An event is classified as serious if it meets one or more of the following criteria: a) resulted in death, b) was life threatening, c) resulted in persistent or significant disability/incapacity, d) prolonged an ongoing hospitalisation or resulted in hospitalisation

unexpected SAEs, i.e. events that are not listed in the study protocol that meet the serious criteria. Such events are captured via separate SAE report forms.

No formal comparisons between treatment groups will be made, as numbers of events are expected to be small.

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7. AMENDMENTS TO THE SAP

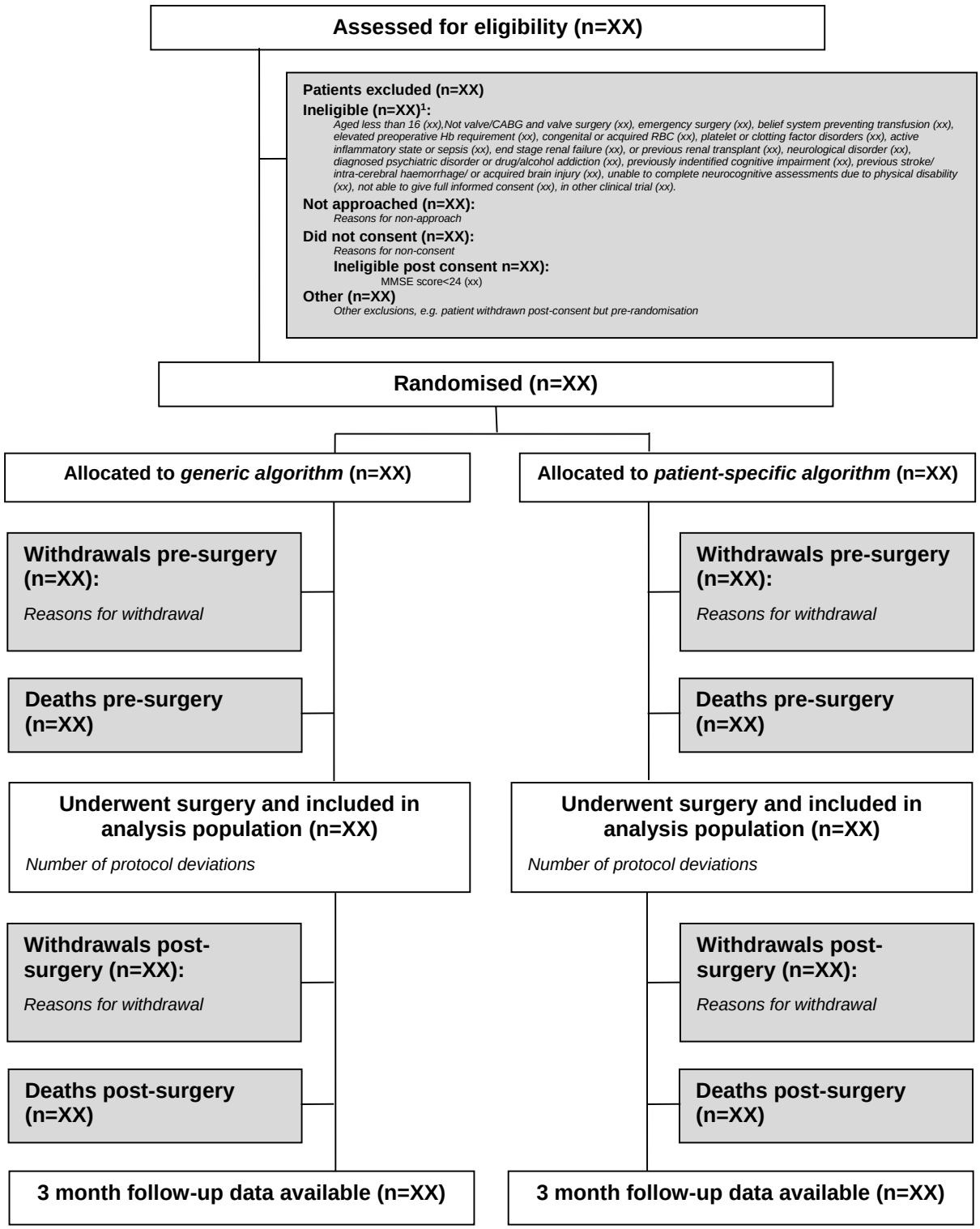
Previous version	Previous date	New version	New date	Brief summary of changes

APPENDIX A: SKELETON TABLES AND FIGURES

Section	Outputs	
Section 1 Population	***Tables, figures and listings detailing the study population***	
	Figure F1	*Flow of participants*
	Table T1	*Protocol deviations*
	Table T2	*Details of protocol deviations*
	Table T3	*Withdrawals*
Section 2 Baseline data	***Summary tables of demographic information***	
	Table T4	*Patient demography and past history*
	Table T5	*Intraoperative characteristics**
Section 3 Primary and secondary outcome data	***Summary data and treatment estimates for primary and secondary outcomes***	
	Table T6	*Post-operative characteristics (not listed as outcomes)**
	Table T7	*Primary outcome*
	Table T8	*Medications at 3 months*
	Table T9	*Secondary outcomes*
	Figure F2	*Secondary outcome: Transfusions*
	Figure F3	*Secondary outcome: Cerebral oxygenation during the operative period*
	Figure F4	*Secondary outcome: Mean oxygen delivery during CPB*
	Table T10	*Secondary outcomes: Biomarkers*
	Figure F5	*Secondary outcome: Kaplan-Meier estimates of time to hospital discharge*
	Table T11	*Secondary outcomes: categorical EQ5D outcomes*
	Table T12	*Secondary outcomes: continuous EQ5D outcomes*
	Table T13	*Secondary outcomes: categorical HADS and GHQ responses**
	Table T14	*Secondary outcomes: continuous HADS and GHQ responses categorised by thresholds*
Section 4 Safety data	**Summary tables and listings of all adverse events and serious adverse events**	
	Table T15	*Adverse events and serious adverse events both in-hospital and during trial follow-up*

**These are likely to be put in an appendix in the final publication*

Figure F1 Flow of participants



Notes:

[1] *Some patients may be ineligible for more than one reason*

Table T1 Protocol deviations

	Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
	Patients	%	Patients	%	Patients	%
ANY PROTOCOL DEVIATION						
Allocated treatment adherence						
Ineligible but treated						
Did not receive any intervention						
Transfusion threshold adherence						
Transfused above HCT 23 (conventional group)						
Transfused above HCT 18 without Murkin protocol being followed (patient-specific group)						
Did not receive a transfusion when HCT dropped below 23 (conventional group)						
Did not receive a transfusion when HCT dropped below 18						
Other non-adherence						
Murkin protocol not followed when NIRS reading drops below 70% of baseline or absolute value of 50%						
Murkin algorithm followed for patient in conventional group i.e patient crossed-over between treatment groups						

Table T2 Details of protocol deviations

Allocated treatment group	Centre	Further details (exact nature dependent upon type of deviation)

Table T3 Withdrawals

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=xx)	
		n	%	n	%	n	%
Any withdrawal							
Of those who withdrew:							
Time of withdrawal	Pre-op						
	Intra-op						
	Post-op						
Decision taken by	Patient						
	Clinician						
Reason for withdrawal	Reason 1						
	Reason 2						
	Reason 3						
	etc						

Table T4 Patient demography and past history

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
BASELINE CHARACTERISTICS							
Height	Mean(SD)						
Weight	Mean(SD)						
NHYA class	I						
	II						
	III						
	IV						
CSS class	Asymptomatic						
	I						
	II						
	III						
	IV						
ANGIOGRAM/ ECHO RESULTS							
LV function	Good (>50%)						
	Moderate (30-50%)						
	Poor<30%)						
>50% disease in left main stem							

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
Coronary disease, number of vessels	Single						
	Double						
	Triple						
	None						
	Not investigated						
BLOOD AND URINE							
Haemoglobin	Median (IQR)						
Haematocrit	Median (IQR)						
Platelets	Median (IQR)						
Creatinine value	Median (IQR)						
Urine output over 3 hours	Median (IQR)						
MEDICAL HISTORY							
Diabetes	Insulin						
	Oral						
	Diet						
	No						
Pacemaker	Permanent						
	Temporary						
	No						
Heart rhythm	Sinus						
	AF						
	VF/VT						
	Block						
	Paced						
CVA/TIAs							
Smoking status	Smoker						
	Ex-smoker						
	Non-smoker						
EuroSCORE							
Operative priority	Elective						
	Urgent						
MEDICATIONS							
Pre-operative medications							
Heparin							
Nitrates until theatre							
Clexane within 12 hours pre-op							
Inotropes until theatre							

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
Aspirin within 5 days pre-op							
Clopidogrel within 5 days pre-op							
Psychotic medications							
Hypnotics							
Sedatives							
Neuroleptics							
Anxiolytics							
Antidepressants							
Beta blockers							
Any psychotic drug							
The Wechsler Test of Adult Reading							
WTAR standard score	Median (IQR)						

Table T5 Intraoperative characteristics

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
BYPASS DATA							
Duration of operation (hours)	Median (IQR)						
Bypass duration (mins)	Median (IQR)						
Cross clamp duration (mins)	Median (IQR)						
Type of surgery	Valve						
	CABG and Valve						
Myocardial protection	Crystalloid						
	Blood						
	Other						
Type of circuit	Closed						
	Open						
Coated circuit							
Oxygenator	D903						
	EOS						

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
	Quadrox						
Prime volumes in bypass circuit:							
Crystolloid	Median (IQR)						
Colloid	Median (IQR)						
Mannitol	Median (IQR)						
Blood	Median (IQR)						
VALVES							
Aortic	Repaired						
	Replaced						
Mitral	Repaired						
	Replaced						
Tricuspid	Repaired						
	Replaced						
Pulmonary	Repaired						
	Replaced						

Table T6 Post-operative characteristics (Appendix table)

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
ON RETURN FROM THEATRE							
Temperature	Median (IQR)						
Hct	Median (IQR)						
Lactate	Median (IQR)						
MABP	Median (IQR)						
PaO_2	Median (IQR)						
$PaCo_2$	Median (IQR)						
BLOOD RESULTS (1ST 24 HOURS)							
Lowest Hb	Median (IQR)						
Lowest Hct	Median (IQR)						
Lowest MABP	Median (IQR)						
Highest lactate	Median (IQR)						
BLOOD LOSS/ FLUID BALANCE							
Fluid balance at 12 hours							

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Overall (n=XX)	
		n	%	n	%	n	%
Total chest tube drainage at 4 hours	Median (IQR)						
Total chest tube drainage at 12 hours	Median (IQR)						
RE-OPERATIONS							
Number of re-operations	Median (IQR)						
Type of reoperation	Chest re-opened						
	Other						
If chest re-opened	Tamponade						
	Bleeding						
	Mediastinitis						
	Cardiac arrest						
	Low cardiac output						
	Other						
Re-intubated							

Table T7 Primary outcome

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Effect[1]	
		Mean	SD	Mean	SD	(95% CI)	p-value
COGNITIVE FUNCTION							
1. Attention - TRAIL MAKING							
Trail B completion (seconds)	Baseline						
	5 days post-op					MD/GMR	
	3 months post-op					MD/GMR	
	Treatment *time interaction						
	Overall					MD/GMR	
2. Verbal memory - RAVLT							
Trial VI having adjusted for age	Baseline						
	5 days post-op					MD/GMR	
	3 months post-op					MD/GMR	
	Treatment *time interaction						
	Overall					MD/GMR	
3. Visuo-spatial skills - WAIS III (Wechsler)							
Block design having adjusted for age	Baseline						
	5 days post-op					MD/GMR	
	3 months post-op					MD/GMR	
	Treatment *time interaction						
	Overall					MD/GMR	
4. Psychomotor speed - WAIS III (Wechsler)							
b. Digital symbol coding having adjusted for age	Baseline						
	5 days post-op					MD/GMR	
	3 months post-op					MD/GMR	
	Treatment *time interaction						
	Overall					MD/GMR	
5. Verbal fluency - MULTILINGUAL APHASIA (COWAT)							
	Baseline						

Word score having adjusted for age and years of education	5 days post-op		MD/GMR
	3 months post-op		MD/GMR
	Treatment *time interaction		
	Overall		MD/GMR
6. Visual motor coordination - PEG BOARD			
Peg board completion (seconds)	Baseline		
	5 days post-op		MD/GMR
	3 months post-op		MD/GMR
	Treatment *time interaction		
	Overall		MD/GMR

Notes:
[1] OR=odds ratio, MD=Mean difference, GMR
Mean differences or geometric mean ratios for the cognitive functions may be presented for each time point or overall depending if there is a time by treatment interaction.
Data summarised will be scaled scores NOT raw scores.
All treatment estimates will be reported with and without adjustment for medications, HADs and GHQ measured after surgery.

Table T8 Medications at 3 months

	Randomised to Generic algorithm (n=XX)		**Randomised to patient-specific algorithm (n=XX)**		**Overall (n=XX)**	
	n	**%**	**n**	**%**	**n**	**%**
Psychotic medications						
Hypnotics						
Sedatives						
Neuroleptics						
Anxiolytics						
Antidepressants						
Beta blockers						
Any psychotic drug						

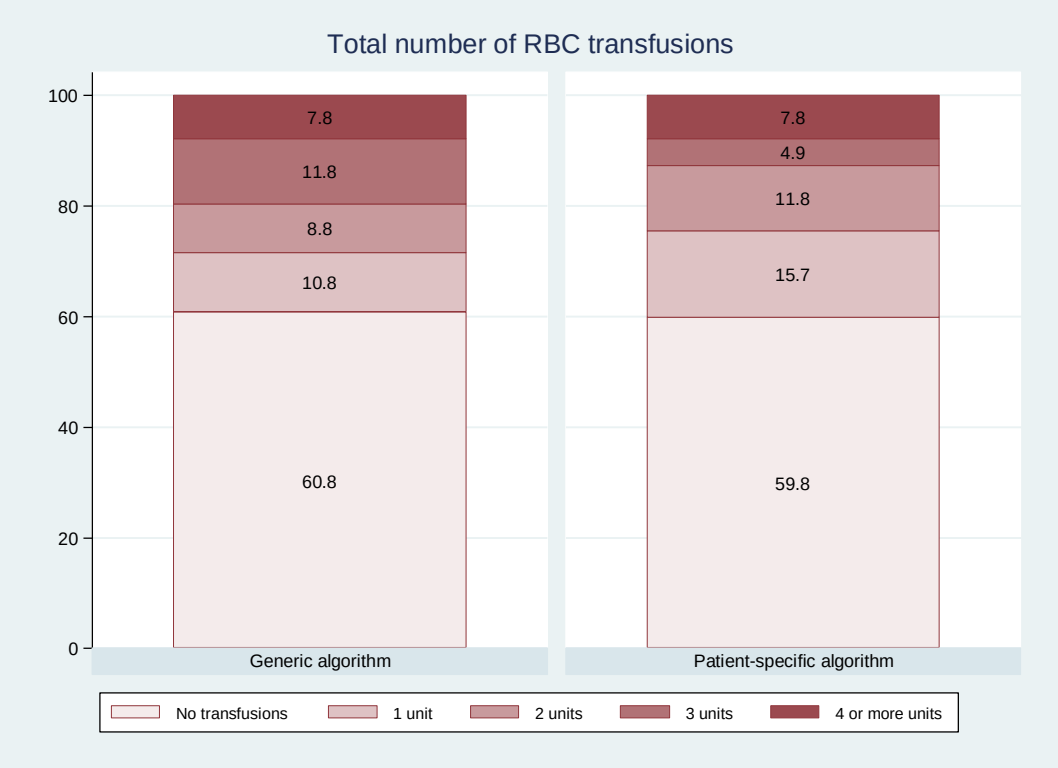
Table T9 Secondary outcomes

			Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)		Effect[1] (95% CI)	p-value
			n	%	n	%		
1	The total number of RBCs units transfused	0						
		1						
		2						
		3						
		>3						
1	Any RBC units						RR	
1	Any FFP							
	Any platelets							
1	Any cryoprecipitates							
1	Any activated factor VII							
2	Cerebral oxygenation during the operative period*							
	Minimum cerebral oxygenation (%)							
	Area under the curve							
3	Oxygen delivery during CPB	Start of CPB						
		20 minutes after the start of CPB						
		40 minutes after the start of CPB						
		Pre-warm						
		Pre-wean						
		Treatment *time interaction						
		Overall					MD/GMR	
	Oxygen utilisation during CPB	Start of CPB						
		20 minutes after the start of CPB						
		40 minutes after the start of CPB						
		Pre-warm						
		Pre-wean						

			Randomised to Generic algorithm (n=XX)		**Randomised to patient-specific algorithm (n=XX)**		**Effect[1] (95% CI)**	**p-value**
			n	%	n	%		
		Treatment *time interaction						
		Overall					MD/GMR	
5	Length of ICU/ HDU stay						HR	
6	Length of hospital stay						HR	
7	Any clinical outcome listed below						RR	
7		Infection						
7		Stroke						
7		STEMI						
7		Post-op kidney injury						
		Stage 1						
		Stage 2						
		Stage 3						
7		Respiratory complications						
9	Death within 30 days of surgery						HR	

Notes:
[1] RR=relative risk, MD=Mean difference, GMR=geometric mean ratio, HR=hazard ratio.

Figure F2 Secondary outcome: Transfusions



Notes:
*It may be necessary to give treatment effect estimates either for each time point or overall, depending on if a treatment*time interaction term is found to be required in the model.*

Table T10 Secondary outcomes: Biomarkers

			Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)	Effect[1] (95% CI)	p-value
BLOOD						
	S100/100B (brain)	Pre-op			MD/ GMR	
		Return from ITU				
		6 hrs post-op				
		24 hrs post-op				
		48 hrs post-op				
		96 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	Troponin T (heart)	Pre-op			MD/ GMR	
		Return from ITU				
		6 hrs post-op				
		24 hrs post-op				
		48 hrs post-op				
		96 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	Creatinine clearance (kidney)	Pre-op			MD/ GMR	
		Return from ITU				
		6 hrs post-op				
		24 hrs post-op				
		48 hrs post-op				
		96 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	IL6	Pre-op			MD/ GMR	
		Return from ITU				

			Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)	Effect[1] (95% CI)	p-value
		6 hrs post-op				
		24 hrs post-op				
		48 hrs post-op				
		96 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	IL8	Pre-op			MD/ GMR	
		Return from ITU				
		6 hrs post-op				
		24 hrs post-op				
		48 hrs post-op				
		96 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
URINE						
	Urinary creatinine	Pre-op			MD/ GMR	
		6 hrs post-op				
		12 hrs post-op				
		24-48 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	NGAL	Pre-op			MD/ GMR	
		6 hrs post-op				
		12 hrs post-op				
		24-48 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	IL18	Pre-op			MD/ GMR	
		6 hrs post-op				

			Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)	Effect[1] (95% CI)	p-value
		12 hrs post-op				
		24-48 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	LFABP	Pre-op			MD/ GMR	
		6 hrs post-op				
		12 hrs post-op				
		24-48 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					
	KIM1	Pre-op			MD/ GMR	
		6 hrs post-op				
		12 hrs post-op				
		24-48 hrs post-op				
	Time* treatment interaction					
	Overall treatment effect					

Figure F3 **Secondary outcome: Cerebral oxygenation during the operative period**

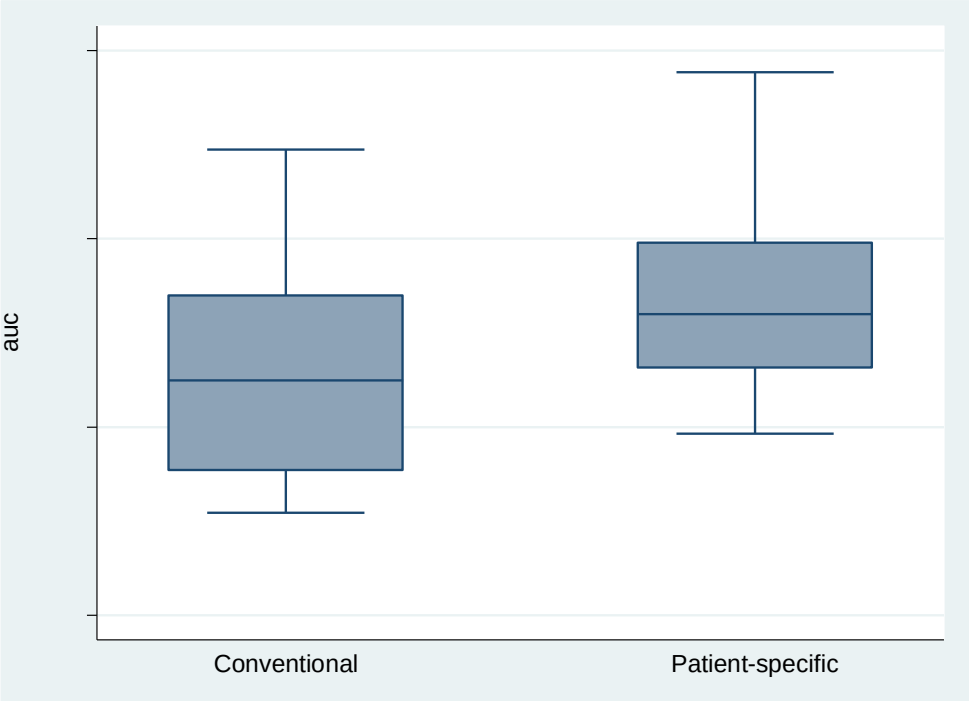
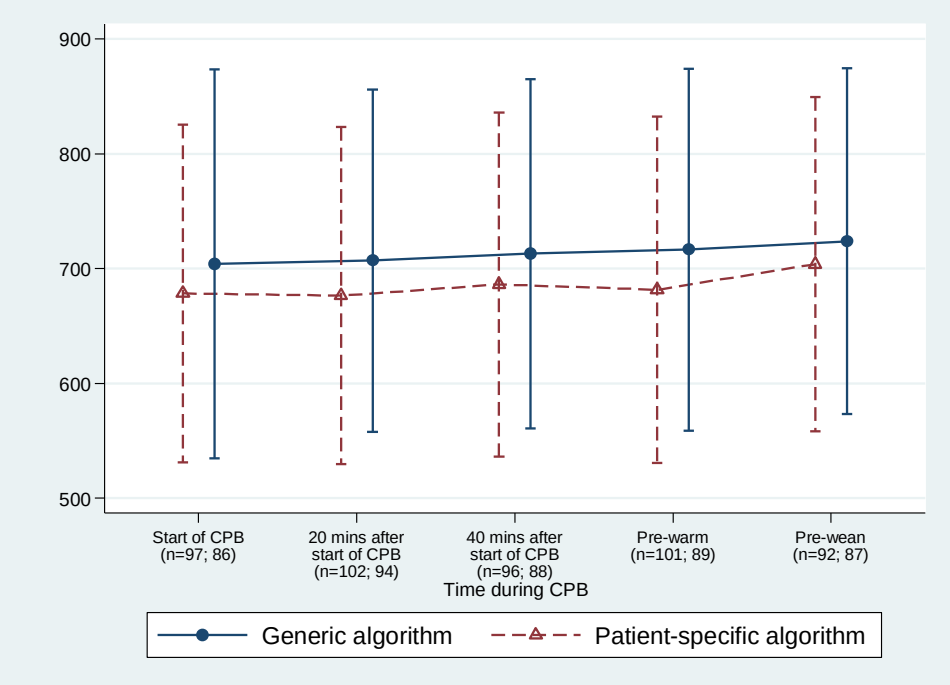


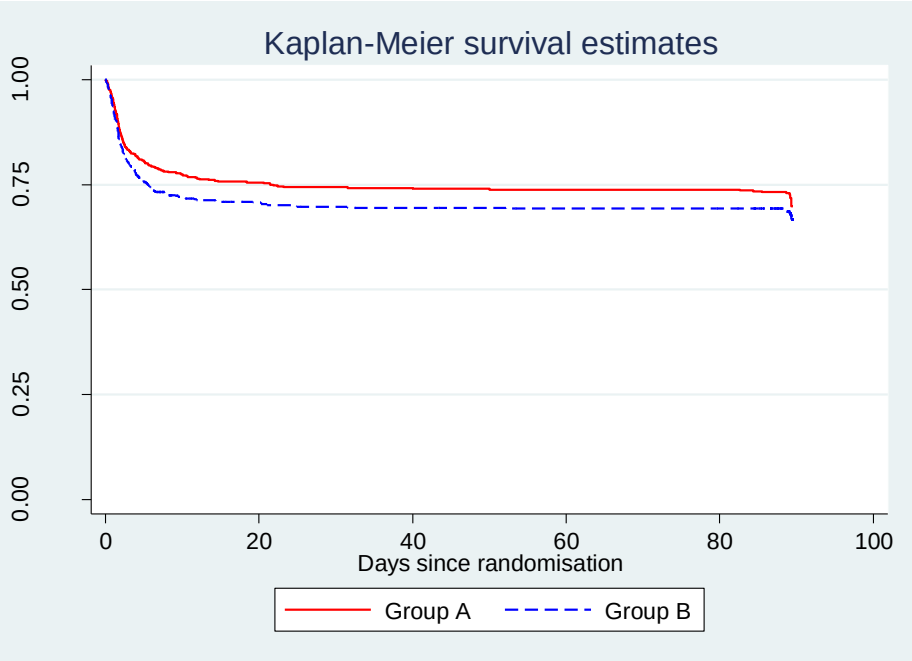
Figure F4 **Secondary outcome: Mean oxygen delivery and utilisation during CPB**



Notes:

Many blood gas and blood test results are reported on the CRFs. All will be described graphically (example given below), with average results (either means and SDs, or medians and IQRs) at each time point, by group.

Figure F5 **Secondary outcome: Kaplan-Meier estimates of time to hospital discharge**



Notes:
The Kaplan-Meier curve will be repeated for time to CICU/HDU and death within 30 days of surgery.

Table T8 **Secondary outcomes: categorical EQ5D outcomes**

		Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)	
Mobility		**n**	**%**	**n**	**%**
Pre-operative	I have no problems walking about				
	I have some problems walking about				
	I am confined to bed				
6 weeks post-operative	I have no problems walking about				
	I have some problems walking about				
	I am confined to bed				
3 months post-operative	I have no problems walking about				
	I have some problems walking about				
	I am confined to bed				
Self-care					
Pre-operative	I have no problems with self-care				
	I have some problems with self-care				
	I am unable to wash or dress myself				
6 weeks post-operative	I have no problems with self-care				
	I have some problems with self-care				
	I am unable to wash or dress myself				
	I have no problems with self-care				

3 months post-operative	I have some problems with self-care
	I am unable to wash or dress myself
Usual activities	
Pre-operative	I have no problems with doing my usual activities
	I have some problems with doing my usual activities
	I am unable to perform my usual activities
6 weeks post-operative	I have no problems with doing my usual activities
	I have some problems with doing my usual activities
	I am unable to perform my usual activities
3 months post-operative	I have no problems with doing my usual activities
	I have some problems with doing my usual activities
	I am unable to perform my usual activities
Pain/Discomfort	
Pre-operative	I have no pain or discomfort
	I have moderate pain or discomfort
	I have extreme pain or discomfort
6 weeks post-operative	I have no pain or discomfort
	I have moderate pain or discomfort
	I have extreme pain or discomfort
3 months post-operative	I have no pain or discomfort
	I have moderate pain or discomfort
	I have extreme pain or discomfort
Anxiety/Depression	
Pre-operative	I am not anxious or depressed
	I am moderately anxious or depressed
	I am extremely anxious or depressed
6 weeks post-operative	I am not anxious or depressed
	I am moderately anxious or depressed
	I am extremely anxious or depressed
3 months post-operative	I am not anxious or depressed
	I am moderately anxious or depressed
	I am extremely anxious or depressed

Table T12 Secondary outcomes: continuous EQ5D outcomes

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)	Effect (95% CI)	p-value
SINGLE SUMMARY INDEX					
Pre-operative	Median (IQR)				
6 weeks post-operative	Median (IQR)				
3 months post-operative	Median (IQR)				
Test for treatment*time interaction					
Overall estimate of treatment effect					
VISUAL ANALOGUE SCALE					
Pre-operative	Mean (SD)				
6 weeks post-operative	Mean (SD)				
3 months post-operative	Mean (SD)				
Test for treatment*time interaction					
Overall estimate of treatment effect					

Notes:
*It may be necessary to give treatment effect estimates either for each time point or overall, depending on if a treatment*time interaction term is found to be required in the model.*

Table T13 Mental health: categorical HADS and GHQ responses

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
I feel tense or wound up:			
Pre-operative	Most of the time		
	A lot of the time		
	Time to time		
	Not at all		
5 days post-operative	Most of the time		
	A lot of the time		
	Time to time		
	Not at all		
3 months post-operative	Most of the time		
	A lot of the time		
	Time to time		
	Not at all		
I still enjoy the things I used to enjoy:			
Pre-operative	Definitely as much		
	Not quite so much		
	Only a little		
	Hardly at all		
	Definitely as much		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
5 days post-operative	Not quite so much		
	Only a little		
	Hardly at all		
3 months post-operative	Definitely as much		
	Not quite so much		
	Only a little		
	Hardly at all		
I get a sort of frightened feeling as if something awful is about to happen:			
Pre-operative	Very definitely and quite badly		
	Yes, but not too badly		
	A little, but it doesn't worry me		
	Not at all		
5 days post-operative	Very definitely and quite badly		
	Yes, but not too badly		
	A little, but it doesn't worry me		
	Not at all		
3 months post-operative	Very definitely and quite badly		
	Yes, but not too badly		
	A little, but it doesn't worry me		
	Not at all		
I can laugh and see the funny side of things:			
Pre-operative	As much as I always could		
	Not quite as much now		
	Definitely not so much now		
	Not at all		
5 days post-operative	As much as I always could		
	Not quite as much now		
	Definitely not so much now		
	Not at all		
3 months post-operative	As much as I always could		
	Not quite as much now		
	Definitely not so much now		
	Not at all		
Worrying thoughts go through my mind:			
Pre-operative	A great deal of the time		
	A lot of the time		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
	From time to time but not too often		
	Only occasionally		
5 days post-operative	A great deal of the time		
	A lot of the time		
	From time to time but not too often		
	Only occasionally		
3 months post-operative	A great deal of the time		
	A lot of the time		
	From time to time but not too often		
	Only occasionally		
I feel cheerful:			
Pre-operative	Not at all		
	Not often		
	Sometimes		
	Most of the time		
5 days post-operative	Not at all		
	Not often		
	Sometimes		
	Most of the time		
3 months post-operative	Not at all		
	Not often		
	Sometimes		
	Most of the time		
I can sit at ease and feel relaxed:			
Pre-operative	Definitely		
	Usually		
	Not often		
	Not at all		
5 days post-operative	Definitely		
	Usually		
	Not often		
	Not at all		
3 months post-operative	Definitely		
	Usually		
	Not often		
	Not at all		
I feel as if I am slowed down:			
Pre-operative	Nearly all the time		
	Very often		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
	Sometimes		
	Not at all		
5 days post-operative	Nearly all the time		
	Very often		
	Sometimes		
	Not at all		
3 months post-operative	Nearly all the time		
	Very often		
	Sometimes		
	Not at all		
I get a sort of frightened feeling like butterflies in the stomach:			
Pre-operative	Not at all		
	Occasionally		
	Quite often		
	Very often		
5 days post-operative	Not at all		
	Occasionally		
	Quite often		
	Very often		
3 months post-operative	Not at all		
	Occasionally		
	Quite often		
	Very often		
I have lost interest in my appearance:			
Pre-operative	Definitely		
	I don't take as much care as I should		
	I may not take quite as much care		
	I take just as much care as ever		
5 days post-operative	Definitely		
	I don't take as much care as I should		
	I may not take quite as much care		
	I take just as much care as ever		
3 months post-operative	Definitely		
	I don't take as much care as I should		
	I may not take quite as much care		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
	I take just as much care as ever		
I feel restless as if I have to be on the move:			
Pre-operative	Very much indeed		
	Quite a lot		
	Not very much		
	Not at all		
5 days post-operative	Very much indeed		
	Quite a lot		
	Not very much		
	Not at all		
3 months post-operative	Very much indeed		
	Quite a lot		
	Not very much		
	Not at all		
I look forward with enjoyment to things:			
Pre-operative	As much as I ever did		
	Rather less than I used to		
	Definitely less than I used to		
	Hardly at all		
5 days post-operative	As much as I ever did		
	Rather less than I used to		
	Definitely less than I used to		
	Hardly at all		
3 months post-operative	As much as I ever did		
	Rather less than I used to		
	Definitely less than I used to		
	Hardly at all		
I get sudden feelings of panic:			
Pre-operative	Very often indeed		
	Quite often		
	Not very often		
	Not at all		
5 days post-operative	Very often indeed		
	Quite often		
	Not very often		
	Not at all		
3 months post-operative	Very often indeed		
	Quite often		
	Not very often		
	Not at all		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
I can enjoy a good book or radio or TV programme:			
Pre-operative	Often		
	Sometimes		
	Not often		
	Very seldom		
5 days post-operative	Often		
	Sometimes		
	Not often		
	Very seldom		
3 months post-operative	Often		
	Sometimes		
	Not often		
	Very seldom		
GHQ-30			
1 – been able to concentrate on whatever you're doing?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
2 – lost much sleep over worry?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
3 – been having restless, disturbed nights?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
4 – been managing to keep yourself busy and occupied?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 – been getting out of the house as much as usual?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
6 – been managing as well as most people would in your shoes?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
7 – felt on the whole you were doing things well?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
8 – been satisfied with the way you've carried out your task?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
9 – been able to feel warmth and affection for those near you?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
10 – been finding it easy to get on with other people?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
11- spent much time chatting with people?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
12 – felt that you are playing a useful part in things?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
13 – felt capable of making decisions about things?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
14 – felt constantly under strain?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
15 – felt you couldn't overcome your difficulties?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
16 – been finding life a struggle all the time?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
17 – been able to enjoy your normal day-to-day activities?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
18 – been taking things hard?			

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
19 – been getting scared or panicky for no good reason?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
20 – been able to face up to your problems?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
21 – found everything getting on top of you?			
Pre-operative	Better than usual		
	Same as usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
22- been feeling unhappy or depressed?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
23 – been losing confidence in yourself?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
24 – been thinking of yourself as a worthless person?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
25 – felt that life is entirely hopeless?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
26 – been feeling hopeful about your own future?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
27 – been feeling reasonably happy, all things considered?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
	Better than usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
5 days post-operative	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
28 – been feeling nervous and stung-up all the time?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
29 – felt that life isn't worth living?			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
3 months post-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
30 – found at times you couldn't do anything because your nerves were too bad			
Pre-operative	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		
5 days post-operative	Better than usual		
	Same as usual		

		Randomised to Generic algorithm (n=XX)	Randomised to patient-specific algorithm (n=XX)
3 months post-operative	Less than usual		
	Much less than usual		
	Better than usual		
	Same as usual		
	Less than usual		
	Much less than usual		

Table T14 Mental health: continuous HADS and GHQ responses

	Randomised to Generic algorithm (n=XX)		Randomised to patient-specific algorithm (n=XX)	
	median	**IQR**	**median**	**IQR**
ANXIETY SUMMARY MEASURE				
Pre-operative				
5 days post-operative				
3 months post-operative				
DEPRESSION SUMMARY MEASURE				
Pre-operative				
5 days post-operative				
3 months post-operative				
GHQ30 SUMMARY MEASURE				
Pre-operative				
5 days post-operative				
3 months post-operative				

Notes
Numbers above and below thresholds will be included as footnotes. HADS-Anxiety (≥8 vs <8), HADS-Depression (≥8 vs <8) and GHQ-30 (≥72 vs <72).

Table T15 Adverse events and serious adverse events in-hospital and during trial follow-up (excluding secondary outcomes) follow-up

	Randomised to Generic algorithm (n=XX)						Randomised to patient-specific algorithm (n=XX)					
	Events		Patients (n=XX)				Events		Patients (n=XX)			
	AE	SAE	AE	%	SAE	%	AE	SAE	AE	%	SAE	%
EXPECTED EVENTS												
Cardiac arrest												
SVT/ VF												
VF/ VT												
New pacing												
Single												
Double												
Permanent												
Any inotropes												
IABP inserted												
Pulmonary artery catheter												
Vasodilator used												
Low cardiac output												
Tracheostomy												
Mask CPAP												
ARDS												
Pneumothorax or effusion requiring draining												
Haemofiltration/ dialysis since heart operation												
Gut infarction												
Peptic ulcer/ GI bleed/ perforation												
Pancreatitis												
Other GI												
TIA												
DVT												
Pulmonary embolism												
Excessive bleeding not requiring re-operation												
Wound dehiscence												
UNEXPECTED EVENT												
Details												

APPENDIX B: ASEPSIS SCORES

In-hospital asepsis scores

For each wound used in the operation (a minimum of one – chest – and a maximum of six – chest, left leg, right leg, left arm, right arm, other, per patient) a wound specific in-hospital asepsis score is derived using the following steps:

1. A daily score is derived for each of the days that the wound was scored (ideally scored on three separate occasions), from the following:
   - If both filter questions (wound hot/wound wet) are "No" then the daily score is zero.
   - Otherwise the daily score is derived from summing the points awarded as follows for the four proportions of wound affects answers given on the CRF:

Proportion of wound affected:	0%	<20%	20-39%	40-59%	60-79%	>80%
Serous exudates	0	1	2	3	4	5
Erythema	0	1	2	3	4	5
Purulent exudates	0	2	4	6	8	10
Wound separation	0	2	4	6	8	10

   Note: *Any missing scores will be assumed to be 0, unless all four scores are missing and then the daily score will be set to be missing.*

2. Data collection is ideally performed on days 3, 5 and 8 post-operatively. The following rules are used to determine if daily scores are valid:
   - A two day window is allowed either side of the intended day, so for example the day 3 score can be done between day 1 and day 5[3].
   - Any assessments done outside of these windows, after the date of discharge, or in an invalid order (e.g. day 5 done before day 3) are invalid and not used.
   - A minimum of one daily score is required to proceed further. If this is not the case then the in-hospital asepsis score for that wound is missing.

3. Scores for days 1 to 10 are calculated; scores for missing days are either propagated from the nearest score or interpolated between scores. Note that the actual day of assessment is used rather than the intended day. See the following examples:

	EXAMPLE 1		EXAMPLE 2	
Day (post-op)	Score	Rule	Score	Rule
1	3	Propagate	6	Propagate
2	3	Observed	6	Propagate
3	2.25	Interpolate	6	Observed
4	1.5	Interpolate	8	Interpolate
5	0.75	Interpolate	10	Observed
6	0	Observed	8	Interpolate
7	0	Propagate	6	Interpolate
8	0	Propagate	4	Interpolate
9	0	Propagate	2	Interpolate
10	0	Propagate	0	Observed

4. Any daily scores after day 7 are then discarded. The remaining scores are summed and then multiplied by 5/7 to give a single score representing five days' worth of daily asepsis scores.

[3] Note the day 8 score is intended to be performed on day 8 or, if the patient discharged sooner, on the day of discharge. Therefore if the patient is discharged prior to day 8 the allowed window will be within two days of discharge (for example if the patient is discharged on day 6 the window will be day 4 to day 6)

5. The final in-hospital asepsis score for the wound is then calculated from adding points to the score derived from point 4 if any of the following events occurred at any time in the post-operative stay for that wound:
   - Antibiotics given for wound infection: 10 points
   - Isolation of bacteria: 10 points
   - Drainage of pus under local anaesthetic: 5 points
   - Drainage of pus under general anaesthetic: 10 points
   - Length of hospital day >14 days: 5 points

   Note: *any missing elements will be assumed to be 0.*

Post-discharge asepsis scores

Post-discharge asepsis scores are calculated by taking the in-hospital asepsis score for each wound and adding additional points if the patient has answered the questions on the 3-month follow-up questionnaire for that wound as follows:

- Been given antibiotics for wound infection=Yes AND patient did not have antibiotics for wound infection in initial hospital admission: 10 points
- Doctor opened/drained an abscess=Yes AND patient did not have drainage of pus under local anaesthetic in initial hospital admission: 5 points
- Wound been opened and cleaned under general anaesthetic in hospital=Yes AND patient did not have drainage of pus under general anaesthetic in initial hospital admission: 10 points
- Wound discharged pus=Yes AND the purulent exudates question on the in-hospital questionnaire was no/missing at all-time points: 5 points
- District nurse had to dress wound=Yes AND patient did not have drainage of pus under local anaesthetic in initial hospital admission: 5 points

Note: *any missing elements will be assumed to be 0*