Conventional versus Minimally Invasive extra-corporeal circulation in patients undergoing Cardiac Surgery: a randomised controlled trial (COMICS)

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Glossary / abbreviations

AKI	Acute kidney injury - an acute increase in serum creatinine > 26.4 µmol/l or a percentage increase in serum creatinine of more than or equal to 50%
ARDS	Acute respiratory distress syndrome
AVR	Aortic valve replacement
CABG	Coronary artery bypass grafting
CE-marked	Conformité Européene marking; designates that a device conforms to EU directives
CECC	Conventional extra-corporeal circulation
CICC	Cardiac intensive care unit
CK-MB	creatinine kinase myocardial band isoenzyme
CRF	Case report form
CT	Computerised tomography scan
CTEU	Clinical Trials and Evaluation Unit
DMSC	Data monitoring and safety committee
ECG	Graphical representation of electrical activity of the heart over time, as recorded by an electrocardiograph
EQ-5D-5L	EuroQol 5-level health status questionnaire
FFP	Fresh frozen plasma
HR	Hazard ration
HRQoL	Health-related quality of life
GCP	Good clinical practice
GI	Gastrointestinal
ICDSC	Intensive care delirium screening checklist
ICU	Intensive care unit
IQR	Interquartile range
IRB	Institutional Review Board
IRI	Ischaemia reperfusion injury
MI	Myocardial infarction
MiECC	Minimally invasive extra-corporeal circulation
MRI	Magnetic resonance imaging scan
PI	Principal investigator
PIL	Patient information leaflet
PLT	Platelets
OR	Odds ratio
QALY	Quality adjusted life year
RBC	Red blood cells
RCT	Randomised controlled trial

REC	Research ethics committee
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SIR	Systemic inflammatory response
SMS	Short message service
SOP	Standard operating procedure
TIA	Transient ischemic attack
TMG	Trial management group
TITRe2	Transfusion indication threshold reduction 2 trial
TSC	Trial steering committee
UH Bristol	University Hospitals Bristol NHS Foundation Trust
UK	United Kingdom

1. Trial summary

Despite a fall in mortality rates over the past decade, patients having cardiac surgery continue to experience serious post-operative complications. The risk of serious and relatively common surgical complications is often a consequence of stopping the heart during the operation, using the heart and lung machine (conventional extra-corporeal circulation; CECC), and restarting and reperfusing the heart at the end of the operation. Although several strategies have been developed to reduce such complications, they still occur and can be life threatening; they also increase the length of time a patient spends in the hospital.

Miniaturised heart lung machines (minimally invasive extra-corporeal circulation; MiECC) have been developed with the aim of reducing the number of post-operative complications arising from using CECC. Because of the variety of miniaturised systems that have been evaluated, the different types of patients and outcomes investigated, and the poor quality of previous studies, the effectiveness of MiECC in reducing post-operative complications has not been established and most hospitals continue to use CECC.

Our primary hypothesis is that, compared to CECC, using a MiECC system during cardiac surgery reduces the proportion of patients having one of several serious post-operative complications (death, heart attack, stroke, gut infarction, severe acute kidney injury, reintubation, tracheostomy, mechanical ventilation for more than 48 hours, or reoperation) up to 30 days after surgery. In addition, we hypothesise that MiECC reduces the amount of blood products transfused, time to discharge from the cardiac intensive care unit and hospital and the health care resources used during the hospital stay.

We propose to carry out a large, multicentre randomised controlled trial in 20 to 30 cardiac surgery centres in Europe and, potentially, Canada, Australia and the United States. Patients will be eligible if they are having coronary artery bypass surgery, aortic valve replace or both using a heart lung machine without circulatory arrest. Centres may recruit patients having all, or a subset of, operation types.

We expect 15% to 18% of patients to experience one or more of the serious complications (the primary outcome). In order to be able confidently to detect a 25% relative reduction in the risk of this outcome, we plan to recruit 3,500 participants across all sites. In the UK we expect the participating centres to contribute around 650 patients of the total during the trial.

2. Background

2.1 Current evidence about the harms of extra-corporeal circulation

Despite a fall in mortality rates over the past decade, patients having cardiac surgery continue to experience significant post-operative morbidity. Morbidity occurs because surgery itself carries a risk of iatrogenic harm, primarily as a result of ischemia reperfusion injury (IRI)[1] and the systemic inflammatory response (SIR).[2] IRI and SIR jointly increase the risk of serious and relatively common surgical complications such as acute kidney injury (AKI). IRI and SIR are unavoidable consequences (to a greater or lesser extent) of extra-corporeal circulation (cardiopulmonary bypass), cardioplegic arrest and of the subsequent reperfusion of the heart during surgery.

Although several strategies have been developed to reduce IRI and SIR (e.g. minimising the effects of perfusion and 'conditioning' the heart to make it more resistant to injury),[3] these harms of surgery are responsible for most post-operative complications and consequent delays in discharge from hospital. With an ageing cardiac surgery population, more likely to have clinically significant preoperative co-morbidities (e.g. diabetes), there remains a need to develop and evaluate new interventions to reduce these iatrogenic harms.

Cardiac surgery with conventional extra-corporeal circulation (CECC) provokes a vigorous SIR due to activation of stress pathways associated with post-operative end-organ complications (e.g. heart failure, renal impairment and neurological dysfunction).[1] SIR is triggered by operative surgical trauma and IRI but is further exacerbated by the interaction of air, blood and synthetic components in the CECC apparatus. Minimally invasive extra-corporeal circulation (MiECC) systems have been developed to reduce the inflammatory response by removing the venous reservoir, using smaller priming volumes and reducing the interface between the blood and synthetic components. Results from two RCTs suggest that MiECC reduces systemic markers of inflammation (e.g. leucocyte and cytokine release, and neutrophil activation).[4,5]

2.2 Evidence about the potential benefits of minimally invasive extra-corporeal circulation

Many RCTs, mostly small and of poor quality, have evaluated diverse MiECC systems compared to CECC.[6] The results of these RCTs have been combined in several meta-analyses,[7,8,9,10] including a recent network meta-analysis which included comparisons with off-pump coronary artery bypass, i.e. avoiding extra-corporeal circulation altogether.[6] All of these meta-analyses concluded that MiECC has substantial benefits over CECC (approximately 50% reduction in risk) with respect to death and in-hospital post-operative complications; the consistency between meta-analyses is unsurprising since there is substantial overlap in the included RCTs.

There are important limitations of these reviews. The MiECC systems evaluated in RCTs have used varied technologies.[6] Trial populations were mainly low risk, whereas one might expect the benefits of MiECC to be larger in a population of 'all-comers', including patients at high risk of experiencing post-operative complications. Most trials were small (the largest recruited 500 patients and most recruited less than 200), at high risk of bias and reported a wide range of outcomes: clinical (mortality, neurological complications, bleeding, transfusion of other blood products, inotrope use, arrhythmias, cardiac ICU/hospital stay), haematology tests of coagulopathy, biomarkers for myocardial damage (CK-MB, troponin I or T), neurological damage (protein s100), renal function (urea, creatinine) and systemic inflammation (C-reactive protein,

leukocytes, interleukins, cytokines). Given their poor methodological quality, this diversity raises suspicion that the reported treatment effects may be substantially biased by selective reporting of whole trials or outcomes and analyses within trials.[11,12]

In summary, there have been many RCTs of MiECC versus CECC. These trials evaluated diverse technologies of varying complexity and degree of miniaturisation, which would be expected to give rise to heterogeneity in findings. Most RCTs have been small and mainly included participants at low risk of post-operative morbidity. Their findings may be biased due to selective reporting. Nevertheless, the available evidence suggests that MiECC may have substantial benefits over CECC with respect to post-operative complications. Therefore, there is an urgent need for a large, high quality RCT to address the uncertainty about the effectiveness of MiECC. If MiECC were shown to be effective and cost-effective in such a trial, the technology is available and could be rapidly implemented in practice.

2.3 Relevance to health services

Cardiac surgery is cost-effective for several common heart conditions. However, the age of patients being listed for cardiac surgery is increasing. Patients are also more likely to have clinically significant preoperative co-morbidities. Both of these factors increase the risk of post-operative morbidity. Post-operative morbidity contributes substantially to the costs of surgery and reduces the surgical capacity of a hospital by blocking beds in cardiac intensive care units (CICU) and wards.

Serious post-operative morbidity is not uncommon after cardiac surgery. Evidence of the incidence and impact of post-operative morbidity is available from the TITRe2 trial, which recruited a very similar population [13]. In this trial, about 50% of all patients experienced a serious adverse event (SAE) in the first 3 months after the operation. The most frequent events qualifying as SAEs were sepsis (defined as antibiotics prescribed for a suspected infection and SIR within the preceding 24 hours), acute kidney injury, arrhythmia, reoperation, pleural effusion requiring drainage (each occurring in >5% of patients, although some patients have multiple SAEs). In an exploratory analysis, participants with sepsis alone (a condition observed in over 15% of participants) had, on average, a post-operative stay 2 days longer compared to participants who did not have sepsis.

Several serious post-operative complications may be caused or exacerbated by IRI and SIR but specific post-operative complications are relatively rare. Therefore, we have chosen a composite primary outcome, defined as any of several serious complications. We have also defined a range of secondary outcomes that are important to patients and health services: health-related quality of life (HRQoL), use of blood products and other resources, duration of ICU and overall hospital stay and cost-effectiveness.

2.4 The proposed trial

Our primary hypothesis is that, compared to CECC, using MiECC during cardiac surgery reduces the proportion of patients experiencing post-operative morbidity.

The proposed trial will overcome most limitations of previous trials of MiECC. It will: (a) evaluate MiECC systems that meet specified criteria which are used in participating centres; (b) be large enough to influence clinical practice, since it will be able to detect a worthwhile benefit in an outcome relevant to patients, surgeons and health services; (c) include a range of features to prevent bias.

3. Aims and objectives

The aim of the trial is to test the hypothesis that MiECC is effective and cost-effective for the majority of cardiac surgery operations requiring extra-corporeal circulation without circulatory arrest.

The trial has three specific objectives:

I To estimate the difference in the proportion of participants experiencing the primary, composite outcome (see 4.5.1) up to 30 days after surgery between the MiECC and CECC groups.

II To compare secondary outcomes between the MiECC and CECC groups: serious adverse events not included in the primary outcome, RBC and other blood products transfused; duration of cardiac ICU and hospital stay following the index admission; resource use, generic health-related quality of life (HRQoL).

III To estimate the cost-effectiveness of MiECC versus CECC.

4. Plan of Investigation

4.1 Trial schema

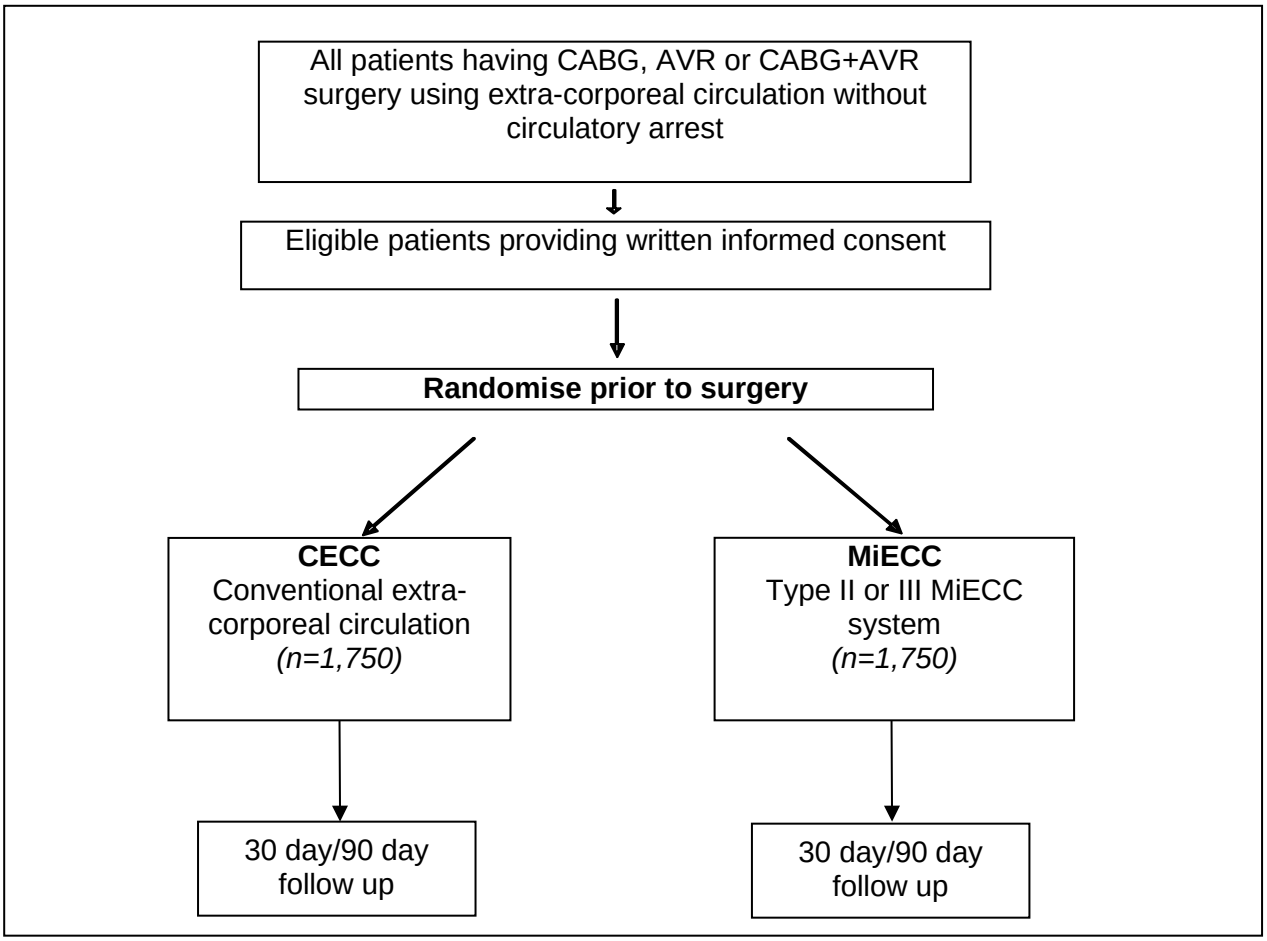

Figure 1: Trial schema

4.2 Trial design

This study is a multi-centre, two-group parallel randomised controlled trial to investigate the effects of using MiECC in all patients having elective or urgent coronary artery bypass grafting (CABG), aortic valve replacement (AVR) or CABG+AVR using extra-corporeal circulation without circulatory arrest. The study will be carried out in two stages: stage 1 is an internal pilot trial [14] for 18 months (12 months recruitment) to ensure that the trial will be able to address the specified research objectives (see 3) in a subset of centres; stage 2 is the main trial, in which additional centres will take part and during which the trial continue recruitment until the target sample size is reached.

The research objectives will be addressed by randomising participants (1:1 ratio) to have surgery using MiECC system or CECC. Randomization will take place as close to surgery as possible and will be performed by an authorised member of the local research team not involved in post-operative data collection. Participants will be blind to their study allocation and where possible members of the local research team responsible for data collection will also be blind to the allocation.

The intervention will be applied only for the duration of extra-corporeal circulation without circulatory arrest. Participants will be followed up twice, at 30 days and 90 days after surgery: questions will elicit information about SAEs experienced since discharge (including readmissions) at 30 days and HRQoL (using the EQ-5D-5L) will be assessed at both times.

4.3 Trial population

4.3.1 Participating centres

We expect to recruit up to 30 cardiac surgery centres in Europe (Belgium, Germany, Greece, Italy, The Netherlands, Switzerland, Turkey, and the UK) and, potentially, elsewhere in the world (Australia, Canada and the United States). A centre (i.e. surgeon and perfusionist team) must be familiar with MiECC and be using MiECC for usual care for operations of the type for which participants are being recruited. This will be assessed locally by the site PI and confirmed with the trial CI.

4.3.2 Trial participants

With respect to the study population, we propose to use eligibility criteria that are as inclusive as possible, to promote the applicability of the evidence obtained during the trial. Therefore, the reference population is all patients having elective or urgent cardiac surgery for: (a) CABG only; (b) AVR surgery only; or CABG+AVR surgery.

4.3.3 Inclusion criteria

A participant may enter the study if ALL of the following apply:

1. Age ≥18 and <85 years
2. Undergoing any elective or urgent CABG, AVR surgery, or CABG+AVR surgery, using extra-corporeal circulation without circulatory arrest.

4.3.4 Exclusion criteria

A patient may not enter study if ANY of the following apply

1. Requirement for emergency or salvage operation
2. Requirement for major aortic surgery (e.g. aortic root replacement)
3. Contraindication or objection (e.g. Jehovah's Witnesses) to transfusion of blood products.
4. Congenital or acquired platelet, red cell or clotting disorders (patients with iron deficient anaemia will not be excluded)
5. Inability to give informed consent for the study (e.g. learning or language difficulties).

Details of all patients approached for the trial, and reason(s) for non-participation (e.g. reason for being ineligible, patient or clinician preference or patient refusal) will be carefully documented.

Trial participants may be recruited to other non-randomized/observational studies but must not be recruited to another randomized trial.

4.4 Trial interventions

4.4.1 Minimally invasive extra-corporeal circulation (MiECC; experimental intervention)

MiECC systems have evolved in a modular fashion, to address safety, volume and blood management issues. Systems have been classified according to their features (Types 1, II, III and IV [15]). Centres will be allowed to use any MiECC circuit which uses CE-marked

components (or components which conform to the required standards for countries outside the European Community) and which have features consistent with Type II, III or IV criteria.

4.4.2 Conventional extra-corporeal circulation (CECC; comparator intervention)

CECC should comprise (required components): standard oxygenator, roller pump, hard-cell reservoir, arterial filter, shed-blood suctions, any of a range of venting options, uncoated tubing, and a cell-saver device. The following optional/alternative components can be integrated (and recorded accordingly): coated oxygenator, coated tubing and centrifugal pump. The following components are prohibited: soft-cell reservoir and vacuum assisted venous drainage (these are advanced components which make CECC resemble a custom-made MiECC circuit).

4.4.3 Aspects of surgery common to both MiECC and CECC

Other aspects of the operations may vary by operation and centre but will be consistent in the MiECC and CECC groups. For example, surgeons may use different cardioplegia solutions at different temperatures in different centres or for different operations. However, a surgeon carrying out a particular type of operation in one centre, e.g. CABG in Centre A, must use the same cardioplegia solution for both MiECC and CECC. Similarly, surgeons have varying preferences with respect to the patient's body temperature during the operation; a surgeon carrying out a particular type of operation in one centre must use the same body temperature for both MiECC and CECC.

We will collect operative details to characterise and report these variations. We believe such diversity in practice within the overall framework of the trial will create greater confidence in the applicability of the findings of the trial to a potential user's clinical setting.

4.5 Primary and secondary outcomes

4.5.1 Primary outcome

The primary outcome is a composite of post-operative SAEs occurring up to 30 days after surgery following the index admission. All SAEs that qualify for the primary outcome will be objectively defined and validated. The following events will qualify:

- death
- myocardial infarction (MI; suspected events will be documented by serum troponin concentrations and electrocardiograph recording (ECG) and adjudicated)
- stroke (report of brain imaging (CT or MRI), in association with new onset focal or generalised neurological deficit)
- gut infarction (diagnosed by laparotomy or post mortem)
- AKI Network criteria for stage 3 AKI [16]
- reintubation
- tracheostomy
- mechanical ventilation for >48 hours, including multiple episodes when separated by more than 12 hours
- reoperation
- percutaneous intervention
- sternal wound infection with dehiscence
- septicaemia confirmed by microbiology

4.5.2 Secondary outcomes

Secondary outcomes are:

- all-cause mortality 30 days after surgery
- other SAEs 30 days after surgery
- units of RBC transfused up to 30 days after surgery
- other blood products transfused up to 30 days after surgery
- time to discharge from cardiac ICU during the index admission
- time to discharge from hospital following the index admission
- delirium in ICU, assessed with the Intensive Care Delirium Screening Checklist (ICDSC) [17] for up to 5 days; this outcome will only be collected in a subset of participating hospitals that have the capability to do so.
- HRQoL using the EQ-5D-5L [18] up to 90 days after surgery; responses to this instrument can be mapped on to 'valuations' for the economic evaluation
- health and social care resources and associated costs up to 90 days after surgery.

An economic evaluation alongside the trial will use quality adjusted life years based on the EQ-5D-5L as the primary outcome.

4.6 Sample size calculation

The trial is designed to answer a superiority hypothesis, i.e. MiECC is hypothesised to reduce the proportion of patients experiencing the primary outcome. Based on the TITRe2 trial dataset (collected from 17 UK centres), the proposed composite outcome will occur with CECC in 15% to 18% of patients, depending on the proportion recruited in the three surgical strata. In order to detect a risk ratio of <=0.75 with 90% power and 5% significance (2-tailed), a sample size of 2,504 to 3,258 is required. We propose to recruit 3,500 patients to allow for uncertainty in the assumptions underpinning this calculation. The target difference of <=0.75 is much closer to the null hypothesis (risk ratio 1.0) than pooled estimates from previous meta-analyses of the effects of MiECC versus CECC with respect to post-operative morbidity.

5. Trial methods

5.1 Randomisation

Randomisation will be stratified by centre and surgical procedure (CABG only, AVR surgery only, CABG+AVR surgery; i.e. separate allocation lists will be maintained for each centre surgical procedure to which a centre is recruiting). The latter important prognostic variable influences duration of extra-corporeal circulation. Randomisation will take place as close to surgery as possible and will be performed by an authorised member of the local research team, using a secure internet-based randomisation system to ensure allocation concealment. Designated staff in participating centres will access the system using a password. Information to identify a participant and to confirm eligibility must be entered before a randomisation number is assigned. The random allocation for a participant will be revealed to a member of the research team who will not have any other role in the trial; if this person is not the perfusionist, this unblinded person will be responsible for informing the perfusionist assigned to the participant's operation, thereby keeping all other members of the local research team responsible for data collection blind to the allocation. Participants will also be blind to the allocation.

5.2 Research procedures

Before admission for cardiac surgery:

- Read a patient information leaflet (PIL) about the study.

Whilst in hospital:

- Give written informed consent to participate if willing to do so.
- Complete an EQ-5D-5L questionnaire.

30 days after surgery :

- Respond to questions about recovery after discharge from hospital, providing details of events and dates that qualify for the primary outcome and any other reason for admission to hospital after discharge;
- Complete an EQ-5D-5L questionnaire.

90 days after surgery:

- Complete an EQ-5D-5L questionnaire.

These questions / questionnaires will be administered face-to-face, by short message service (SMS) text, post or telephone, depending on the preferences of participants and the capabilities of participating centres.

5.3 Duration of treatment period

The duration of treatment in the trial is limited to the duration of extra-corporeal circulation, on average about 45 to 120 minutes depending on the type of surgical procedure being carried out. Therefore, there will be no opportunity for patients to withdraw from the intervention after the operation.

5.4 Definition of end of trial

The end of the trial will be up to 90 days (when data for the last EQ-5D-5L questionnaire is obtained) after recruiting the last patient.

5.5 Data collection

There will be five elements to data collection (**Table 1**):
(a) data at the time of screening and recruitment, carefully checking eligibility;
(b) baseline assessment including details of randomisation and operation;
(c) blood products received and adherence of transfusions to local transfusion protocols;
(d) details of post-operative course, including resources used and SAEs experienced during the index admission;
(e) at 30 days, details of events and dates of any hospital readmission and HRQoL (EQ-5D-5L);
(f) at 90 days, HRQoL (EQ-5D-5L).

Table 1: Schedule of recruitment and other activities during the trial

	T1	T2	T3	T4	T5
Date PIS sent, date approached, age, sex, type of procedure	✓				
Eligibility check, reason for ineligibility		✓			
Consent, reason for declining		✓			
Baseline data collection		✓			
Randomisation details		✓			
Primary outcome events			✓	✓	
Blood products transfused *			✓	✓	
Serious adverse events			✓	✓	
Resources use *			✓	✓	✓
HRQoL (EQ-5D-5L)		✓		✓	✓

* The local research team at each centre will follow-up any hospital readmission to find out whether any RBC transfusion was given during a readmission and to collect information about resource use.
T1: Pre-consent (anonymised).
T2: Pre-admission clinic / day before operation.
T3: During index admission.
T4: 30 days.
T5: 90 days.

Centres will maintain logs of all patients approached, and reasons for ineligibility and refusal. This information and recruitment details of patients who are recruited will be entered on to the trial database immediately to ensure accrual data are available in a timely manner. Subsequent data will be documented on case report forms (CRFs) by research nurses in participating centres. After a patient has been discharged, CRFs will be transcribed on to the trial database which will be made available through the internet. Such databases are used routinely for other multicentre trials hosted by the Bristol Clinical Trials and Evaluation Unit (CTEU). Centres will be required to enter data within one week of discharge so that the data can be validated promptly, and queries raised before the 4- to 6- week outpatient follow-up appointment (which provides an opportunity to resolve such queries).

At 30 days, participants will be contacted (by SMS text, post or by telephone) and asked whether they have been readmitted since discharge. If yes, further questions will be asked about: the approximate date, the admitting hospital and the reason for admission. All participants who report having been admitted will be considered potentially to have had a qualifying event. During the pilot phase, details of admissions for all participants who report

having been admitted will be checked by the recruiting hospital or country lead site (contacting any other hospital to which a participant may have been admitted). The sensitivity of participants' responses to questions about reasons for admission will then be reviewed against data collected from hospitals in order to decide whether, for the main trial, validation can be restricted to admissions that participants report to be for cardiac-related reasons.

5.6 Source data

The primary data source will be the participant's medical notes, held on paper and/or electronically, collected specifically for the trial or routinely as part of a participant's care. These data will be transferred on to the CRFs or entered directly onto to the trial database.

5.7 Planned recruitment rate

We expect to recruit the target sample of 3,500 participants over 21 months (months 7 to 27), with an additional 90 days to follow-up the last participant (months 28 to 30). Based on our experience in the TITRe2 trial, we plan for three centres to be ready to recruit by beginning of month 7, with seven additional centres starting to recruit over the first six months of recruitment (months 7 to 12) and another 10 centres recruiting by month 18. This will allow centre-specific activities such as obtaining local approvals and training to be staggered. The target number recruited by month 18 (end of Stage 1) is 150 randomized participants. Other progression criteria are: >=16 centres recruiting; adherence to allocated intervention >90%.

The projected flow of participants, the cumulative number of patients over time, and research activities during the trial are shown in **Table 2**. We plan to recruit about 120 participants from each centre (some centres will recruit more and some less) and justify this recruitment rate as follows. We expect, on average, two surgeons from each centre to take part, with each surgeon operating on 24 patients per month. Assuming 50% are eligible, 75% are approached and 50% consent (lower than in the TITRe2 trial [19]), we should reach the target sample size in month 27 (see **Table 2**). With 21 months recruitment and up to 30 centres ultimately taking part, the recruitment target will be reached even with the staggered start across centres.

Key milestones include:

- Half of the target sample size recruited, - month 19
- Total target sample size recruited, - month 27
- 90 days follow-up completed - month 30
- Report describing the results of the trial - month 36

Table 2 shows the information described above, based on the stated assumptions. The assumptions (e.g. that two surgeons will participate at a centre and that each surgeon will operate on average on 12 eligible patients per month are not requirements; some centres may have more surgeons and some fewer.

Table 2: Key trial activities and projected recruitment over the duration of the trial.

Main trial activity		Trial month	Centres recruiting	Patients recruited per month	Total patients recruited	Patients being studied
Finalise protocol, design CRFs, write database, etc.		1 to 6	0	0	0	0
Recruiting		7	3	27	27	27
Recruiting	Follow-up	8	4	36	63	63
Recruiting	Follow-up	9	5	45	108	108
Recruiting	Follow-up	10	6	54	162	135
Recruiting	Follow-up	11	8	72	234	171
Recruiting	Follow-up	12	10	90	324	216
Recruiting	Follow-up	13	12	108	432	270
Recruiting	Follow-up	14	14	126	558	324
Recruiting	Follow-up	15	16	144	702	378
Recruiting	Follow-up	16	18	162	864	432
Recruiting	Follow-up	17	20	180	1044	486
Recruiting	Follow-up	18	22	198	1242	540
Recruiting	Follow-up	19	24	216	1458	594
Recruiting	Follow-up	20	26	234	1692	648
Recruiting	Follow-up	21	28	252	1944	702
Recruiting	Follow-up	22	30	270	2214	756
Recruiting	Follow-up	23	30	270	2484	792
Recruiting	Follow-up	24	30	270	2754	810
Recruiting	Follow-up	25	30	270	3024	810
Recruiting	Follow-up	26	30	270	3294	810
Recruiting	Follow-up	27	30	270	3564	810
	Follow-up	28	30	0	3564	540
	Follow-up	29	30	0	3564	270
	Follow-up	30	30	0	3564	0
final data cleaning[1]; draft analysis programmes[2]; lock database; final analyses; draft report[3]; finalise report & submit		31	0	0	0	0
		32	0	0	0	0
		33	0	0	0	0
		34	0	0	0	0
		35	0	0	0	0
		36	0	0	0	0

1 Data validation/cleaning will be carried out throughout the trial, as data are entered into the database. Queries about suspect or missing data will be fed back to centres through the online database.

2 Analysis programmes will be developed during the last year of the trial, but without access to the data designating random allocation of participants.

3 The final report will be drafted during the last months of recruitment and follow-up in the trial, so that finalising the report can be carried out promptly once the final analyses are available.

5.8 Participant recruitment

Patients undergoing any elective or urgent CABG, AVR, or CABG+AVR, with extra-corporeal circulation and without circulatory arrest will be invited to participate. Potential trial participants will be identified from operating lists. All potential participants will be sent or given an invitation letter and a PIL (approved by the local Research Ethics Committee (REC) or Institutional Review Board (IRB)) describing the study. The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. Most patients will have at least 24 hours to consider whether to participate. In a few cases, this time interval may be as little as 12 hours, for example for patients admitted for urgent surgery without prior notification to the surgical team. Despite the short notice, it is important to include these patients for the applicability of the trial findings since a substantial proportion of patients having cardiac surgery (mainly CABG surgery) are admitted as urgent cases.

After admission to the cardiac unit for their operation, patients will be seen by a member of the local research team (study surgeon/research nurse/trial coordinator) who will answer any questions, confirm the patient's eligibility and take written informed consent if the patient decides to participate. Details of all patients approached for the trial and reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) will be documented.

5.9 Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. If a patient wishes to withdraw, we will continue to analyse any data already collected, unless the patient expresses a wish for their samples and any associated data to be destroyed.

5.10 Frequency and duration of follow up

This trial has not requested funding to follow-up patients in the longer term (i.e. beyond 90 days).

5.11 Likely rate of loss to follow-up

Until discharge from hospital, the only losses to follow-up will be due to death or a participant withdrawing; these losses are expected to be very few. Participants may be lost to follow-up after discharge but every attempt will be made to obtain follow-up data for them, e.g. from consulting participants' medical records, contacting family doctors or searching national registries.

5.12 Expenses

Participants will not be reimbursed for any travel expenses since they are not required to make any additional visit exclusively for the research.

5.13 Measures taken to avoid bias

Concealment of randomized allocations until after a participant has been recruited and his/her identity has been recorded will prevent selection bias.

Participants will not know the type of system used during the operation, preventing knowledge of their allocation influencing their responses on the EQ-5D-5L (avoiding detection bias) or their actions/behaviour with respect to their health after the operation (avoiding performance bias).

Events that qualify for the primary outcome will be documented and validated or adjudicated, minimising bias in outcome ascertainment. Trial personnel responsible for collecting data will also be blind to a participant's allocation, wherever possible, minimising outcome ascertainment bias for secondary outcomes.

The secondary outcome of transfusion of blood products could be at risk of serious performance/detection bias if doctors caring for participants know the allocation and want or expect MiECC to 'do better', i.e. doctors might be less likely to give a RBC transfusion to a patient known to have had MiECC rather than CECC during the operation. It is not possible to blind theatre staff to the use of MiECC or CECC because the equipment required is very different. Therefore, centres will be required to provide local transfusion protocols (both intra-operative and post-operative) before starting to recruit. Data describing the adherence of transfusions given to participants will be checked against these protocols, based on methods developed for the TITRe2 trial.[19]

The short follow-up period will protect against bias due to attrition. Randomisation will take place close to the time of the operation, so there will be only a very small risk of a participant withdrawing after randomisation and before the intervention. Participants will be free to withdraw from active follow-up (e.g. EQ-5D-5L questionnaires) but, since we intend to blind participants until 90 days after their operations, attrition initiated by participants should not differ by group.

A detailed trial protocol and analysis plan, finalised before the trial database is locked, will prevent selective reporting.

6. Statistical analyses

6.1 Plan of analysis

Reporting of the study results will follow the CONSORT guidelines [www.consort-statement.org]. All analyses will be carried out on the basis of intention to treat and treatment comparisons will be presented with 95% confidence intervals. We will adjust all comparative analyses for centre and operative procedure.

6.1.1 Analysis of primary outcome

The primary analysis will compare the proportion of patients who experience one or more events qualifying for the primary outcome up to 30 days after randomization in the MiECC and CECC groups using logistic regression, with the treatment effect presented as an odds ratio (OR).

6.1.2 Analyses of secondary outcomes

The frequencies of other SAEs will be described but formal statistical comparisons will only be performed if more than ten patients in total experience the outcome.

The proportion of patients receiving any RBC transfusion, any platelet (PLT) transfusion, and any fresh frozen plasma (FFP) transfusion, up to 30 days after surgery will be compared between groups using logistic regression, with the treatment effects presented as ORs. Additional analyses will compare amount of RBC, PLT and FFP transfused in the two groups, using methods that are appropriate given the distributions of number of units transfused. The total number of units of blood products transfused will be analysed using linear regression (assuming similar loss to follow-up in the two groups).

Time to event outcomes (i.e. time to death, discharge from CICU and from hospital) will be presented as median and interquartile range (IQR) and compared using Cox proportional hazards regression, with the treatment comparisons presented as hazard ratios (HR).

The EQ-5D-5L single summary index will be analysed using linear mixed effects methods. A multivariate normal model will be fitted incorporating separate parameter estimates for the mean baseline response (to avoid either excluding or imputing missing preoperative values), and for each treatment at the two follow-up times. If the time by treatment interaction is not statistically significant at the 5% level an overall treatment effect will be reported. If the interaction is statistically significant, the changes in treatment effect will be described at each time.

The validity of the assumptions underpinning the regression models (e.g. proportional hazards or constant variance and normally distributed random errors) will be examined and, if the assumption is violated, alternative models will be explored.

6.2 Subgroup analyses

For the primary outcome only, subgroup analyses will investigate the applicability of the primary analysis to subgroups of the trial population with different characteristics, by fitting interaction terms for the subgroup of interest (e.g. operation type) and circuit type (MiECC vs CECC). We have no a priori hypotheses in terms of the characteristics that may interact with the type of CPB circuit or about the direction of any interaction. Subgroups that will be investigated are as follows, dichotomising scaled covariates* at the median to maximise the power for interaction tests: age*; sex; operation type; Euroscore*; preoperative renal dysfunction*; preoperative Hb*. If sufficient surgical teams participate who have experience of using MiECC in usual care in less

than 50 operations, a further subgroup analysis will explore the impact of experience of the team with MiECC. This analysis will compare the patients who have operations in the trial involving teams with experience of less than 50 operations, with patients who have operations involving teams with 50 or more operations.~~,~~

The influence of different MiECC circuits and cardioplegia techniques will also be explored by investigating the extent to which they explain variation in centre-specific treatment effects (adjusted for operation type). These covariates will almost certainly apply at the level of participating centre, not participants, and will be chosen (not randomly assigned) by centres.

6.3 Frequency of analyses

No interim analyses are planned. The Data Monitoring and Safety Committee (DMSC; see 7.3.2) will advise on the frequency of interim analyses for the DMSC to review and set any stopping rules that the DMSC considers appropriate. There is no intention to compare any outcomes between groups after the completion of Phase 1; the only analyses will be descriptive statistics to summarise eligibility and recruitment to decide whether the trial satisfies the progression criteria. The primary analyses of the main trial (all outcomes) will be carried out when all recruited patients have completed the 90 days post-operative follow-up period.

6.4 Secondary analysis for non-inferiority

If the primary analysis (see 6.1.1) of the primary outcome fails to establish a sufficient margin of benefit to establish superiority, a secondary analysis will be carried out to test the non-inferiority of MiECC compared to CECC for the predefined non-inferiority margin of 3% for the primary outcome (alpha=0.025, 1-tailed).

6.5 Criteria for the termination of the trial

The trial may be terminated early on safety grounds or if another study makes it redundant.

6.6 Economic issues

The aim of the economic evaluation is to estimate the costs and effects of MiECC versus CECC. The evaluation will provide information on which system represents the best use of health service resources. Established guidelines will be used for the conduct of the COMICS economic evaluation[20,21]. The main outcome measure will be quality adjusted life years (QALYs) using the EQ-5D-5L[18]. This questionnaire instrument will be administered face-to-face at baseline and face-to-face, by telephone or post at 30 days and 90 days after their operations. Respondents will be assigned valuations using the approach of Devlin and Van Hout [22] and the mean number of QALYs per trial arm and incremental QALYs will be calculated. Secondary outcomes measures for the economic evaluation will include, for example, deaths avoided, hospital readmissions avoided, and RBC transfusions avoided.

Data will be collected on surgical resource use for MiECC and CECC systems. Information about key cost drivers (CICU and hospital stay) will be collected during the index and any subsequent admission up to 30 days. Information about the use of health care resources associated with complications such as AKI, including subsequent treatments and the consequences of the complications, and other items of resource use and cost data will be taken from the TITRe2 trial.

Our baseline analysis will calculate the average cost and outcome per patient. Using this information, incremental cost-effectiveness ratios for the MiECC and CECC systems will be

derived, producing an incremental cost per QALY. Probabilistic sensitivity analysis will be used to show the impact of variation in key parameters on the baseline cost-effectiveness results. Parameters likely to be varied include the costs of the MiECC and CECC systems. Results will be described in a cost-effectiveness acceptability curve; this curve indicates the likelihood that the results fall below a given cost-effectiveness ceiling. It will help decision makers to assess whether the MiECC system is likely to represent value for money for health services when compared to either the CECC system or a completely disparate health care intervention.

7. Trial management

The trial will be overseen by a Trial Steering Committee (TSC) and a DMSC (see below). Both committees will be convened before the start of recruitment. The DMSC will be asked to confirm/specify details of planned interim analyses, which will be forwarded to the TSC and to the RECs/IRBs for participating centres.

7.1 Day-to-day management

The trial will be managed by a Trial Management Group (TMG), which will 'meet' approximately monthly by teleconference. The TMG will be chaired by the Chief Investigator and will consist of the applicants, country representatives (local PIs for lead centres in different countries) and members of the Bristol CTEU co-ordinating staff (including the trial manager). The trial will adapt cardiac surgery templates and practices implemented for other cardiac surgery trials managed by the Bristol CTEU. Communications between centres will be managed primarily by electronic means and through periodic TMG teleconferences.

The following actions will be taken in order to ensure adherence to the principles of good clinical practice (GCP):

- Establish a Lead Coordinating Centre for the trial and lead centres for each participating country
- Establish an independent TSC
- Obtain REC/IRB approval in all participating countries/centres
- Establish an independent DMSC
- Obtain written informed consent from all participants
- Record and report SAEs in accordance with the principles of GCP
- Carry out centralised monitoring (by implementing automatic validation and reports on the trial database) of compliance of centres with key aspects of GCP and data collection procedures

7.2 Monitoring of sites

7.2.1 Initiation visit

Before the study commences, training session(s) for local research staff will be organised by the Bristol CTEU. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study. A checklist will be prepared to ensure that a centre has completed all of the required steps before allowing the centre to start recruiting (by providing password-protected access to the internet randomization facility).

7.2.2 Site monitoring

The Bristol CTEU will carry out regular monitoring by inspecting accruing data and uploads (e.g. consent forms). Regular feedback will be provided to participating centres, identifying required actions. If a centre does not act on the feedback, a teleconference will be scheduled. If the

required actions are not taken in a prompt timeframe, the Bristol CTEU will suspend a centre's ability to randomise participants.

7.3 Trial Steering Committee and Data Monitoring and Safety Committee

7.3.1 Trial Steering Committee (TSC)

Membership (n=5/6) of the TSC will include:

- An independent chair
- An independent patient representative/ service user
- An independent anaesthetist
- An independent perfusionist
- An independent trialist / statistician

In addition, key members of the research team and the Lead Coordinating Centre will be invited to attend as non-voting members:

- Trial representatives

Lead Coordinating Centre representative

7.3.2 Data Monitoring and Safety Committee (DMSC)

Membership of the DMSC will include:

- An independent chair and trialist / statistician
- An independent intensive care specialist
- An independent cardiac surgery specialist
- An independent perfusionist

Key members of the trial team will attend open sessions of DMSC meetings to provide report on progress and provide any additional information requested.

8. Safety reporting

Serious and other adverse events will be recorded and reported in accordance with the GCP guidelines and the Lead Coordinating Centre's Research Related Adverse Event Reporting Policy (see **Figure 2**).

8.1 Expected adverse events

The following adverse events are 'expected':

Perioperative MI, identified by:
- Raised Troponin or ECG changes

Cardiac arrest, requiring:
- Resuscitation involving ventricular defibrillation/DC shock
- Chest reopening
- External/internal cardiac massage

Neurological complications
- Permanent stroke
- Transient ischaemic attack (TIA)

Thromboembolic complications, including:
- Deep vein thrombosis
- Pulmonary embolus

Haemodynamic support, including use of:
- Any inotropes
- IABP
- Pulmonary artery catheter
- Vasodilator
- Low cardiac output, requiring a Swan-Ganz catheter, an intra-aortic balloon pump, or left ventricular assist device

Bleeding complications
- Pericardial effusion/tamponade
- Excess bleeding not requiring reoperation (400ml/h for 1h or 200ml/h for 4h)

Renal complications, including:
- New haemofiltration/dialysis

Arrhythmias, including:
- Supraventricular tachycardia or atrial fibrillation requiring treatment
- VF/VT requiring intervention
- Pacing

Pulmonary complications, including:
- Re-intubation and ventilation
- Tracheostomy
- Initiation of mask continuous positive airway pressure ventilation after weaning from ventilation
- Acute respiratory distress syndrome
- Pneumothorax or effusion requiring drainage

Infective complications, including:
- Sepsis
- Wound infection
- Respiratory infection
- Mediastinitis
- Wound dehiscence requiring rewiring or treatment
- Urinary tract infection

Gastrointestinal (GI) complications, including:
- Peptic ulcer/GI bleed/perforation
- Pancreatic (amylase >1500iu)
- Other (e.g. laparotomy, obstruction)

In cardiac surgery, post-operative transient complications are not unexpected and occur quite often. As part of the data collection for the study, information on the expected events listed above will be collected on the study CRF by local study teams up to 30 days post-surgery. These events will not undergo expedited reporting to the Lead Coordinating Centre and an SAE form will not be completed. Data collection for fatal and 'unexpected' non-fatal SAEs will take place on SAE forms and be reported to CTEU Bristol within 24 hours of the local site staff becoming aware of the event. The local PI will decide the causality of the event. If this event occurred at a UK site, the SAE form will be forwarded immediately by CTEU Bristol to the Lead Coordinating Centre.

. Elective non-cardiac surgery, or any other intervention or treatment during the follow-up period but scheduled before a participant is recruited to the trial is not an unexpected SAE.

Data on all complications and adverse events will be reviewed by the TMG and DMSC, either as routine reporting or as expedited reports as detailed in **Figure 2**.

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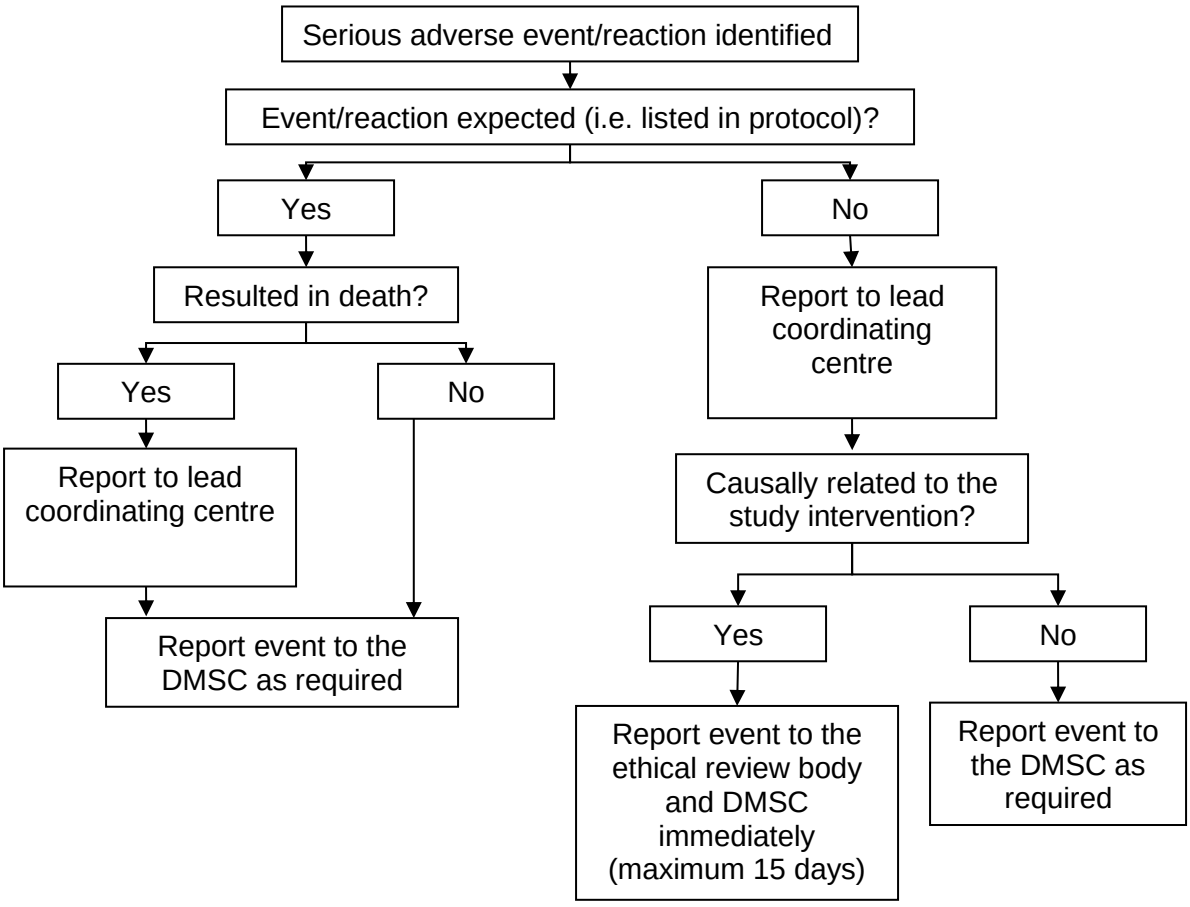
Figure 2 Serious adverse event reporting flow chart for the coordinating centre (CTEU, Bristol) (UK Sites only)



8.2 Period for recording serious adverse events

Data on any SAE will be collected from the day of surgery up to 30 days after.

9. Ethical considerations

9.1 Review by a Research Ethics Committee or Institutional Review Board

Ethics review of the protocol for the trial and other trial related essential documents (e.g. PIL and consent form) will be carried out by an appropriate REC or IRB at a participating centre.

Any amendments to these documents, after a favourable opinion from a REC/IRB has been given, will be submitted to the REC/IRB for approval before the amendments are implemented.

9.2 Risks and anticipated benefits

As described in section 2, although cardiac surgery is cost-effective for several common heart conditions, the operation itself carries a risk of harm. We hypothesise that, compared to CECC, the MiECC system will reduce the risk of the primary outcome.

Potential harms to participants include the possibility of randomisation to an inferior treatment (a possible harm of participating in any RCT) and possible SAEs attributable to the treatment to which participants are allocated. The 'reasonableness' of asking participants to take part, i.e. the prevailing uncertainty about the research questions of interest and the benefits and risk of carrying out the trial to participants, future patients and society, will be judged by our application to RECs/IRBs for ethical approval for the study.

Potential harms of CECC have been characterised over more than 20 years [1] and include IRI and SIR as described above (see 2.1). These harms are explained when the surgeon obtains a patient's consent for the operation and are accepted as part of the risks of cardiac surgery. Potential harms of the MiECC system arise from the human factor demands that MiECC can create for the perfusionists, surgeons and anaesthetists responsible for a patient's care in theatre. The trial will only use MiECC systems comprising commercially available components, CE-marked for the purpose (or conforming to required standards for non-European countries).

Our hypothesis assumes that there are benefits to patients from reducing blood loss and avoiding peri-operative complications. We will summarise information from the literature about the risks of post-operative morbidity with MiECC and CECC, and the benefits of avoiding transfusion, in a patient information leaflet submitted to the REC. We do not envisage any ethical issue arising from this application.

9.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PIL.

9.4 Obtaining informed consent from participants

All participants will be required to give written informed consent before their operation. The process for obtaining informed consent, including the information in the patient information leaflet about the trial, will be described in our applications to RECs/IRBs for ethical approval.

9.5 Co-enrolment

Patients who consent to participate in the COMICS trial will be unable to participate in another interventional study unless agreed by the trial manager/ CI prior to enrolment. Co-enrolment in a concurrent observational study is not precluded and will be considered on a case-by-case basis by the trial manager / CI.

10. Research governance

This study will be conducted in accordance with the principles of Good Clinical Practice (GCP).

10.1 Lead Coordinating Centre approval

Any amendments to the trial documents must be approved by the Lead Coordinating Centre before submission to a REC/IRB and implementation. In the case of an urgent safety measure, an amendment can be implemented immediately, but the Lead Coordinating Centre and RECs/IRBs must be notified as soon as possible.

10.2 Approval from participating centres

Approval from a participating centre is required before starting to recruit to the trial.

10.3 Principal investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participants. Investigators will be required to ensure adherence to the protocol and study manual; completion of the CRFs; allow access to study documentation or source data if required by the Lead Coordinating Centre, the Bristol CTEU or any regulatory authority.

Investigators will be required to read, acknowledge and inform their trial team of any amendments to the trial documents approved by the REC/IRB and ensure that the changes are implemented and adhered to.

10.4 Monitoring by Lead Coordinating Centre

The study will be monitored and audited in accordance with the policy of the Lead Coordinating Centre, which is consistent with the UK Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the Lead Coordinating Centre or a REC/IRB overseeing participation by a centre.

10.5 Indemnity

The University of Bristol is the Lead Coordinating Centre for this study and holds Public Liability insurance in respect of the University's legal liability for injuries to research participants as a result of negligence by the University or its employees. The University has not arranged non-negligent harm ("no fault compensation") insurance for this study.

The University is not responsible for the clinical care of participants. Therefore, each participating centre needs to ensure it has appropriate insurance or other indemnity provision in respect of the clinical care of its patients while they are participating in the research.

10.6 Clinical Trial Authorisation

All devices used for MiECC and CECC will be CE-marked for the purposes for which they will be used (or conforms to the required standards for non-European countries). Therefore, the trial is not classed as a clinical trial of an investigational medicinal product or device and a Clinical Trial Authorisation (or similar) from a regulatory authority is not required. However, the lead centres for the United States and Canada will be expected to obtain and administer Federal Wide Assurances for their respective countries.

11. Data protection and participant confidentiality

11.1 Data protection

Data will be collected and retained in accordance with country-specific data protection laws.

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be entered onto a purpose designed database. Data validation and cleaning will be carried out throughout the trial. Standard operating procedures (SOPs) for database use, data validation and data cleaning will be available and regularly maintained.

Trial data will be entered into the trial database (developed and managed by Bristol CTEU) by staff at participating centres. Data collected at T1 must be entered within 15 days of screening; data collected at T2 must be entered immediately to allow randomization; data collected during the index admission (T3) must be entered within 15 days of discharge from hospital or death in hospital (see Table 1); and data collected at T4 and T5 must be entered within 15 days of the dates when these data are collected (if applicable), in order to allow satisfactory monitoring of trial conduct at sites (7.2.2). The database will be accessed by the internet.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 10 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Prior to destruction, paper records will be scanned and stored securely with limited password-controlled access. Where trial related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the trial. Relevant 'meta'-data about the trial and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely. A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and health service/hospital number) will also be held indefinitely, but in a separate file and in a physically different location. These will be retained because of the potential for the raw data to be used subsequently for secondary research.

11.2.3 Data sharing

Any data shared outside of the research team will first be fully anonymised. Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a REC/IRB or other similar, approved review body.

12. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available. As the study compares surgical techniques no commercially exploitable findings are anticipated.

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14. Amendments to protocol

Amendment number (i.e. REC and/or MHRA amendment number)	**Previous version**	**Previous date** (dd/mm/yyyy)	**New version**	**New date** (dd/mm/yyyy)	**Brief summary of change**	**Date of ethical approval (or NA if non-substantial)** (dd/mm/yyyy)
Pre-submission	V1.0	18/01/2017	V2.0	09/10/2017	• Clarified timepoints for data collection and data to be collected • Added delirium as secondary outcome • Revised time period for safety reporting • Added more information about follow-up	
1	V2.0	09/10/2017	V3.0		• Removed references to 60 day follow up • Corrected inconsistencies about post-surgery/randomisation for follow up • Section 4.3.1 amended to allow for the inclusion of additional surgeons • Additional analysis added to Section 6.2. • Updated TSC/DMSC memberships • Appendix 1 removed.	