

BMJ Open Efficacy and safety of carbon dioxide insufflation for brain protection for patients undergoing planned left-sided open heart valve surgery: protocol for a multicentre, placebo-controlled, blinded, randomised controlled trial (the CO2 Study)

Rachel Todd ¹, Chris A Rogers,² Maria Pufulete,² Lucy Culliford,² Pieter Pretorius,³ Natalie Voets,³ Enoch Akowuah ⁴, Rana Sayeed ⁵, Michelle Lazaroo,² Surinder Kaur,¹ Gianni D Angelini,^{6,7} Ben Gibbison^{6,7}

To cite: Todd R, Rogers CA, Pufulete M, *et al.* Efficacy and safety of carbon dioxide insufflation for brain protection for patients undergoing planned left-sided open heart valve surgery: protocol for a multicentre, placebo-controlled, blinded, randomised controlled trial (the CO2 Study). *BMJ Open* 2023;**13**:e074221. doi:10.1136/bmjopen-2023-074221

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2023-074221>).

Received 30 March 2023

Accepted 26 April 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Rachel Todd;
rachel.todd@bristol.ac.uk

ABSTRACT

Introduction Brain injury is common following open heart valve surgery. Carbon dioxide insufflation (CDI) has been proposed to reduce the incidence of brain injury by reducing the number of air microemboli entering the bloodstream in surgery. The CO2 Study will evaluate the efficacy and safety of CDI in patients undergoing planned left-sided open heart valve surgery.

Methods and analysis The CO2 Study is a multicentre, blinded, placebo-controlled, randomised controlled trial. Seven-hundred and four patients aged 50 years and over undergoing planned left-sided heart valve surgery will be recruited to the study, from at least eight UK National Health Service hospitals, and randomised in a 1:1 ratio to receive CDI or medical air insufflation (placebo) in addition to standard de-airing. Insufflation will be delivered at a flow rate of 5 L/min from before the initiation of cardiopulmonary bypass until 10 min after cardiopulmonary bypass weaning. Participants will be followed up until 3 months post-surgery. The primary outcome is acute ischaemic brain injury within 10 days post-surgery based on new brain lesions identified with diffusion-weighted MRI or clinical evidence of permanent brain injury according to the current definition of stroke.

Ethics and dissemination The study was approved by the East Midlands–Nottingham 2 Research Ethics Committee in June 2020 and the Medicines and Healthcare products Regulatory Agency in May 2020. All participants will provide written informed consent prior to undertaking any study assessments. Consent will be obtained by the principal investigator or a delegated member of the research team who has been trained in the study and undergone Good Clinical Practice training. Results will be disseminated through peer-reviewed publications and presentations at national and international meetings. Study participants will be informed of results through study notifications and patient organisations.

Trial registration number ISRCTN30671536.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ The largest randomised controlled trial investigating the neuroprotective effect of carbon dioxide insufflation after cardiac surgery.
- ⇒ Inclusion criteria offer a large patient population to recruit to the study with widespread generalisability.
- ⇒ The participant, clinical care team, research team responsible for data collection and imaging reviewer are blinded to the allocated intervention to minimise bias.
- ⇒ The pragmatic study design complements the surgical pathway to reduce the burden on participants.
- ⇒ The number of neurocognitive and functional assessments at baseline and 3-month follow-up may deter potential participants or result in missing data.

INTRODUCTION

Around 12 000 people undergo open heart surgery to repair or replace a heart valve every year in the UK.¹ Brain injury or dysfunction following open heart surgery is common, with severity varying from mild confusion and memory problems^{2 3} to perioperative stroke.² Although the risk of major stroke in major cardiac surgery is 1%–2%,² the rate of so-called ‘silent’ neurological dysfunction identified on MRI is up to 50%.^{4 5} Neurological complications are associated with longer hospital stays, slower recovery, poor quality of life, increased hospital resource use and reduced long-term survival.

One of the major causes of brain injury and dysfunction at the time of cardiac surgery is thought to be microemboli travelling to the

brain causing ischaemia and infarction. Transcranial Doppler (TCD) ultrasound has demonstrated around 80% of these emboli are air.⁶ The putative mechanism is that air bubbles enter the blood during opening of the heart chambers.

Carbon dioxide insufflation (CDI) into the surgical field before and during cardiopulmonary bypass (CPB) may reduce the formation of air microemboli.^{7,8} Carbon dioxide is more dense than air and therefore, displaces air from the wound. It is also more water soluble than air leading to fewer microemboli entering the blood, and those that form will be of shorter duration.⁸

A meta-analysis of eight randomised controlled trials (RCTs) found that CDI during open heart valve surgery was associated with fewer air microemboli in the heart when the cross-clamp was removed. However, no significant influence on the incidence of postoperative neurocognitive decline was identified.⁹ The findings of this meta-analysis are limited due to the small number of RCTs included, the timing and selection of postoperative psychometric tests, and the method of CDI delivery used in the RCTs. Therefore, a well-designed RCT to evaluate the neuroprotective effect of CDI during open heart valve surgery is required.

Diffusion-weighted MRI (DW MRI) is regarded as the 'gold standard' for identifying perioperative brain injury in RCTs of neuroprotective interventions in cardiac surgery.^{5,10–12} Unlike conventional MRI and CT imaging, DW MRI can detect very small lesions within minutes of occurring that are not seen with other imaging modalities. It has been reported that DW MRI lesions are present in around 50% of patients following heart valve surgery.^{4,5} However, only around 9% of patients with such lesions displayed any clinical signs of brain dysfunction or injury.⁴ The clinical impact of these brain lesions in patients undergoing cardiac surgery is currently unclear, and neurocognitive and functional assessments are necessary to evaluate CDI effectively.^{4,11}

There is no robust evidence to suggest CDI reduces brain injury. A short survey of all cardiothoracic units in the UK, for this funding application, found clinical equipoise for using the intervention because of this lack of evidence.

The CO₂ Study aims to evaluate the efficacy and safety of CDI in patients undergoing planned left-sided open heart valve surgery. It also aims to characterise the mechanism of brain injury after open heart valve surgery.

METHOD AND ANALYSIS

Trial design and population

The CO₂ Study is a multicentre, blinded, placebo-controlled RCT. Seven-hundred and four participants will be recruited to the study, from at least eight UK National Health Service (NHS) hospitals, by their clinical care teams, and will provide written informed consent before undertaking any study procedures (figure 1).

An internal pilot phase will determine the feasibility of recruitment and adherence to the protocol and will be reviewed by the Trial Steering Committee (TSC) and funder (National Institute for Health and Care Research Efficacy and Mechanism Evaluation (EME) 17/145/40) after 6 months of recruitment. Progression from the pilot phase will be determined if at least 69 participants are recruited in the first 6 months of recruitment, or a feasible plan to satisfy any recruitment shortfall is in place.

In addition to the internal pilot, the TSC will review the following outcomes throughout the study and may recommend early termination if, in a number of participants, there is:

1. A failure to deliver the intervention as allocated.
2. A failure to complete the DW MRI scan according to the protocol before discharge after surgery.

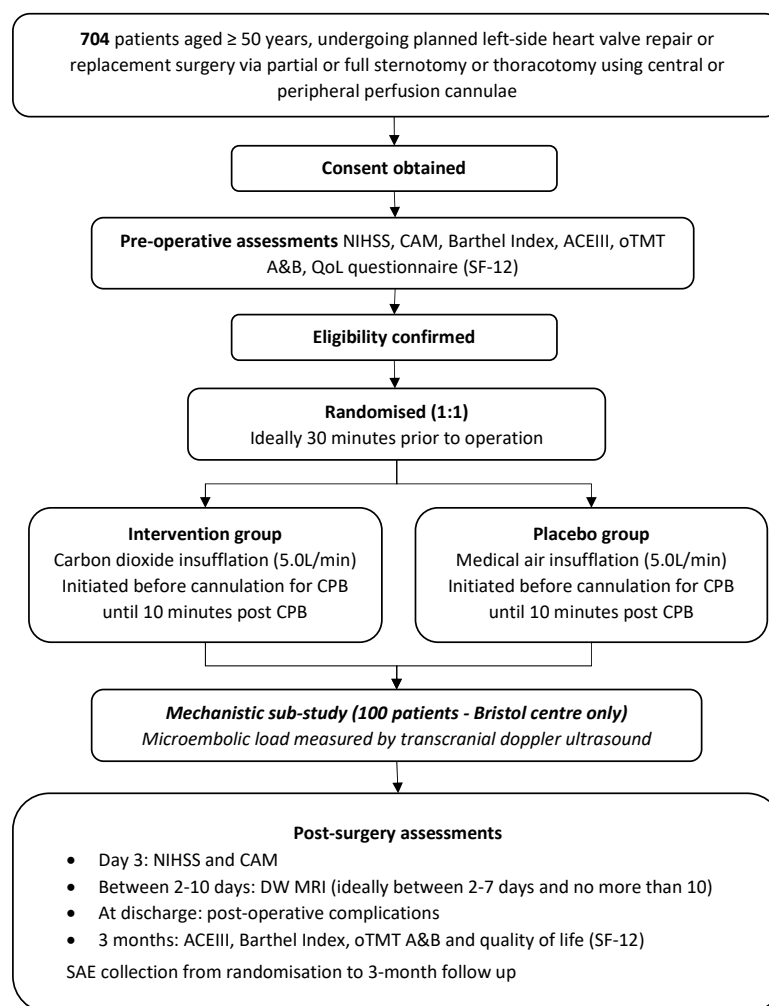
Patients eligible for the study are those aged 50 years or over and undergoing planned left-sided valve (aortic or mitral) surgical repair or replacement (with or without another procedure, for example, coronary artery bypass graft) via a partial or full sternotomy or thoracotomy using central (ie, aortic) or peripheral (ie, femoral) perfusion cannulae.

Patients will be ineligible if they have any of the following: contraindication to medical carbon dioxide; acquired or genetic acidosis; contraindication to MRI; history of clinical stroke within 3 months prior to randomisation; cardiac catheterisation within 3 days of the planned surgery; cerebral and/or aortic arch arteriography or interventions within 3 days of the planned surgery; active endocarditis at time of randomisation; planned concomitant aortic procedure such as root replacement; clinical signs of cardiogenic shock or treatment with intravenous inotropic therapy prior to randomisation; previous cardiac surgery or participation in an interventional (drug or device) trial; unable to provide written informed consent or are a prisoner.

Participants have the right to withdraw at any time. If they withdraw, data collected up until the time of withdrawal will be included in the analyses. Participants who choose to withdraw from the study will continue to be treated according to standard care and may give permission for data to continue to be collected.

Randomisation

Eligibility will be confirmed by the principal investigator, delegated medically qualified doctor or advanced nurse practitioner at the research site. Participants will be randomised as close to surgery as possible, to receive either medical CDI (Investigational Medicinal Product, IMP) or medical air insufflation (placebo) in a 1:1 ratio, following written informed consent and completion of baseline assessments. Randomisation will be performed using a secure internet-based randomisation system ensuring allocation concealment by a member of the research team not involved in data collection or participant follow-up (eg, the perfusionist). Allocation will be stratified by centre, type of surgery (valve or valve and

1 **Figure 1. Trial schema**

2

3 Abbreviations: National Institute for Health Stroke Scale – NIHSS; Confusion Assessment Method –
 4 CAM; Addenbrookes Cognitive Examination III – ACEIII; Oral Trail Making Test part A&B – oTMT A&B
 5 Quality of Life – QoL; Short Form 12 questionnaire – SF12; Cardiopulmonary Bypass – CPB; Diffusion
 6 Weighted Magnetic Resonance Imaging – DW MRI; Serious Adverse Events – SAE

1

CO2 study protocol paper – Figure 1 Trial Schema V2.0

Figure 1 Trial schema. ACEIII, Addenbrooke's Cognitive Examination III; CAM, Confusion Assessment Method; CPB, cardiopulmonary bypass; DW MRI, diffusion-weighted MRI; NIHSS, National Institutes for Health Stroke Scale; oTMT A&B, oral Trail Making Tests part A&B; QoL, Quality of Life; SAE, serious adverse event; SF-12, Short-Form Health Survey Questionnaire.

another procedure, ie, coronary artery bypass graft), and if the planned surgery is minimally invasive or not.

Blinding

The perfusionist will be unblinded to the treatment allocation in order to deliver the intervention and monitor the participant throughout surgery. An unblinded member of the research team may also be used to carry out randomisation if the perfusionist is unable to do so. They will provide the perfusionist with the paper case report form (CRF) stating the allocated intervention assigned at randomisation, in a sealed envelope. The perfusionist will

complete details of the insufflation delivery, CPB and any evidence of hypercapnia (increased carbon dioxide in the bloodstream) on the CRF and return it to the unblinded member of the research team, who will be responsible for entering the data and addressing any queries on the database. The completed CRF will be stored in a folder separate from the rest of the CRFs to ensure blinding of the rest of the team is maintained.

Cylinders of medical carbon dioxide and medical air are both grey in colour and can be purchased in the same size. Only the collar of the cylinders differs in colour.

Cylinders of the allocated intervention will be brought into the operating theatre covered with surgical drapes to ensure blinding of the surgical team. There are no obvious external clinical cues as to which intervention is being used. The mode of delivery has been standardised for both interventions.

Blinding of the research nurse responsible for data collection and the imaging reviewer will be assessed using the Bang Blinding Index.¹³

Unblinding

Participants will be made aware before entering the study that they will not be told which intervention they receive until after the study has finished. Requests to unblind during surgery on clinical grounds (eg, treating a complication) are not anticipated. However, if unblinding is requested, this will be facilitated by the perfusionist. Requests to unblind after leaving the operating theatre should not occur given the effect of insufflation is limited to the period of delivery. Therefore, management of subsequent clinical events would not be altered by knowledge of the allocation. All incidences of unblinding will be fully documented on the CRF including the person requesting the unblinding and the reason, and will be monitored by the Trial Management Group (TMG).

Trial intervention

Both the study IMP and placebo are licensed and commercially available in the UK. In this trial, medical carbon dioxide (IMP) and medical air (placebo) will be used 'off label'. Cylinders will be labelled by the trial's pharmacist with Medicines and Healthcare products Regulatory Agency (MHRA)-approved Annex 13-compliant labels in accordance with Good Clinical Practice and local pharmacy standard operating procedures.

The allocated intervention will be insufflated into the cardiotomy wound at a flow rate of 5 L/min through a gas diffuser that provides an almost 100% atmosphere of the allocated gas in the cardiotomy wound. Insufflation will start before cannulation for CPB and continue until 10 min after discontinuation of CPB. Cardiotomy suction will be limited to a maximum of 1.5 L/min and the additional suction set to 10 L/min to avoid affecting gas concentrations in the surgical field.

Withdrawals during treatment should not occur due to the nature and duration of the intervention; the duration of intervention is from before cannulation for CPB, until 10 min after CPB has stopped. Problems with adherence (eg, failure to follow the randomisation allocation) are also expected to be low. The perfusionist will document whether the allocated treatment was given, if there were any deviations from the allocated intervention and the reason. Deviations will be monitored by the TMG and Data Monitoring and Safety Committee (DMSC).

Surgical procedure

Surgery will be performed through complete or partial median sternotomy or right thoracotomy. Central or

peripheral cannulation for CPB may be used. Myocardial preservation and de-airing manoeuvres will be carried out in accordance with existing local protocols as will all other aspects of the participants' preoperative, intraoperative and postoperative management.

Research procedures

Neurocognitive and functional assessments will be carried out for all participants by a suitably trained member of the local research team. At baseline (up to 2 months pre-surgery), the National Institutes of Health Stroke Scale (NIHSS), Confusion Assessment Method (CAM),¹⁴ Barthel Index,¹⁵ Addenbrooke's Cognitive Examination III (ACEIII)¹⁶ and oral Trail Making Tests part A&B (oTMT)^{17 18} are completed in person. At 3 days post-surgery, the NIHSS and CAM are repeated in person. At 3 months post-surgery, the Barthel Index, ACEIII and oTMT are repeated remotely via video call.

Quality of life will be assessed using the Short-Form Health Survey (SF-12)¹⁹ at baseline (in person) and 3-month follow-up (remote, postal or online). Participants will be able to choose the method of questionnaire administration at 3 months when they enter the study.

A DW MRI brain scan will be carried out no more than 10 days post-surgery (ideally between 2 and 7 days) for all participants. Images will be pseudonymised by sites and transferred for independent blinded review by a clinical neuroradiologist.

Adverse events will be recorded between randomisation and discharge from hospital after the index operation. Serious adverse events will be recorded between randomisation and the 3-month follow-up. Between randomisation and discharge, all serious adverse events that are unexpected of the IMP or surgery and/or fatal will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

Outcomes

The primary outcome is acute ischaemic brain injury within 10 days post-surgery based on new brain lesions identified with DW MRI or clinical evidence of permanent brain injury according to the An Updated Definition of Stroke for the 21st Century.²⁰

Secondary outcomes are: number and volume of DW MRI brain lesions; objective quantification of the impairment caused by new ischaemic brain injury assessed using the NIHSS; delirium assessed using the 3 min diagnostic interview for CAM; functional status assessed using the Barthel Index score; neurocognitive function in six domains (verbal memory, visual memory, executive functioning, visuospatial or constructional praxis, attention and information processing speed) assessed using ACEIII and oTMT; quality of life assessed using the physical and mental subscales of the SF-12; the composite of all-cause mortality, clinical stroke or acute kidney injury within 30 days of surgery; serious adverse events to 3 months; survival to 3 months.

Table 1 Schedule for data collection

	Baseline	Intraoperative	Post-surgery				
			Day 3 (between 3 and 5 days postop)	Days 2–7 (but no more than 10 days)	Discharge	Routine postop follow- up	Three- month follow- up
National Institutes of Health Stroke Scale	✓		✓				
Confusion Assessment Method	✓		✓				
Functional status: Barthel Index score	✓						✓
Neurocognitive function tests: Addenbrooke's Cognitive Examination III and oral Trail Making Tests part A&B	✓						✓
Short-Form Health Survey Quality of Life Questionnaire	✓						✓
Assessment of postoperative complications					✓		
Diffusion-weighted MRI brain scan				✓			
Assessment of serious adverse events			✓	✓	✓	✓	✓
Assessment of blinding success							✓
Transcranial Doppler ultrasound*		✓					
Near-infrared spectroscopy*		✓					

*Only conducted for mechanistic substudy participants at one site.

Mechanistic substudy

One-hundred participants at a single centre will take part in the mechanistic substudy. Participants who consent will undergo a TCD ultrasound during surgery to monitor microembolic load and cerebral blood flow velocity (CBFV). In parallel, participants will undergo near-infrared spectroscopy (NIRS) to monitor tissue oxygenation index (TOI) in the frontal lobes during surgery.

Objectives of the mechanistic substudy are to determine whether there is a relationship between ischaemic brain injury detected by DW MRI and (1) intraoperative air embolic load detected by TCD, (2) cerebral blood flow detected by TCD, (3) TOI of the frontal lobes by NIRS, and whether these relationships differ between the CDI and medical air insufflation groups.

Substudy outcomes are: cerebral gaseous microembolic load assessed using TCD; CBFV from both middle cerebral arteries; TOI of the frontal lobes measured using NIRS.

Data management

Data will be collected by local research teams on paper CRFs and then entered into a purpose-designed password-protected, restricted access, bespoke electronic database. Images from the postoperative brain DW MRI scans will be pseudonymised and uploaded to a bespoke database separate from the main database for transfer to the consultant neuroradiologist central reviewer. The schedule for data collection is shown in [table 1](#). Study documentation will be retained for 15 years after the end of the study in a secure location and then confidentially destroyed. Data

will not be made available for sharing until after publication of the main results of the study.

Sample size

The target sample size is 704 participants, 352 per group, which will provide 90% power at a 5% significance level (two-sided) to detect a 25% relative reduction in the incidence of postoperative cerebral infarcts with CDI, assuming a 48% rate in the placebo group. Missing data for the primary outcome are expected to be minimal as the DW MRI brain and assessment of stroke will be completed prior to the participant's discharge home.

The anticipated event rate in the placebo group was chosen based on a meta-analysis of all available observational studies where brain MRI was routinely performed early after open heart valve surgery.⁹ Eight studies were identified with sample sizes ranging from 15 to 129 participants and rates of new ischaemic lesions at MRI ranging from 38% to 72%. The pooled random-effects estimate of new ischaemic lesions was 55% (95% CI 48% to 63%). We used the lower limit of the 95% CI (48% event rate) to calculate our sample size.

Statistical analysis plan

Analyses will take place when follow-up has been completed for all participants and the database has been locked. Analyses will be performed on an intention-to-treat basis as directed by a prespecified statistical analysis plan. The analysis population will comprise all patients randomised. Primary and secondary outcomes will be compared using logistic (binary variables), Poisson (count variables), Cox proportional hazards (time to

event variables) or linear (continuous variables) regression, with placebo as the reference group. Model validity will be checked using standard methods; if a model is a poor fit, alternative models or transformations will be explored. Continuous outcomes analysed on a logarithmic scale will be transformed back to the original scale after analysis and results presented as geometric mean ratios. Analyses will be adjusted for baseline values and stratification variables (centre, type of surgery and type of incision). Findings will be reported as effect sizes with 95% CIs.

Mechanistic substudy

There are no previous studies investigating the association between embolic load and brain injury post-cardiac surgery, but embolic load detected by TCD shows a strong correlation with DW MRI positive lesions ($r=0.70$) during coil embolisation of unruptured intracranial aneurysms.²¹ Assuming a weaker association during open heart surgery, the sample size for substudy has been set at 100 participants, which will provide 90% power at a 5% significance level (two-sided) to detect a correlation of 0.32 (linear regression r^2 of 0.1).

Trial management and oversight

This study will be designed and delivered in collaboration with the Bristol Trial Centre, a UK Clinical Research Collaboration (UKCRC)-registered clinical trials unit (UKCRC registration number 70). The CO2 Study will be sponsored by the University Hospitals Bristol and Weston NHS Foundation Trust (www.uhbristol.nhs.uk/research-innovation/), which are responsible for the oversight of the study and ensuring it is managed appropriately. The trial will be coordinated in accordance with Good Clinical Practice guidelines and current legislation.

The study will be managed by the TMG, chaired by the chief investigator and members of the CO2 Study research team and will be overseen by an independent TSC and independent DMSC.

Patient and public involvement

The study was initially reviewed by the Bristol Biomedical Research Centre Cardiovascular patient and public involvement (PPI) group in March 2018. Overall, they responded positively to the study and did not raise any issues with the DW MRI scan or neurocognitive function testing. The group further reviewed changes to the study in August 2020 to discuss the inclusion of remote consent and remote follow-up by video call. The group were encouraging of the changes, which simplified the participant pathway, and did not find these changes as barriers to involvement. We will continue to engage with this PPI group throughout the trial as required and for the dissemination of the study results. The CO2 Study TSC includes a PPI member who reviews all amendments to the study.

ETHICS AND DISSEMINATION

Research ethics approval was granted by the UK (East Midlands–Nottingham 2) Research Ethics Committee (reference 20/EM/0130) on 15 June 2020. Regulatory approvals were obtained from the MHRA in May 2020 and Health Research Authority in June 2020.

All participants will be required to provide written informed consent (online supplemental material 1) before participating in the study. Information will be given to patients in advance of recruitment. Consent will be obtained by the principal investigator or a delegated member of the local research team who has been trained in the study and received Good Clinical Practice training in the last 3 years. Consent will be obtained either face to face at a clinic appointment or remotely by telephone/video call with the consent recorded on either a paper consent form or electronically using a purpose-designed database.

Results of the study will be fully reported to the funder, presented at national and international conferences and published in peer-reviewed journals. We will link with the British Heart Foundation, with the valve group of the Society of Cardiothoracic Surgery in Great Britain & Ireland and Guidelines Committees of the European Association for Cardiothoracic Surgery to inform them of the results and provide any recommendations. Participants will be informed of results of the study through notifications from the study team and patient organisations.

Changes to the protocol

The protocol has been amended seven times since initial approval to provide clarification on the surgical guidance, introduce remote consent and remote follow-up, update the inclusion criteria, clarify randomisation strata to include patients undergoing minimally invasive surgery and remove the NIHSS and CAM assessments from the 3-month follow-up.

The current approved protocol is version 8.0 (14 December 2022). A full study protocol is available in online supplemental material 2 and Carbon Dioxide Insufflation and Brain Protection During Open Heart Surgery. A Randomized Controlled Trial (CO-Two) - NIHR Funding and Awards.

Changes resulting from the COVID-19 pandemic

The global COVID-19 pandemic affected the start of the study and posed serious logistical issues. Significant delays were experienced starting recruitment due to COVID-19, which led to the redeployment of local research teams to clinical areas, prioritisation of COVID-19 research and the reduction in elective cardiac surgery. Initially, due to start in June 2020, recruitment opened on 6 October 2021, 17 months behind target. Capacity issues within local research teams and MRI departments have limited the number of sites we have been able to open. To mitigate the slow start, more sites have been approached to take part in the study. The study was also adapted to introduce remote consent, allowing more time for in-person

baseline assessments to be completed prior to surgery, and remote follow-up, to reduce research-specific hospital visits, and it is intended that these changes remain in place for the remainder of the study.

DISCUSSION

The CO2 Study is the largest RCT assessing the efficacy and safety of CDI in patients undergoing open heart valve surgery. With the addition of the mechanistic substudy, it will determine the relationship between intraoperative air microemboli and ischaemic brain injury detected on DW MRI.

The study was designed to complement the surgical pathway to ensure participants did not have to attend additional research-specific visits. Changes to the pathway due to COVID-19 replaced the only in-person trial specific visit at 3 months with a remote call, which allows flexibility in the time and location where the call can be carried out making it easier for participants to attend. Inclusion of patients aged over 50 years and undergoing open heart valve surgery, by any access, allows a large population of participants to be included in the study.

The large battery of assessments to assess the neuro-cognitive and functional ability of participants has the potential to deter patients from taking part in the study or result in missing data. Originally, 12 assessments, taking 2 hours to complete, were proposed. Following concerns from research nurses, this was reduced to five, taking 1 hour to complete, while maintaining the same number of domains assessed. This ensured assessments would be less of a barrier to recruitment. We further updated the protocol in December 2022 to remove the NIHSS and CAM from the 3-month follow-up as they offered little value at this time point. Stroke would be detected via the NIHSS at 3 days post-surgery and delirium only occurs up to 7 days post-surgery, following which persisting symptoms would be considered 'postoperative cognitive dysfunction', which would be identified using the ACEIII and oTMT at 3 months. This further streamlined the study and reduced the research burden at this time point for both sites and participants.

By assessing the neuroprotective effect of CDI, we aim to provide an answer to a question for which there is surgical clinical equipoise. More importantly, with more elderly and high-risk patients being offered cardiac surgery, it is critical to identify ways to reduce the impact of heart valve surgery-related neurological complications, that is, longer hospital stays, slower recovery, poor quality of life, increased healthcare use and reduced long-term survival.

The study was designed to complement the surgical pathway, completing the primary outcome while the participant is still in hospital post-surgery, making it feasible for local research teams to conduct and less burdensome for the participant.

Author affiliations

¹Bristol Trials Centre, University of Bristol, Bristol, UK

²Bristol Trials Centre, Bristol Medical School, University of Bristol, Bristol, UK

³Wellcome Centre for Integrative Neuroimaging, University of Oxford, Oxford, UK

⁴James Cook Hospital, South Tees Hospitals NHS Foundation Trust, Middlesbrough, UK

⁵John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

⁶Bristol Heart Institute, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, UK

⁷Bristol Medical School, University of Bristol, Bristol, UK

Twitter Rachel Todd @co2study, Enoch Akowuah @EnochAkowuah1 and Rana Sayeed @rana_sayeed

Acknowledgements The authors thank all the research and clinical team members at participating sites and the members of the independent Trial Steering Committee and independent Data Monitoring and Safety Committee.

Contributors RT set up and manages the day-to-day running of the study and wrote the first draft of the manuscript. CR is the statistical lead for the study. MP identified the funding opportunity and co-designed the study. LC provides senior trial management for the study. PP and NV provide DW MRI expertise and independently review the primary outcome data. EA, RS and GDA contributed to the development of the protocol with their surgical expertise. ML is the statistician for the study. SK assists with the set-up and conduct of the study. BG is chief investigator responsible for delivery and reporting of the study. All authors read and approved the final manuscript.

Funding The CO2 Study is funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation (EME) programme (ref. EME 17/145/40). This study is being conducted in collaboration with Bristol Trials Centre, a UKCRC-registered clinical trials unit which is in receipt of NIHR Clinical Trials Unit support funding.

Disclaimer The views expressed in this paper are those of the author(s) and not necessarily of the NHS, the NIHR or Department of Health and Social Care.

Competing interests CR, GDA and BG received support from the National Institute for Health and Care Research for the project associated with this manuscript, which was paid to the University of Bristol. RT, MP, LC, ML and SK received support from the National Institute for Health and Care Research for the project associated with this manuscript, which contributed to their salary. PP, NV and RS received support from the National Institute for Health and Care Research for the project associated with this manuscript, which was paid to the University of Oxford. EA received support from the National Institute for Health and Care Research for the project associated with this manuscript, which was paid to the RS reports ad hoc payments for providing expert testimony for the Parliamentary & Health Service Ombudsman. RS is the director and shareholder of Oxford Heart Surgery, chairs the Intercollegiate Speciality Board on Cardiothoracic Surgery, and is a member of the Special Advisory Committee in Cardiothoracic Surgery for the Royal Society of Medicine. RS is an honorary secretary of the Society for Cardiothoracic Surgery in Great Britain and Ireland. No other conflicts were reported.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iDs

Rachel Todd <http://orcid.org/0000-0002-4107-4300>

Enoch Akowuah <http://orcid.org/0000-0002-2429-3579>

Rana Sayeed <http://orcid.org/0000-0002-2887-1874>

REFERENCES

- 1 SurgerySfC. National cardiac surgery activity and outcomes report 2002–2016. *Soc Cardio Surg* 2020.
- 2 Cropsey C, Kennedy J, Han J, et al. Cognitive dysfunction, delirium, and stroke in cardiac surgery patients. *Semin Cardiothorac Vasc Anesth* 2015;19:309–17.
- 3 Kotfis K, Szylińska A, Listewnik M, et al. Early delirium after cardiac surgery: an analysis of incidence and risk factors in elderly (≥65 years) and very elderly (≥80 years) patients. *Clin Interv Aging* 2018;13:1061–70.
- 4 Sun X, Lindsay J, Monsein LH, et al. Silent brain injury after cardiac surgery: a review: cognitive dysfunction and magnetic resonance imaging diffusion-weighted imaging findings. *J Am Coll Cardiol* 2012;60:791–7.
- 5 Mack MJ, Acker MA, Gelijns AC, et al. Effect of cerebral embolic protection devices on CNS infarction in surgical aortic valve replacement: a randomized clinical trial. *JAMA* 2017;318:536–47.
- 6 Abu-Omar Y, Cader S, Guerrieri Wolf L, et al. Short-Term changes in cerebral activity in on-pump and off-pump cardiac surgery defined by functional magnetic resonance imaging and their relationship to microembolization. *J Thorac Cardiovasc Surg* 2006;132:1119–25.
- 7 Mitz MA. Co2 biodynamics: a new concept of cellular control. *J Theor Biol* 1979;80:537–51.
- 8 Ng WS, Rosen M. Carbon dioxide in the prevention of air embolism during open-heart surgery. *Thorax* 1968;23:194–6.
- 9 Benedetto U, Caputo M, Guida G, et al. Carbon dioxide insufflation during cardiac surgery: a meta-analysis of randomized controlled trials. *Semin Thorac Cardiovasc Surg* 2017;29:301–10.
- 10 Haussig S, Mangner N, Dwyer MG, et al. Effect of a cerebral protection device on brain lesions following transcatheter aortic valve implantation in patients with severe aortic stenosis: the CLEAN-TAVI randomized clinical trial. *JAMA* 2016;316:592–601.
- 11 Lansky AJ, Messé SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an academic research Consortium initiative. *J Am Coll Cardiol* 2017;69:679–91.
- 12 Van Mieghem NM, van Gils L, Ahmad H, et al. Filter-Based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. *EuroIntervention* 2016;12:499–507.
- 13 Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004;25:143–56.
- 14 Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014;161:554–61.
- 15 Mahoney FI, Barthel DW. Functional evaluation: the barthel index. *Md State Med J* 1965;14:61–5.
- 16 Hsieh S, Schubert S, Hoon C, et al. Validation of the Addenbrooke's cognitive examination III in frontotemporal dementia and Alzheimer's disease. *Dement Geriatr Cogn Disord* 2013;36:242–50.
- 17 Army Individual Test Battery. *Manual of directions and scoring*. Washington, DC: War Department, Adjutant General's Office, 1944.
- 18 Kaemmerer T, Riordan P. Oral adaptation of the TRAIL making test: a practical review. *Appl Neuropsychol Adult* 2016;23:384–9.
- 19 Ware J, Kosinski M, Keller SD. A 12-Item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33.
- 20 Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American heart association/american stroke association. *Stroke* 2013;44:2064–89.
- 21 Cho JH, Kang DH, Kim YW, et al. Microembolic signal monitoring and the prediction of thromboembolic events following coil embolization of unruptured intracranial aneurysms: diffusion-weighted imaging correlation. *Neuroradiology* 2015;57:189–96.