CLINICAL STUDY REPORT

COPIA Feasibility Trial

Comparison between Propofol and Inhalational Anaesthetic Agents (COPIA) on Cardiovascular Outcomes following Cardiac Surgery – a Randomised Controlled Feasibility Trial

Sponsor Protocol Code:	KCH-PRO:19/001
EudraCT Number:	2019-000171-16
ClinicalTrials.gov Identifier:	NCT04039854
ISRCTN number:	216646
REC Number:	19/LO/1071
Investigational Drugs (IMPs):	Propofol, Isoflurane, Sevoflurane, Desflurane
Indication:	Maintenance of Anaesthesia
Development Phase:	Phase 4
Study Begin (FPFV):	December 2019
Study End (LPLV):	March 2022
Report Version & Issue Date:	~~10th Feb 2024~~ 21st January 2026
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SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

This was a non-commercial academic trial, the results of this study are not intended to be used or licensing application.

Chief Investigator:

Printed name	**Signature**	**Date**
Gudrun Kunst		~~**10th February 2024**~~ ~~**22nd December 2025**~~ **21st January 2026**

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved on 2nd August 2019 by a National Research Ethics Service, London Chelsea Research Ethics Committee, REC London Centre, Skipton House, 80 London Road, London SE1 6LH.

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent

The research team contacted eligible patients before their scheduled hospital appointment via post, email or telephone in order to introduce the trial to the patient. A copy of the Participant Information Sheet (PIS) and patient invitation letters were supplied to patients who were contacted by post and email. If contacted by telephone, patients were given a copy of the PIS at a pre-assessment appointment before their planned surgery date.

2. Data Monitoring

A Trial Management Group (TMG) was set up and it met regularly every 4-6 weeks during the recruitment period, until March 2020, when the Covid pandemic started. Thereafter there was a recruitment and meeting hiatus due to the pandemic until 2022, when the database and study were closed.
The TMG was responsible for the day to day running of the trial. It included:
Dr Gudrun Kunst (King's College Hospital), Chief Investigator
Dr Martin John (St Thomas' Hospital), Co-Investigator
Professor Michael Marber (St Thomas' Hospital and King's College London), Co-Investigator
Mr Richard Evans (London School of Hygiene and Tropical Medicine), CTU Senior Trialist
Mr Tim Clayton (London School of Hygiene and Tropical Medicine), CTU Senior Statistician
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Mr Steven Robertson (London School of Hygiene and Tropical Medicine), CTU Trialist
Miss Farandeep Dhaliwal (London School of Hygiene and Tropical Medicine), CTU Trialist
Professor Gavin Murphy (Leicester University), Co-Investigator

The data monitoring committee included an independent statistician and two independent members:
Tim Morris (MRC Clinical Trials Unit, University College London) – independent statistician
Professor Alexander Wahba, Consultant cardio-thoracic surgeon and Professor of Thoracic Surgery at the St. Olavs University Hospital in Trondheim, Norway
Dr. Vladimir Lomivorotov, Penn State University, USA

The Data Monitoring Committee met periodically, 6-monthly, until the Covid pandemic in March 2020 and it carefully monitored recruitment and safety of the study during the first months of recruitment.

3. Sponsors, Investigators and Trial Sites

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5. Study Synopsis

Title of clinical trial	Comparison between Propofol and Inhalational Anaesthetic Agents (COPIA) on Cardiovascular Outcomes following Cardiac Surgery - a Randomised Controlled Feasibility Trial
Protocol Short Title/Acronym	COPIA Feasibility Trial
Study Phase	Phase 4
Sponsor name	Name: King's College Hospital NHS Foundation Trust Sponsor Contact: Ann-Marie Murtagh Address: King's Health Partners Clinical Trial Office, 16th Floor, Tower Wing, Guy's Hospital, Great Maze Pond, London, SE1 9RT Telephone: 020 7188 5732 Email: annmariemurtagh@nhs.net
Chief Investigator	Name: Dr Gudrun Kunst Address: Department of Anaesthetics and Pain Therapy King's College Hospital NHS Foundation Trust Denmark Hill, London, SE5 9RS Telephone: 020 3299 3154 Email: gudrun.kunst@kcl.ac.uk
Eudract number	2019-000171-16
REC number	19/LO/1071
IRAS project ID:	216646
Medical condition or disease under investigation	Cardiac Coronary artery disease plus/minus cardiac valve disease
Purpose of clinical trial	Myocardial revascularisation and cardiopulmonary bypass (CPB) can cause ischemia-reperfusion injury, leading to myocardial and other end-organ damage. Volatile anaesthetics protect the myocardium in experimental studies. However, there is uncertainty whether this translates into clinical benefits, because of co-administration of propofol, restricting myocardial protective processes.
Primary objective	i) determination of the likely rate of recruitment at two centres with the aim to complete recruitment within 10 months; ii) the identification of potential recruitment barriers with the existing protocol.
Secondary objective (s)	Secondary outcomes included: i) an assessment of effective patient identification, screening and recruitment; ii) the feasibility of collecting the planned

	perioperative data in more than 95% of enrolled patients at the 30-day follow-up point; iii) an assessment of trial processes, including outcome measures; iv) an assessment of feasibility of collecting a number of clinically relevant outcomes until 30 days after surgery, including low cardiac output syndrome (LCOS), Stroke, MI or death from any cause, cardiac related mortality, postoperative atrial fibrillation (AF) requiring treatment, ICU and hospital length of stay, patients reported disability and Quality of Life (European Quality of Life – 5),
Trial Design	Single blinded parallel group randomised controlled feasibility trial
Endpoints	We intend to assess whether a volatile-only anaesthetic strategy, i.e. total inhalational anaesthesia, for coronary artery bypass surgery on CPB, compared with a propofol anaesthetic strategy, reduces postoperative cardiovascular morbidity (major adverse cardiovascular and cerebral events, MACCE) as the overarching hypothesis.
Planned number of subjects	50
Summary of eligibility criteria	Inclusion criteria ▪ Patients aged 18 years and above ▪ Written informed consent to participate ▪ Patients undergoing Coronary Artery Bypass Graft (CABG) ▪ surgery on Cardiopulmonary bypass (CPB) with or without valve ▪ surgery ▪ Additive European System for Cardiac Operative Risk Evaluation ▪ (EuroSCORE) of 5 or higher Exclusion criteria ▪ Pregnant or lactating women ▪ Allergy to propofol ▪ Previous diagnosis or suspected malignant hyperthermia ▪ Patients with a known sensitivity to any of the IMPs or other ▪ halogenated anaesthetics ▪ Concomitant therapy with glibenclamide, allopurinol, ▪ theophylline or nicorandil (medications that may interfere with ▪ cardioprotection) ▪ Inclusion in another clinical trial of an investigational medicinal ▪ product within the last 3 months.

IMP, dosage and route of administration	Volatile anaesthetics, either isoflurane, sevoflurane or desflurane, used for maintenance of anaesthesia. Administration via inhalation / ventilation through alveolar membrane in lungs. The maintenance dose of the volatile anaesthetic agent will be titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia and blood pressure.
Active comparator product(s)	Propofol, an intravenous anaesthetic used for maintenance of anaesthesia. The maintenance dose of the propofol infusion will be titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia without blood pressure.
Maximum duration of treatment of a subject	10hrs (The intraoperative maintenance of general anaesthesia with the above drugs depends on the duration of surgery, which usually lasts 4-6hrs, and does not normally exceed 10hours)
Version and date of protocol amendments	~~Not applicable~~ Protocol version 1.0 dated 26Apr2019 version 2.0 dated22Jan2020

6. Glossary of terms

ACE Angiotensinogen Converting Enzyme
AE Adverse Event
AF Atrial Fibrillation
AKI Acute Kidney Injury
AR Adverse Reaction
ARB Angiotensin Receptor Blockers
BIS Bispectral Index
CABG Coronary Artery Bypass Graft
CAM Confusion Assessment Method
CCS Canadian Cardiovascular Society
CCU Critical Care Unit
CKD Chronic Kidney Disease
COPD Chronic Obstructive Pulmonary Disease
CPAP Continuous Positive Airway Pressure
CPB Cardiopulmonary Bypass
CRF Case Report Form
CRP C-Reactive Protein
cTn Cardiac Troponin T
CTO Clinical Trials Office
CTU Clinical Trials Unit
CVA Cerebrovascular Accident
DMC Data Monitoring Committee
DSUR Development Safety Update Report
EACTA European Association of Cardiothoracic Anaesthesiology ECG Electrocardiogram
EEG Electroencephalogram
EQ-VAS Visual Analogue Scale
EQ-5D-5L 5-level Euroqol-5D (Quality of Life Questionnaire)
GCP Good Clinical Practice
GDPR General Data Protection Regulation

HDU High Dependency Unit
HRQoL Health-related Quality of Life
hsTnT High sensitive Troponin T
IABP Intra-aortic Balloon Pump
IGFBP7 Insulin-Like Growth Factor Binding Protein 7
IHD Ischaemic Heart Disease
IME Important Medical Events
IMP Investigational Medicinal Product
KDIGO Kidney Disease Improving Global Outcomes KHP-CTO King's Health Partners Clinical Trials Office
LSHTM London School of Hygiene and Tropical Medicine LA Left Atrium
LCOS Low Cardiac Output Syndrome
LVEF Left ventricular Ejection Fraction
MACCE Major Adverse Cerebral or Cardiac Event
MAP Mean Arterial Pressure
MH Malignant Hyperthermia
MHRA Medicines and Healthcare Products Regulatory Agency
MI Myocardial Infarction
mPTP Mitochondrial Permeability Transition Pore
MyC Myosin binding protein C
NGAL Neutrophil Gelatinase Associated Lipocalin
NHS National Health Service
NYHA New York Heart Association
PI Principal Investigator
PIS Participant Information Sheet
RCT Randomised Controlled Trial
REC Research Ethics Committee
RISK Reperfusion Injury Salvage Kinases
SAE Serious Adverse Event
SAFE Survivor Activating Factor Enhancement
SAR Serious Adverse Reaction
SIRS Systematic Inflammatory Response Syndrome
SmPC Summary of Product Characteristics
SOP Standard Operating Procedure
SUSAR Suspected Unexpected Serious Adverse Reaction
TIA Transient Ischaemic Attack
TIMP-2 Tissue Inhibitor of Metalloproteinase-2
TIVA Total Intravenous Anaesthesia
TMG Trial Management Group
TNF Tumour Necrosis Factor
TSC Trial Steering Committee
UAR Unexpected Adverse Reaction
VT Ventricular Tachycardia
VF Ventricular Fibrillation
WHODAS World Health Organization Disability Assessment Schedule

7. Publication (reference)

Milne B, John M, Evans R, Robertson S, Ó Scanaill P, Murphy GJ, Landoni G, Marber M, Clayton T, **Kunst G**. Comparison between propofol and total inhalational anaesthesia on cardiovascular outcomes following on-pump cardiac surgery in higher-risk patients: a randomised controlled pilot and feasibility study. *Open Heart* 2024, 11:e002630

8. Study period (years)

2 years and 7 months
(Nov 2019 until May 2022)

FPFV
The first patient was visited and recruited on 20th Nov 2019.
LPLV
The last patient was visited and recruited on 16th Nov 2021.

The trial was ended after the follow up of the last patients and after the closure of the database and the unblinding in May 2022.
The trial was not terminated prematurely.

There was an interruption of recruitment for 13 months during the COVID pandemic from 12th March 2020 until 21st April 2021

9. Phase of development

Phase 4. The IMPs and comparator are licensed anaesthetic maintenance drugs which are used in common practice.

10. Objectives

The objective of the COPIA study was to assess whether a volatile-only anaesthetic strategy, i.e. total inhalational anaesthesia, for coronary artery bypass surgery on CPB, compared with a propofol anaesthetic strategy, reduces postoperative cardiovascular morbidity (major adverse cardiovascular and cerebral events, MACCE) as the overarching hypothesis. We describe here the findings of a feasibility study designed to investigate recruitment and protocol adherence to the randomised treatment allocation.

11. Background and Context

Coronary artery bypass graft (CABG) surgery is the revascularisation strategy of choice for patients with multi-vessel coronary artery disease. However, cardiopulmonary bypass (CPB) and myocardial revascularisation cause ischemia-reperfusion injury, leading to myocardial and other end-organ damage. Myocardial protection has been demonstrated in experimental settings and it can be triggered by ischemic preconditioning via two main intracellular signal transduction pathways, the reperfusion injury salvage kinases (RISK) and survivor-activating factor enhancement (SAFE) pathways.[1,2] These pathways converge in the mitochondria and act upon the mitochondrial permeability transition pore (mPTP) to favour cell survival over cell death.[3,4] Interestingly, volatile anaesthetics mimic the activation of these myocardial protective pathways while propofol might be an inhibitor.[5,6]
Potential beneficial myocardial effects of volatile anaesthetics have been compared with intravenous agents in many clinical trials and meta-analyses, indicating some benefit on patient cardiovascular outcomes, but without a definitive answer.[7-9] Crucially, many of these studies have examined the use of volatile anaesthesia in combination with propofol infusions compared to propofol use alone. This concomitant administration of propofol with volatile anaesthetics conflicts with the demonstrable evidence that volatile agents used during CPB without additional propofol administration can reduce postoperative markers of myocardial injury, when compared with propofol use alone.[10,11] Also, in both clinical and experimental studies, propofol has been shown to restrict myocardial protective processes.[6,12-15]
The MYRIAD study randomised 5400 patients undergoing CABG to either total intravenous

anaesthesia (TIVA) or volatile anaesthesia.[16] However, within the volatile anaesthesia group, there were high rates (59%) of coadministration of propofol during the anaesthesia maintenance. In addition, patients undergoing off-pump procedures and patients with a low risk of ischemia reperfusion injury were included in this study. The authors reported no significant difference for relevant clinical outcomes, including mortality at 1-year, between the two groups.[16] A post-hoc analysis of the MYRIAD study, however, demonstrated a lower rate of myocardial infarction (MI) with hemodynamic instability and a reduction of 1-year cardiac mortality in patients receiving volatile anaesthetics. The authors conclude that these post-hoc results indicate potential clinically relevant cardioprotective effects by volatile anaesthetics, and they suggest that this should be further assessed, despite neutral effects on all-cause mortality.[17]

There has been recent demonstration that the administration of volatile anaesthesia during CPB is feasible, with oxygenator exhaust volatile concentrations correlating with arterial blood concentrations, and attainment of adequate hypnosis and amnesia by this technique.[18,19]

Overall, there is sufficient equipoise, even amongst noncardiac surgery, that a large randomised controlled trial (RCT) is underway for anaesthesia maintenance with volatile anaesthetic agents compared with TIVA including numerous clinical outcomes (VITAL; ISRCTN62903453). Currently there is heterogeneity in clinical practice for anaesthesia in cardiac surgical procedures in the UK and in Europe with approximately 50% of patients receiving intravenous anaesthesia alone without volatile anaesthesia.[20,21] Therefore, demonstration of a clinically important reduction in myocardial injury with a volatile-based anaesthetic technique during the maintenance phase of anaesthesia, including CPB, and without additional propofol (total inhalational anaesthesia) would have far-reaching practice implications.

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12. Methodology

12.1. Trial objectives and design

This single-blind randomised controlled trial was designed to assess the feasibility of the COPIA trial, in terms of recruitment and adherence to the randomised treatment allocation.

12.2. Hypothesis

Our overarching hypothesis was that the use of volatile anaesthetics, as the only maintenance for general anaesthesia, without propofol, would reduce postoperative LCOS and myocardial injury in higher risk adult patients undergoing elective CABG or CABG plus valve surgery, when compared to propofol maintenance of anaesthesia.

12.2.1. Definition of Volatile Anaesthetics

Volatile anaesthetic agents are halogenated ethers. Isoflurane (1-chloro-2,2,2-trifluoroethyl difluoromethyl ether) is commonly used in cardiac anaesthesia in the UK. However, sevoflurane (fluoromethyl-2,2,2-trifluoro-1-ethyl ether) or desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether) are also in use. Volatile anaesthetics are commonly administered via inhalation by vaporisers together with oxygen and air through the endotracheal tube. In the lungs they diffuse through the alveolar membrane into the blood stream, which is dependent on many variables such as inhaled concentration, alveolar ventilation, blood/gas partition coefficient and pulmonary blood flow. They are used for maintenance of anaesthesia and maintenance dose of the volatile anaesthetic agent was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia according to clinical signs of depth of anaesthesia and the blood pressure.

12.3. Inclusion criteria

1. Patients aged 18 years and above
2. Written informed consent to participate
3. Patients undergoing Coronary Artery Bypass Graft (CABG) surgery on Cardiopulmonary
4. bypass (CPB) with or without valve surgery
5. Additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 5 or higher (higher scores indicating a greater risk of death; 0 indicates minimum risk and ≥6 indicates high risk)

12.4. Exclusion criteria

1. Pregnant or lactating women
2. Allergy to propofol
3. Previous diagnosis or suspected malignant hyperthermia
4. Patients with a known sensitivity to any of the IMPs or other halogenated anaesthetics
5. Concomitant therapy with Glibenclamide, Allopurinol, Theophylline or Nicorandil (medications that may interfere with cardioprotection)
6. Inclusion in another clinical trial of an investigational medicinal product within the last 3 months.

12.5. Statement on co-enrolment

Patients may have been entered into registries or observational studies while also participating in COPIA. Patients may not have been entered into other IMP trials, research where co-enrolment would be burdensome for the patient, or into any other research where the trial treatment will interfere with the COPIA intervention and primary outcome.

12.6. Primary objectives

Feasibility of the study protocol:

1. Feasibility of meeting recruitment targets. The aim was to recruit 50 patients across two tertiary cardiac surgery centres within approximately 10 months.
2. Identification of potential recruitment barriers with current protocol.

12.7. Secondary objectives

- Feasibility of collecting event data in more than 95% of enrolled patients at the 30 day follow-up.
- Assessment of effectiveness of patient identification and screening processes.
- Identification and analysis of any reasons for failure to recruit patients.
- Assessment of trial processes, including the choice of outcome measures and impact on staff.
- Assessment on the feasibility of collecting the following, planned to be endpoints in the full trial:
    - Low Cardiac Output Syndrome
    - Myocardial injury, assessed by ischaemic serum markers: hsTnT, MyC, pre-operatively, at 6 hrs after arrival in CCU and on the 1st and 2nd postoperative mornings, area under the curve and peak postoperative levels
    - MACCE (stroke, non-fatal myocardial infarction, death from any cause) at 30 days
    - Cardiac related mortality at 30 days
    - Postoperative in hospital atrial fibrillation requiring treatment
    - Acute kidney injury (according to KDIGO)
    - In-hospital postoperative delirium (assessed by the confusion assessment method)
    - Respiratory complications needing prolonged ventilation (>24 hours)
    - Length of stay in the critical care unit (CCU)
    - Length of hospital stay
    - WHO Disability Assessment Schedule (WHODAS) at 30 days
    - Quality of Life Questionnaire, Euroqol EQ-5D-5L at baseline and 30 days
    - Days alive and at home until 30 days after surgery

12.8. Study endpoint definitions

12.8.1. Low Cardiac Output Syndrome (LCOS)

The clinical consequence of ischaemia reperfusion injury or inadequate myocardial protection is LCOS secondary to myocardial stunning or necrosis, which is characterised by an episode of left ventricular dysfunction requiring inotropic support or the insertion of an intra-aortic balloon pump (IABP). It is associated with increased morbidity and mortality [19]. The incidence is at least 10% after cardiac surgery and at least 20% after higher risk cardiac surgery [20] [21] [13].

LCOS is defined by new postoperative requirements of dopamine or dobutamine > 4 mcg. kg-1. min-1 iv , epinephrine or norepinephrine > 0.04 mcg. kg-1. min-1 iv, or milrinone > 0.125 mcg. kg-1. min-1 iv and/or intra-aortic balloon pump for > 30min started within six hours after reperfusion. These treatments help to maintain systolic blood pressure above 90 mmHg, the cardiac index > 2.1 L. min-1. m-2 and the ejection fraction >40% following optimization of heart rate, heart rhythm, preload, and afterload [19]. LCOS will be excluded if norepinephrine will be used to treat low systemic vascular resistance in the presence of a normal or elevated cardiac index or when there are echocardiography identified non-cardiac causes of hemodynamic instability [19].

12.8.2. Myocardial injury
This is defined as marked isolated elevation of cTn values above the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-operative cTn, with stable or falling cTn levels (<_ 20% variation), the postoperative cTn must rise by > 20%. ECG or imaging changes of MI don't have to be present.

12.8.3. Death
All deaths, and cause of death, within 30 days of surgery.

12.8.4. Myocardial infarction
According to the recently published 4th Universal Definition for type 5 (CABG-related) myocardial infarction (MI), this is defined as an elevation of cTn values >10 times the 99th percentile URL in patients with normal baseline cTn values. In patients with elevated pre-operative cTn, with stable or falling cTn levels (<_ 20% variation), the postoperative cTn must rise by > 20%. However, the absolute post procedural value still must be > 10 times the 99th percentile URL. In addition, one of the following is required: development of new pathological Q w[av]es; angiographic documented new graft occlusion or new native coronary artery occlusion; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology. Isolated development of new pathological Q waves meets the type 5 MI criteria if cTn values are elevated and rising but < 10 times the 99th percentile URL.

12.8.5. Stroke
A stroke was confirmed by a documented cerebral infarction or hemorrhage on computed tomographic or magnetic resonance imaging scan or by the occurrence of new neurologic signs (paralysis, weakness, or speech difficulties) lasting longer than 24 hours or leading to earlier death.

12.8.6. Acute kidney injury
Acute renal failure was confirmed by a 1.5 – 1.9 increase of serum creatinine from baseline or an absolute value rise of creatine greater than 0.3mg/dl (27mmol/L) from baseline.

12.8.7. In-hospital postoperative delirium
In-hospital postoperative delirium was assessed using the confusion assessment method (CAM).
For the diagnosis of delirium by the CAM method, the following features were necessary:

- Presence of acute onset and fluctuating course
  and
- Inattention (e.g. being easily distractible or having difficulty keeping track of what was being said)
  and either
- Disorganised or incoherent thinking (e.g. rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable, switching from subject to subject)
  or
- Altered level of consciousness (alert, hyper alert, drowsy, difficult to arouse, unarousable)

12.8.8.WHO Disability Assessment Schedule (WHODAS) at 30 days
The 12-item WHODAS assesses the following 12 items on a scale of 0 to 4 (with 0=no difficulties and 4= extreme difficulties):
Standing for long periods, household responsibilities, learning a new task, joining in community activities, emotional affection by health problems, concentration, walking a long distance, washing, getting dressed, dealing with people one does not know, maintaining a friendship and day-to-day work.

12.8.9.Quality of Life measurement
The European Quality of Life – 5 Dimensions – 5 Levels (EQ-5D-5L) questionnaire is a brief, utility-based HRQoL instrument. It consists of a health descriptive system and a visual analogue scale (EQ-VAS) for respondents to self-classify and rate their health on the day of administration of the instrument. The EQ-5D-5L was scheduled to take place at baseline and 30 days after randomisation.

12.9. Trial Medication
12.9.1. Investigational Medicinal Product (IMP) and Comparator
Volatile anaesthetic agents and propofol (the comparator) are frequently used in cardiac anaesthesia for the maintenance of general anaesthesia. The most commonly used volatile anaesthetic agent at each site, either isoflurane, sevoflurane or desflurane, were used.

12.9.2. Dosing Regimen
The volatile anaesthetic agent was administered via inhalation, i.e. ventilation through alveolar membrane in lungs, for induction and during the maintenance of anaesthesia. During CPB the volatile anaesthetic agent was administered through the oxygenator oxygen inflow of the CPB machine.
The maintenance dose of the volatile anaesthetic agent was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia (titrated to a depth of anaesthesia with an approximate BIS of 30-60) and mean arterial pressure (MAP) of 50-80mmHg by the treating anaesthetist.
The administration of the volatile anaesthetic agent was started with the induction of anaesthesia and ended at the end of surgery, before the patient transferred to the CCU. Propofol was administered via an infusion. Patients received propofol only during the surgical procedure. The maintenance dose of the propofol infusion was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia (titrated to a depth of anaesthesia with an approximate BIS of 30-60) and mean arterial pressure (MAP) of 50-80mmHg by the treating anaesthetist.

12.9.3. Risks of the IMP and Comparator
An extremely rare side effect of volatile anaesthetic agents is malignant hyperthermia (MH), a genetic disorder with an incidence in the adult population of approximately 1:80,000- 1:200,000. The mortality of MH is less than 5% and treatment is dantrolene therapy. Diagnosis is via monitoring of temperature and end-expiratory CO2, both of which are common practice in cardiac anaesthesia. Patients with known malignant hyperthermia were not included in this trial.
In addition, unspecific side effects of volatile anaesthetic agents include dose-dependent haemodynamic depression.
Unspecific side effects of propofol include bradycardia, tachycardia, hypotension, movement, burning/stinging/pain at the injection site, rash, and pruritus. In addition a prolonged infusion of propofol exceeding a dose of 4mg/kg/hr may very rarely result in rhabdomyolysis, metabolic acidosis, arrhythmias and cardiac failure.

12.9.4. Drug Accountability
Volatile anaesthetics and propofol are frequently used in cardiac anaesthesia as part of standard care. As COPIA wass a pragmatic trial comparing two common anaesthetic techniques and using local supplies of IMP there was no specific drug accountability for this trial.

12.9.5. Storage of IMP
Sites used their own local supplies of volatile anaesthetics (Isoflurane, sevoflurane or desflurane) and propofol, stored under their own local pharmacy protocol.

12.9.6. Deviations from allocated trial treatment

The COPIA feasibility trial was set up to be pragmatic and it was expected that some crossover of the arms may occur. Patient safety was not expected to be affected by an inappropriate crossover of the treatment allocation, as both treatments are frequently used in cardiac anaesthesia. Anaesthetic use in both arms was collected in the CRF and analysed as part of the primary objective of the trial.
If inappropriate crossover of the allocated trial treatment occurred multiple times it would be considered a potential protocol deviation.

12.9.7. Concomitant Medication
For management of concomitant therapies, all other medications used during cardiac anaesthesia were administered as required by the local clinical team. These included benzodiazepines, muscle relaxants, analgesic medications, and drugs to treat haemodynamic parameters, electrolytes and antibiotics.
Both groups received propofol as the sedation agent of choice at the very end of surgery for transferral to the CCU and until tracheal extubation in the CCU.
All medication patients taken prior to surgery was recorded. During the general anaesthesia, data on use of tranexamic acid and magnesium was collected. Following surgery the inotropes and vasoconstrictors were recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication was recorded.

12.10. Study visits, treatment plan and research procedures
12.10.1. Patient identification
Patients undergoing CABG or CABG plus valve procedures at participating sites were initially identified by members of the direct care team from the hospital waiting list or at pre-assessment.

12.10.1.1. Initial patient agreement
A member of the direct care team would ask the patient's permission for them to pass on their details to the research team. If the patient agreed, their notes would then be reviewed in order to confirm that they were eligible to participate. The research team may also have been a member of the direct care team.

12.10.1.2. Informed consent at the Pre-Assessment clinic
The research team approached eligible patients before their scheduled hospital appointment via post, email or telephone in order to introduce the trial to the patient. A copy of the Participant Information Sheet (PIS) and patient invitation letter were supplied to patients who were contacted by post and email. If contacted by telephone, patients were given a copy of the PIS at a pre-assessment appointment before their planned surgery date.
At the pre-assessment appointment, the PI or another delegated surgeon or anaesthetist were available to discuss the trial further and answer any questions the patient had. Freely given written informed consent was obtained by a physician prior to admission. The person who took consent was trained in GCP (Good Clinical Practice), and if they were not the Principal Investigator (PI) then the PI will have delegated them this responsibility.
Patients willing to take part could consent at the preoperative visit. Patients were offered a minimum of 24 hours to consent but could agree to consent earlier than this. Consent may have been taken when they were admitted to hospital for their surgery. Written informed consent was obtained on a consent form.
Furthermore, the patients were notified that participation was voluntary, and that they were free to discontinue treatment or revoke consent from the study at any time without any disadvantages for their subsequent care.

12.10.1.3. Informed consent for In-patients from another hospital
Patients attending for surgery who had been transferred from another hospital may not have had a pre- assessment appointment beforehand.
The PI or another delegated surgeon or anaesthetist would approach the patient after they arrived

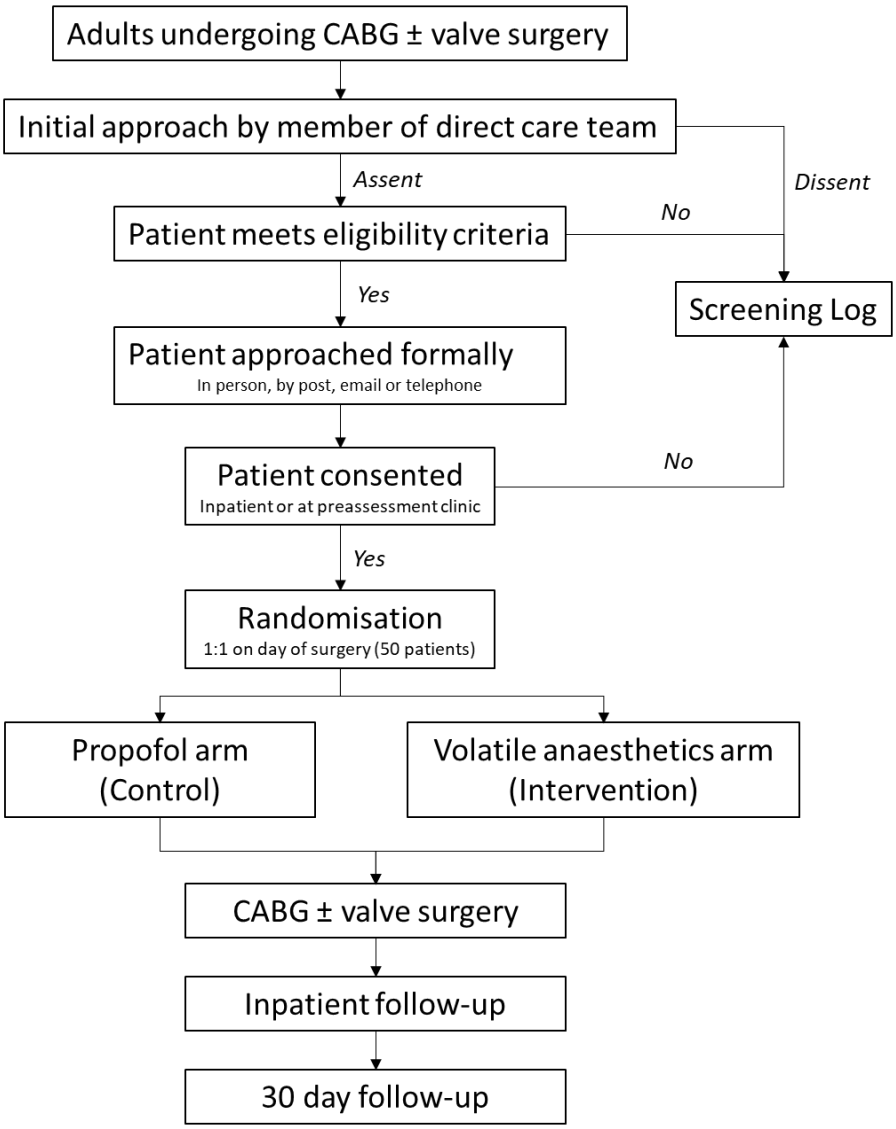
at the hospital. They would be given a copy of the PIS to read, and given the opportunity to discuss the trial with the PI (or another suitably delegated surgeon or anaesthetist) and the PI (or suitable surgeon/anaesthetist) would be available to answer any queries that the patient may have had. Patients were be offered a minimum of 24 hours to consent but could agree to consent earlier than this. Consent may have been taken when they were admitted to hospital for their surgery. Written informed consent was obtained on a consent form.
Furthermore, the patients were notified that participation was voluntary, and that they were free to discontinue treatment or revoke consent from the study at any time without any disadvantages for their subsequent care.
The maximum timeframe permitted between consent and randomisation was 30 days.

12.10.2. Randomisation
On the morning of surgery, patients were randomised in a 1:1 ratio to one of two groups:

1. Volatile anaesthetics
2. Propofol

Randomisation was coordinated centrally by the London School of Hygiene and Tropical Medicine (LSHTM) Clinical Trials Unit (CTU) via a secure web-based computerised system provided by Sealed Envelope.

12.10.3. Trial flowchart



12.11 Trial Procedures

~~12~~
11.1. Trial Procedures Table

12.11.1 Trial procedures table

	Pre-admission or inpatient	Day of surgery	Postop day 1	Postop day 2	Postop day 3	Discharge	3 0 day post-randomisation
Eligibility review	X						
Informed Consent	X						
Demographics	X						
Medical and Surgical History	X						
Routine blood results	X						
Imaging data	X						
Randomisation		X					
Study Drug Administration		X					
Surgery details		X					
Concomitant medications	X*	X*	X*	X*	X*	X*	
Study endpoints (quantitative):							
Rate of Recruitment	X						
Adherence to treatment allocation		X					
Follow-up Rates							X
Study endpoints (qualitative):							
LCOS		X	X	X	X		
serum hsTnT, MyC levels		X	X	X			
MACCE (death, stroke , MI)	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X
ECG	X					X	
Delirium (CAM assessment)	X				X		
Length of ICU and Hospital stay						X	
Days after surgery at home							X
Quality of Life (EQ-5D-5L)	X						X
WHODAS	X						X

* All medication patients taken prior to surgery will be recorded. In addition all administered drugs during the general anaesthesia will be collected. Following surgery the inotropes and vasoconstrictors will be recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication will be recorded.

12.11.2. Data collection
12.11.2.1. Before Surgery

- Assessment of rate of recruitment (trial feasibility)
- Eligibility review
- Informed consent
- Demographics and vital signs:
  Age (month and year of birth), ethnic origin, gender, height weight, BMI, blood pressure, heart rate
- Medical and surgical history:

Arrhythmia, chronic obstructive pulmonary disease (COPD) / lung disease, diabetes mellitus (and type), hypertension, pulmonary hypertension, myocardial infarction (MI), chronic kidney disease (CKD), transient ischaemic attack (TIA) or stroke / cerebrovascular accident (CVA), extracardiac arteriopathy (including claudication, carotid occlusion, previous or planned surgery on abdominal aorta, limb artery or carotid artery), previous cardiac surgery, hypercholesteraemia, smoking history, family history of ischaemic heart disease (IHD), Canadian Cardiovascular Society (CCS) grading of angina pectoris and New York Heart Association (NYHA) Classification for shortness of breath, medication (particularly antiplatelet agents such as aspirin or P2Y12 antagonists; metformin, sulfonylureas, insulin, antihypertensive drugs, diuretics).

- Concomitant medication:
  All medication the subject was taking prior to surgery including beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE-) inhibitors, angiotensin receptor blockers, (ARBs), anti-platelets, anticoagulation) plus other medication such as insulin, metformin, sulfonylureas, statins.
- Routine (standard of care) blood results:
  Including cardiac biomarkers, serum creatinine, platelets, serum glucose and haemoglobin.
- Imaging data:
  Left ventricular ejection fraction (LVEF) / left atrial (LA) size, mitral regurgitation or stenosis (defined as moderate or worse).
- MACCE (death, stroke, MI) including cause of death
- ECG
- Delirium (CAM assessment)
- Quality of Life questionnaire (EQ-5D-5L)
- WHODAS

12.11.2.2.Day of Surgery

- Randomisation
- Study drug administration
- Assessment of adherence to treatment allocation (feasibility)
- Surgery details;
  Including surgery time, cross clamp time, temperature during CPB, type of myocardial protection (cardioplegia, cross clamp-fibrillation), number of grafts and type of operation, type of induction agent, type and highest/lowest dose of volatile agent /propofol before, during and after CPB, AF ablation, highest and lowest mean arterial blood pressure, highest and lowest depth of anaesthesia variable (BIS), inotropes used, type of analgesia, type of muscle relaxants, new onset AF.
- Concomitant medications
  Only Tranexamic acid and magnesium were recorded
- LCOS
- serum hsTnT, MyC levels (pre-operatively and 6hrs after the end of surgery)
- MACCE (death, stroke, MI) including cause of death
- Adverse Events

12.11.2.3. Postoperative day 1

- Concomitant medications
  Following surgery the inotropes were recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication was recorded.
- LCOS
- serum hsTnT, MyC levels
- Assessment of MACCE (death, stroke, MI) including cause of death
- Adverse Events

12.11.2.4.Postoperative day 2

- Concomitant medications
  Following surgery the inotropes were recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication was recorded.
- LCOS
- serum hsTnT, MyC levels
- MACCE (death, stroke, MI) including cause of death
- Adverse Events

12.11.2.5. Postoperative day 3

- Concomitant medications
  Following surgery the inotropes were recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication was recorded.
- LCOS
- MACCE (death, stroke, MI) including cause of death
- Adverse Events
- Delirium (CAM assessment)

12.11.2.6. Discharge from Hospital

- Concomitant medications
  Following surgery the inotropes were recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication was recorded.
- Assessment of MACCE (death, stroke, MI) including cause of death.
- Adverse events
- ECG* (including AF and heart rate)
- Length of ICU stay
- Length of hospital stay
  *An ECG to be performed in hospital on postoperative day 9 if the patient had not been discharged before then.

12.11.2.7. 30 days telephone follow up

- Assessment of trial follow-up rates (feasibility)
- MACCE (death, stroke, MI) including cause of death
- Adverse Events
- Days alive, out of hospital and at home
- EQ-5D-5L
- WHODAS

The 30 day follow up period was 30 days after randomisation. This could take place up to 14 days after the 30 day period.

12.11.3. Storage of samples
Serum hsTnT and MyC levels for analysis of myocardial and renal injury markers were stored with clinical biochemistry (Viapath) at King's College Hospital in -80 freezers.

12.11.4.Definition of end of trial
The end of trial was defined by database lock (completion of all data fields to eCRF and resolution of queries).

12.12. Statistical considerations

12.12.1. Power calculations and sample size determination 50 patients were to be recruited from two centres allocated in a ratio of 1:1.
As this was a feasibility trial, power calculations are not appropriate.

12.12.2. Trial statistician
Statistical analysis was coordinated by the CTU at LSHTM.

12.12.3. Statistical analysis

The primary outcome measure of this feasibility trial was in terms of assessments of the rate of recruitment over time and adherence to the protocol. These statistics informed a CONSORT diagram reporting recruitment, treatment and retention.

Descriptive summaries of baseline data by arm were performed, but no significance tests were performed at baseline. Descriptive statistics for continuous variables include the mean, standard deviation, median, range and the number of observations. Categorical variables are presented as numbers and percentages. Exploratory analysis for the main trial outcomes is by intention to treat. However, given that this is a feasibility trial, no interpretation can be made of any effect sizes and findings will primarily be used to help refine the design of the full trial. This includes assessment of rates of missing data.

13. Number of patients (planned and analysed)

13.1 Planned

50

13.2 Analysed

Table 1: Participants screened, treated, completed and failed to complete treatment

Arm	Active	Placebo
# patients screened	416	
# patients randomised/treated/ study arm	25	25
# patients completed/ study arm	22	22
Reasons for non-completion if applicable	1 patient did not have surgery 1 patient died before discharge 1 patient died after discharge	1 patient withdrew consent after randomisation 1 patient died after discharge 1 patient data not complete

Table 2: The reasons for patient withdrawal from the study

Patient	Comments
3 in volatile group	1 patient did not have surgery 1 patient died before discharge 1 patient died after discharge

~~2~~ 3 in propofol group	1 patient withdrew consent after randomisation before surgery, for personal reasons 1 patient died after discharge 1 patient only had an incomplete dataset

14. Diagnosis and main criteria for inclusion

Inclusion criteria

1. Patients aged 18 years and above
2. Written informed consent to participate
3. Patients undergoing Coronary Artery Bypass Graft (CABG) surgery on Cardiopulmonary bypass (CPB) with or without valve surgery
4. Additive European System for Cardiac Operative Risk Evaluation (EuroSCORE) of 5 or higher (higher scores indicating a greater risk of death; 0 indicates minimum risk and ≥6 indicates high risk)

15. Test product, dose and mode of administration

15.1. Investigational Medicinal Product (IMP) and Comparator

Volatile anaesthetic agents and propofol (the comparator) are frequently used in cardiac anaesthesia for the maintenance of general anaesthesia. The most commonly used volatile anaesthetic agent at each site, either isoflurane, sevoflurane or desflurane, was used.

15.2. Dosing Regimen

The volatile anaesthetic agent was administered via inhalation, i.e. ventilation through alveolar membrane in lungs, for induction and during the maintenance of anaesthesia. During CPB the volatile anaesthetic agent was administered through the oxygenator oxygen inflow of the CPB machine.

The maintenance dose of the volatile anaesthetic agent was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia (titrated to a depth of anaesthesia with an approximate BIS of 30-60) and mean arterial pressure (MAP) of 50-80mmHg by the treating anaesthetist.

The administration of the volatile anaesthetic agent was started with the induction of anaesthesia and it ended at the end of surgery, before the patient was transferred to the CCU. Propofol was administered via an infusion. Patients received propofol only during the surgical procedure. The maintenance dose of the propofol infusion was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia (titrated to a depth of anaesthesia with an approximate BIS of 30-60) and mean arterial pressure (MAP) of 50-80mmHg by the treating anaesthetist.

15.3. Risks of the IMP and Comparator

An extremely rare side effect of volatile anaesthetic agents is malignant hyperthermia (MH), a genetic disorder with an incidence in the adult population of approximately 1:80,000- 1:200,000. The mortality of MH is less than 5% and treatment is dantrolene therapy. Diagnosis is via monitoring of temperature and end-expiratory CO2, both of which are common practice in cardiac anaesthesia.

Patients with known malignant hyperthermia were be included in this trial.
In addition, unspecific side effects of volatile anaesthetic agents include dose-dependent haemodynamic depression.
Unspecific side effects of propofol include bradycardia, tachycardia, hypotension, movement, burning/stinging/pain at the injection site, rash, and pruritus. In addition a prolonged infusion of propofol exceeding a dose of 4mg/kg/hr may very rarely result in rhabdomyolysis, metabolic acidosis, arrhythmias and cardiac failure.

16. Duration of treatment

Duration of surgery: about 4 – 6 hours

17. Reference therapy, dose and mode of administration

The maintenance dose of the propofol infusion was titrated to doses deemed necessary in order to provide sufficient depth of anaesthesia (titrated to a depth of anaesthesia with an approximate BIS of 30-60) and mean arterial pressure (MAP) of 50-80mmHg by the treating anaesthetist.
Unspecific side effects of propofol include bradycardia, tachycardia, hypotension, movement, burning/stinging/pain at the injection site, rash, and pruritus. In addition a prolonged infusion of propofol exceeding a dose of 4mg/kg/hr may very rarely result in rhabdomyolysis, metabolic acidosis, arrhythmias and cardiac failure.

18. Criteria for evaluation: Endpoints

Feasibility of the study protocol:

1. Feasibility of meeting recruitment targets. The aim was to recruit 50 patients across two tertiary cardiac surgery centres within approximately 10 months.
2. Identification of potential recruitment barriers with current protocol.

Secondary Endpoints

- Feasibility of collecting event data in more than 95% of enrolled patients at the 30 day follow-up.
- Assessment of effectiveness of patient identification and screening processes.
- Identification and analysis of any reasons for failure to recruit patients.
- Assessment of trial processes, including the choice of outcome measures and impact on staff.
- Assessment on the feasibility of collecting the following, planned to be endpoints in the full trial
- Low Cardiac Output Syndrome
- Myocardial injury, assessed by ischaemic serum markers: hsTnT, MyC, pre-operatively, at 6 hrs after arrival in CCU and on the 1st and 2nd postoperative mornings, area under the curve and peak postoperative levels
- MACCE (stroke, non-fatal myocardial infarction, death from any cause) at 30 days
- Cardiac related mortality at 30 days
- Postoperative in hospital atrial fibrillation requiring treatment
- Acute kidney injury (according to KDIGO)
- In-hospital postoperative delirium (assessed by the confusion assessment method)
- Respiratory complications needing prolonged ventilation (>24 hours)
- Length of stay in the critical care unit (CCU)
- Length of hospital stay

- WHO Disability Assessment Schedule (WHODAS) at 30 days
- Quality of Life Questionnaire, Euroqol EQ-5D-5L at baseline and 30 days
- Days alive and at home until 30 days after surgery

19. Statistical Methods

As above under methods chapter 12, paragraph 12, statistical methods

20. Changes in the Trial Plan
Not applicable

20.1 Protocol Deviations

No major breaches or major protocol deviations occurred and no planned changes to analysis.

There were no inappropriate crossovers during the study. Due to poor communication, the treating anaesthetists chose propofol instead of volatile anaesthetics in 2 patients. This was assessed to be part of the pragmatic design and it was not considered an inappropriate cross over, and not a major or inappropriate protocol deviation.

21. Summary – Conclusions

21.1 Demographic data

The following table summarises the demographics and preoperative variables of the study population:

Table 3. Patient characteristics by treatment assignment (age & gender)

Number of Subjects			
Age (years)	**Male**	**Female**	**Total**
Pre-term new-born infants (<37 weeks)	0	0	0
New-borns (0-27 days)	0	0	0
Infants and toddlers (28 days – 23 months)	0	0	0
Children (2-11 years)	0	0	0

Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	11	4	15
Elderly (≥65 years)	27	7	34
Total	**38**	**11**	**49**

Table 4: Patient characteristics by treatment assignment (all other data)			Propofol (n=25)	Volatile (n=25)
Age *years*	Mean (SD)		73.0 (8.5)	73.6 (9.1)
	Missing data		1 (4%)	1 (4%)
Male/Female	n (%)		18 (72%)/ 6 (24%)	20 (80%)/ 5 (20%)
	Missing data		1 (4%)	0
Ethnicity n (%)	White		21 (84%)	23 (92%)
	Black		1 (4%)	0 (0%)
	Asian		1 (4%)	1 (4%)
	Missing data		2 (8%)	1 (4%)
BMI *kg/m²*	Mean (SD)		27.0 (5.8)	28.8 (4.4)
	Missing data		2 (8%)	3 (12%)
Preoperative BP *mmHg*	Mean (SD)	Systolic	134 (21)	132 (19)
		Diastolic	72 (10)	71 (12)
	Missing data		2 (8%)	3 (12%)
Preoperative HR *bpm*	Mean (SD)		66 (9)	64 (9)
	Missing data		2 (8%)	3 (12%)

CCS Angina Grade n (%)	0		6 (24%)	7 (28%)
	1		3 (12%)	2 (8%)
	2		5 (20%)	6 (24%)
	3		7 (28%)	7 (28%)
	4		2 (8%)	2 (8%)
	Missing data		2 (8%)	1 (4%)
NYHA Stage n (%)	I		6 (24%)	8 (32%)
	II		7 (28%)	10 (40%)
	III		10 (40%)	4 (16%)
	IV		0 (0%)	1 (4%)
	Missing data		2 (8%)	2 (8%)
CVS Comorbidity	Arrhythmia	n (%)	6 (24%)	2 (8%)
		Missing data	2 (8%)	2 (8%)
	Hypertension	n (%)	19 (76%)	15 (60%)
		Missing data	1 (4%)	2 (8%)
	Previous MI	n (%)	13 (52%)	10 (40%)
		Missing data	1 (4%)	1 (4%)
Smoking Status n (%)	Current		3 (12%)	4 (16%)
	Previous		12 (48%)	10 (40%)
	Never		8 (32%)	10 (40%)
	Missing data		2 (8%)	1 (4%)
Other Comorbidity	COPD	n (%)	1 (4%)	3 (12%)
		Missing data	1 (4%)	1 (4%)

	CKD	n (%)	6 (24%)	3 (12%)
		Missing data	1 (4%)	1 (4%)
	DM n (%)	None	14 (56%)	19 (76%)
		Diet-controlled	1 (4%)	0 (0%)
		Oral Medication	4 (16%)	3 (12%)
		Insulin	5 (20%)	2 (8%)
		Missing data	1 (4%)	1 (4%)
	TIA	n (%)	4 (16%)	5 (20%)
		Missing data	1 (4%)	1 (4%)
Previous Surgery	n (%)		1 (4%)	1 (4%)
	Missing data		1 (4%)	2 (8%)
Preoperative Medications n (%) .	Aspirin		16 (64%)	18 (72%)
	P2Y12 Antagonist		4 (16%)	6 (24%)
	Beta-blocker		16 (64%)	15 (60%)
	CCB		9 (36%)	7 (28%)
	ACEi		11 (44%)	12 (48%)
	ARB		5 (20%)	4 (16%)
	Diuretic		2 (8%)	5 (20%)
	Anticoagulant		11 (44%)	4 (16%)
	Metformin		6 (24%)	5 (20%)
	Sulfonylurea		3 (12%)	0 (0%)
	Insulin		5 (20%)	2 (8%)
	Missing data		1 (4%)	1 (4%)

Preoperative Laboratory Results	CBG *mmol/L*	Mean (SD)	6.0 (1.2)	6.7 (1.9)
		Missing data	12 (48%)	9 (36%)
	Creatinine *micromol/L*	Mean (SD)	96 (26)	107 (63)
		Missing data	1 (4%)	1 (4%)
	Platelets *x10^9/L*	Mean (SD)	232 (61)	211 (52)
		Missing data	1 (4%)	1 (4%)
	LVEF *%*	Median [IQR]	52 [45-56]	49 [40-55]
		Missing data	7 (28%)	7 (28%)
Preoperative Cardiac Parameters (Imaging & ECG)	AF	n (%)	1 (4.2%)	3 (12.5%)
		Missing data	1 (4%)	2 (8%)
	Median [IQR]	16 [14-17]	15.5 [14-20]	
	Missing data	0 (0%)	1 (4%)	
WHODAS Score	Median [IQR]		16 [14-17]	15.5 [14-20]
	Missing data		0 (0%)	1 (4%)
EQ-5D – Health Status (0-100)	Median [IQR]		72 [50-78]	75 [65-82]
	Missing data		1 (4%)	0 (0%)

ACEi – Angiotensin-Converting Enzyme Inhibitor; AF – Atrial Fibrillation; ARB – Angiotensin-Receptor Blocker; BMI – Body Mass Index; BP – Blood Pressure; CBG – Capillary Blood Glucose; CCB – Calcium Channel Blocker; CCS – Canadian Cardiovascular Society; CKD – Chronic Kidney Disease; COPD – Chronic Obstructive Pulmonary Disease; CVS – Cardiovascular System; DM – Diabetes Mellitus; ECG – Electrocardiogram; EQ-5D – EuroQOL-5D; HR – Heart Rate; IQR – Interquartile Range; LVEF – Left Ventricular Ejection Fraction; MI – Myocardial Infarction; NYHA – New York Heart Association; TIA – Transient Ischaemic Attack; WHODAS – World Health Organisation Disability Assessment Schedule

21.2 Primary outcome

50 participants were recruited across both centres within 11 months of active recruitment, from November 2019 until November 2021, with a 13-month hiatus (March 2020 – April 2021) due to the COVID-19 pandemic. A single site was open to recruitment before COVID with 19 patients randomised in 3.7 months. Both sites were open to recruitment for 6.9 months post-COVID; with 31 patients recruited. The pre-pandemic recruitment rate in the single site was 5.1 patients per month and following resumption the rate was 4.5 patients per month across the two sites. Of the 416 patients screened for eligibility, 308 were not eligible and 58 patients declined consent. Apart from the COVID-19 pandemic, no other systemic recruitment barriers were identified.

A total of 416 patients were screened during the study period. 74% (n=308) were ineligible, 14% (n=58) were eligible but not recruited, and 12% (n=50) were eligible and successfully recruited. 50/108 (46%) of eligible patients were recruited to the study.
All 50 recruited patients underwent randomisation, with one withdrawing consent prior to surgery, and one patient not undergoing surgery. Of the remaining 48 patients, 47 completed in-hospital and 30-day follow-up.
In the propofol arm, all 24 patients were managed as per allocation throughout the operative period. In the volatile arm, 22/24 patients received treatment as per allocation with two protocol violations where propofol was administered. Both types of anaesthesia (volatile or propofol) are commonly used by preference of the anaesthetist. In these 2 protocol violations, there was poor communication regarding the type of anaesthesia to be used in these patients and the anaesthetist used their preferred type of anaesthesia, propofol, and was not according to the allocated arm. These protocol violations were only observed after the surgery was finished.
Data completeness was good for the majority of perioperative variables including pre- and intra-operative variables as well as clinical outcomes including LCOS, AF, ICU and hospital length of stay, MACCE and cardiac-related 30-day mortality. Overall, the median time at the time point of the 30-day follow up was 33 [30-54] days in the propofol arm, and 37.5 [31-49] days in the volatile arm.

21.3 Safety results

Table 5: Listing of Adverse Events for all patients *(state which version of the MedDRA dictionary or other medical dictionary was used to code the events)*

Adverse Events	Treatment Arm	Comparator
Total Number of AEs per Study Arm	n/a	n/a
Subjects affected by non-serious adverse events:	n/a	n/a

Table 6: Listing of Serious Adverse Events for all patients

Serious Adverse Events	Treatment Arm	Comparator
Total Number of SAEs per Study Arm	0	1
Total number of all cause deaths per Study Arm*/**	3	2
Total number of deaths resulting from adverse events per Study Arm	0	0

Mortality after cardiac surgery is not uncommon and 30-day/in hospital mortality has an incident of in 2-3 % of all cardiac surgical patients (https://www.nicor.org.uk/interactive-reports/national-adult-cardiac-surgery-audit-nacsa). In high-risk patients 1-year mortality has an incident of 5% (Hausenloy et al. NEJM 2015).

***** The deaths listed in this table happened during the postoperative periods and follow-ups, and clearly were not related to any of the intraoperative time periods.***

Within the per protocol population (n= 50), a total of "1" SAE, was identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

The proportion that experienced at least one SAE was 2% (n=1).

Incidence of adverse drug reactions (ADRs): N/A

22 Conclusion

All 50 patients were recruited within 11 months in two centres allowing for a 13-month hiatus in

recruitment due to the COVID-19 pandemic. Overall, 50/108 (46%) of eligible patients were recruited. One patient withdrew before surgery and one patient did not undergo surgery. All but one completed in-hospital and 30-day follow-up.
It is feasible to recruit and randomise higher-risk patients undergoing CABG surgery to a study comparing total inhalational and propofol anaesthesia in a timely manner and with high acceptance and completion rates.

23. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated ~~22ndth December 2025~~
21st January 2026

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

N/A

ii) Summary of treatment-emergent ARs in the per protocol population

N/A

iii) Summary of treatment-emergent SAEs in the study population

There was one treatment-emergent SAE for multiple organ failure, the patient randomization number was C11027.

System Organ Class	Preferred Term	Number of Subjects Experiencing the SAE in Active Arm	Total Number of Occurrences of the SAE	Number of Subjects Experiencing the SAE in Placebo Arm	Total Number of Occurrences of the SAE

General disorders and administration site conditions	*Multiple organ dysfunction syndrome*	0	1	1	1

iv) Summary of treatment-emergent SARs in the study population

N/A