KING'S HEALTH PARTNERS

An Academic Health Sciences Centre for London

Pioneering better health for all

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

CLINICAL TRIALS UNIT

Comparison between Propofol and Inhalational Anaesthetic Agents on Cardiovascular Outcomes following Cardiac Surgery - a Randomised Controlled Feasibility Trial

Protocol Version 1.1
Date: 26 JUL 2019

Sponsored by King's College London

Managed by London School of Hygiene and Tropical Medicine Clinical Trials Unit

Funded by the National Institute for Academic Anaesthesia

PROTOCOL IDENTIFICATION NUMBER: KCH-PRO:19/001 EudraCT Number: 2019-000171-16
IRAS ID 216646 NCT 04039854

Full title

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

Short Title / Acronym

COPIA Feasibility Trial

Trial Identifiers

REC reference: 19/LO/1071

Clinicaltrials.gov reference: NCT 04039854

EudraCT number: 2019-000171-16

IRAS ID: 216646

Funders reference: WKR0-2018-0025

Sponsor protocol number: KCH-PRO:19/001

Sponsor

Name: King's College Hospital NHS Foundation Trust
Sponsor Contact: Helen Critchley
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: helen.critchley@kcl.ac.uk

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

Name and address of Co-Investigator(s)

Name: Dr Martin John
Address: Department of Anaesthesia and Perioperative Medicine
Guy's & St Thomas' Hospital,
Westminster Bridge Road, Lambeth, London SE1 7EH
Telephone: 020 7188 7188
Email: m1john@yahoo.co.uk

Name: Mr Max Baghai, Consultant Cardiac Surgeon
Address: Department of Cardiothoracic Surgery
King's College Hospital NHS Foundation Trust,
Denmark Hill, London SE5 9RS
Telephone: 020 3299 9000
Email: mbaghai@nhs.net

Name: Mr Richard Evans
Address: London School of Hygiene and
Tropical Medicine, Keppel Street, London, WC1E 7HT
Telephone: 020 7927 2665
Email: Richard.Evans@LSHTM.ac.uk

Name: Mr Tim Clayton
Address: London School of Hygiene and
Tropical Medicine, Keppel Street, London, WC1E 7HT
Telephone: 020 7927 2640
Email: Tim.Clayton@LSHTM.ac.uk

Name: Professor Giovanni Landoni
Address: Vita-Salute San Raffaele University of Milan,
Via Olgettina 58,
Milano, Italy
Telephone: +39 02 2643 6158
Email: Landoni.giovanni@hsr.it

Name: Professor Gavin Murphy
Address: Department of Cardiovascular Sciences
College of Life Sciences
University of Leicester, Clinical Sciences Wing
Glenfield General Hospital, Leicester, LE3 9QP
Telephone: 0116 2583021
Email: gjm19@leicester.ac.uk

Name: Professor Mike Marber
Address: Guy's & St Thomas' Hospital
Westminster Bridge Road, Lambeth, London SE1 7EH
Telephone: 020 7188 7188
Email: mike.marber@kcl.ac.uk

Local sites

King's College Hospital NHS Foundation Trust

King's College Hospital
Denmark Hill
London
SE5 9RS

PI: Mr Max Baghai

Guy's & St Thomas' Hospitals NHS Foundation Trust

St Thomas' Hospital
Westminster Bridge Road
London
SE1 7EH

PI: Dr Martin John

Contents

1. Study Synopsis

Title of clinical trial	**Co**mparison between **P**ropofol and **I**nhalational **A**naesthetic Agents (COPIA) on Cardiovascular Outcomes following Cardiac Surgery - a Randomised Controlled Feasibility Trial
Sponsor name	King's College Hospital NHS Foundation Trust
Chief Investigator	Dr Gudrun Kunst
IRAS Reference	216646
Clinicaltrials.gov number	NCT 04039854
EudraCT number	2019-000171-16
Methodology	Randomised controlled single blind two-centre feasibility trial
Research Sites	• King's College Hospital NHS Foundation Trust • Guy's & St Thomas' NHS Foundation Trust
Primary objective	The primary objective of the COPIA feasibility trial is to determine feasibility of the proposed multicentre study: 1. Determination of the likely rate of recruitment at two centres. 2. Identification of potential recruitment barriers with current protocol.
Secondary objectives	• Feasibility of maintaining follow-up rates of over 95%. • 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 completeness and feasibility of collection of the endpoints planned for the main trial.
Sample Size	50 patients across 2 centres

Summary of eligibility criteria	**Inclusion criteria** • Patients (male and female) 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 preconditioning) • 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.
Version and date of protocol	Version 1, 26th March 2019
Proposed start date	**1st February 2019** (grant start date) **1st September 2019** (planned recruitment start)
Proposed end date	Trial enrolment is projected to complete approximately 10 months after the start of the recruitment period. Follow-up of trial participants will complete approximately 30 days from the end of the recruitment period. The end date of the grant is the 31st January 2021.
Study duration	The duration of the trial is **24 months** in total. The duration of the trial for each individual patient is **30 days**.

Glossary of terms and abbreviations

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

2. Signature page

2.1. Chief investigator agreement

The clinical study as detailed within this research protocol **(Version 1, 26th March 2019)**, or any subsequent amendments will be conducted in accordance with the UK Policy Framework for Health & Social Care, the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief investigator name: Dr Gudrun Kunst

Chief investigator site: King's College Hospital NHS Foundation Trust

Signature: _____ Date: _____

3. Background & scientific rationale

Cardiopulmonary bypass (CPB) and revascularisation-induced ischaemic reperfusion injury is a common problem during cardiac surgery, resulting in myocardial and other organ damage. Myocardial protection describes the experimentally observed phenomenon that an intervention or a trigger before a prolonged ischaemic insult to the myocardium results in a reduction of the infarcted area [1]. The trigger can either be an ischaemic intervention or a pharmacological stimulus, such as volatile anaesthetics [1] [2] [3] .

There are two main intracellular signal transduction pathways directing cardioprotection from cell surface receptors to convergent targets in the mitochondria proposed as models to explain myocardial protection: the Reperfusion Injury Salvage Kinases (RISK)-pathway, and the Survivor Activating Factor Enhancement (SAFE)-pathway [1]. In mitochondria, protection is triggered by inhibition of the opening of the mitochondrial permeability transition pore. Volatile anaesthetics protect the myocardium against ischaemic injury by multiple intracellular interactions activating the RISK- and SAFE-pathways, and eventually by delaying the opening of the mPTP. In addition, it has been demonstrated that volatile anaesthetics provide endothelial protection by preventing tumour necrosis factor (TNF)-alpha induced adhesion molecule expression [1].

3.1. Need for improved cardioprotection in cardiac surgery

Coronary artery bypass graft (CABG) surgery remains the revascularisation strategy of choice for patients with multi-vessel coronary artery disease. In 2015, 16,200 isolated CABG operations and another 4100 CABG operations in combination with valve surgery were performed in the UK (http://bluebook.scts.org). The overall in-hospital mortality rate for cardiac surgery was about 2.7%, and 1-year mortality can be up to 5% [4].

The risk for patients undergoing cardiac surgery has increased recently, due to the ageing population, more patients undergoing combined CABG and valve surgery, and the presence of co-morbidities, such as diabetes, renal failure and hypertension [5]. This results in postoperative complications such as myocardial infarction (22%), acute renal injury (AKI) (38%) and stroke (2%) [4].
Therefore, improved cardio- and organ protection during cardiac surgery can potentially result in less cardiac, renal and cerebral ischaemia in this high-risk patient group.

3.2. Inhaled anaesthesia and cardioprotection during cardiac bypass surgery

Volatile anaesthetics have been reported to protect the myocardium against myocardial injury in clinical proof-of-concept trials and meta-analyses when compared to intravenous anaesthesia, however inconclusively [2] [3] [6] [7]. The majority of these studies compared volatile anaesthetics in addition to a propofol infusion, versus propofol only. Recent studies indicate however that volatile anaesthetics administered during CPB without concomitant propofol can significantly reduce postoperative myocardial injury markers, when compared with propofol only [8] [9]. Furthermore, clinical and experimental evidence suggests that propofol has the potential to block myocardial protection [10] [11] [12] and it has been shown in patients undergoing cardiac surgery that propofol increases myocardial oxidative stress [13].
There is currently a large variation in clinical practice for cardiac procedures in the UK, given the lack of consensus regarding the benefits of volatile versus intravenous anaesthesia and lack of large trials assessing clinical outcomes, with about 50% of patients receiving intravenous anaesthesia only without volatile anaesthetics [4].

The proposed COPIA feasibility trial will compare volatile anaesthetic agents in higher risk patients undergoing cardiac surgery (including the administration of volatile anaesthetics during CPB without added propofol) with the administration of propofol only for the maintenance of anaesthesia.
Recent pharmacokinetic studies demonstrated that administering volatile anaesthetics only during CPB is feasible. It was shown that oxygenator exhaust concentrations of volatiles correlate with arterial blood concentrations [14] and that hypnosis can be maintained with adequate plasma concentrations and end-tidal concentrations of volatiles [15]. Administration of volatile anaesthetics during CPB is feasible with adequate hypnosis and amnesia and this technique has been reviewed recently [15] [16].

In summary, the proposed feasibility trial will, for the first time, compare volatile anaesthetics as the only anaesthetic agent (without propofol), with the administration of propofol only for maintenance of anaesthesia and investigate meaningful clinical outcomes. The results of the feasibility trial will be used to assess whether it is clinically acceptable and achievable to compare propofol anaesthesia with inhalational anaesthesia as the induction and maintenance agent during cardiac surgery.

3.3. Proposed multicentre randomised controlled trial

In order to perform a multicentre randomised controlled trial, with LCOS and myocardial injury as the primary outcome measures, we will assess feasibility of the rate of recruitment and protocol adherence.
If the anticipated recruitment, follow-up and retention rates are demonstrated over a 10 month recruitment period, this would demonstrate the feasibility of a proposed 2900 patient multicentre randomised controlled trial, recruiting at 20-30 sites over three years with an estimated eligible cohort of at least 14,500 patients.

4. Assessment and management of risk

Using the MHRA guidelines this trial has been categorised as: Type A = No higher than the risk of standard medical care. Volatile anaesthetics and propofol are commonly used, standard of care, methods of anaesthesia. In this trial, the IMP will be used within the licensed indication and as per the Summary of Product Characteristics (SmPC).

The side effects for volatile anaesthetics are listed in the SmPC.

Patients that are pregnant, with a known allergy to propofol or with known malignant hyperthermia will be excluded from the trial.

5. Trial objectives and design

5.1. Objective

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

5.2. Hypothesis

Our overarching hypothesis is that the use of volatile anaesthetics, as the only maintenance for general anaesthesia, without propofol, will 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.

5.2.1. 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 will be 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.

5.3. Inclusion criteria

1. Patients (male and female) 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)

5.4. 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 remote ischemic preconditioning)
6. Inclusion in another clinical trial of an investigational medicinal product within the last 3 months.

5.5. Statement on co-enrolment

Patients may be entered into registries or observational studies while also participating in COPIA. Patients may not be 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.

5.6. Primary objectives

Feasibility of the study protocol:

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

5.7. 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) [17]
    - 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 [18]
    - Quality of Life Questionnaire, Euroqol EQ-5D-5L at baseline and 30 days
    - Days alive and at home until 30 days after surgery

5.8. Study endpoint definitions

5.8.1. 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].

5.8.2. 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.

5.8.3. Death

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

5.8.4. 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 waves; 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.

5.8.5.Stroke

A stroke will be 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.

5.8.6.Acute kidney injury

Acute renal failure will be 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.

5.8.7.In-hospital postoperative delirium

In-hospital postoperative delirium will be assessed using the confusion assessment method (CAM).
For the diagnosis of delirium by the CAM method, the following features are 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)

5.8.8.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.

5.8.9.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 is scheduled to take place at baseline and 30 days after randomisation.

6. Trial Medication

6.1. 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**, will be used.

6.2. Dosing Regimen

The volatile anaesthetic agent will be 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 will be administered through the oxygenator oxygen inflow of the CPB machine.
The maintenance dose of the volatile anaesthetic agent will be 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 will be started with the induction of anaesthesia and it will be ended at the end of surgery, before the patient is transferred to the CCU. Propofol will be administered via an infusion. Patients will receive propofol only during the surgical procedure. The maintenance dose of the propofol infusion will be 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.

6.3. 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 will not 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.

6.4. Drug Accountability

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

6.5. Storage of IMP

Sites will use their own local supplies of volatile anaesthetics (Isoflurane, sevoflurane or desflurane) and propofol, stored under their own local pharmacy protocol.

6.6. Deviations from allocated trial treatment

The COPIA feasibility trial is set up to be pragmatic and it is expected that some crossover of the arms may occur. Patient safety is 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 will be collected in the CRF and will be analysed as part of the primary objective of the trial.
If inappropriate crossover of the allocated trial treatment occurs multiple times it will be considered a potential protocol deviation.

6.7. Concomitant Medication

For management of concomitant therapies, all other medications used during cardiac anaesthesia may be administered as required by the local clinical team. These include benzodiazepines, muscle relaxants, analgesic medications, and drugs to treat haemodynamic parameters, electrolytes and antibiotics.

Both groups are going to receive 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 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.

7. Study visits, treatment plan and research procedures

7.1. Patient identification

Patients undergoing CABG or CABG plus valve procedures at participating sites will initially be identified by members of the direct care team from the hospital waiting list or at pre-assessment.

7.1.1. Initial patient agreement

A member of the direct care team will ask the patient's permission for them to pass on their details to the research team. If the patient agrees, their notes will then be reviewed

in order to confirm that they will be eligible to participate. The research team may also be a member of the direct care team.

7.1.1.Informed consent at the Pre-Assessment clinic

The research team will approach 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 are supplied to patients who will be contacted by post and email. If contacted by telephone, patients will be 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 will be available to discuss the trial further and answer any questions the patient may have. Freely given written informed consent must be obtained by a physician prior to admission. The person who takes consent will be trained in GCP (Good Clinical Practice), and if they are not the Principal Investigator (PI) then the PI will have delegated them this responsibility.

Patients willing to take part can consent at the preoperative visit. Patients will be offered a minimum of 24 hours to consent but can agree to consent earlier than this. Consent may be taken when they are admitted to hospital for their surgery. Written informed consent will be obtained on a consent form.

Furthermore, the patients will be notified that participation is voluntary, and that they are free to discontinue treatment or revoke consent from the study at any time without any disadvantages for their subsequent care.

7.1.2.Informed consent for In-patients from another hospital

Patients attending for surgery who have been transferred from another hospital may not have a pre-assessment appointment beforehand.

The PI or another delegated surgeon or anaesthetist will approach the patient after they arrive at the hospital. They will be given a copy of the PIS to read, and will be given the opportunity to discuss the trial with the PI (or another suitably delegated surgeon or anaesthetist) and the PI (or suitable surgeon/anaesthetist) will be available to answer any queries that the patient may have.

Patients will be offered a minimum of 24 hours to consent but can agree to consent earlier than this. Consent may be taken when they are admitted to hospital for their surgery. Written informed consent will be obtained on a consent form.

Furthermore, the patients will be notified that participation is voluntary, and that they are 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 is 30 days.

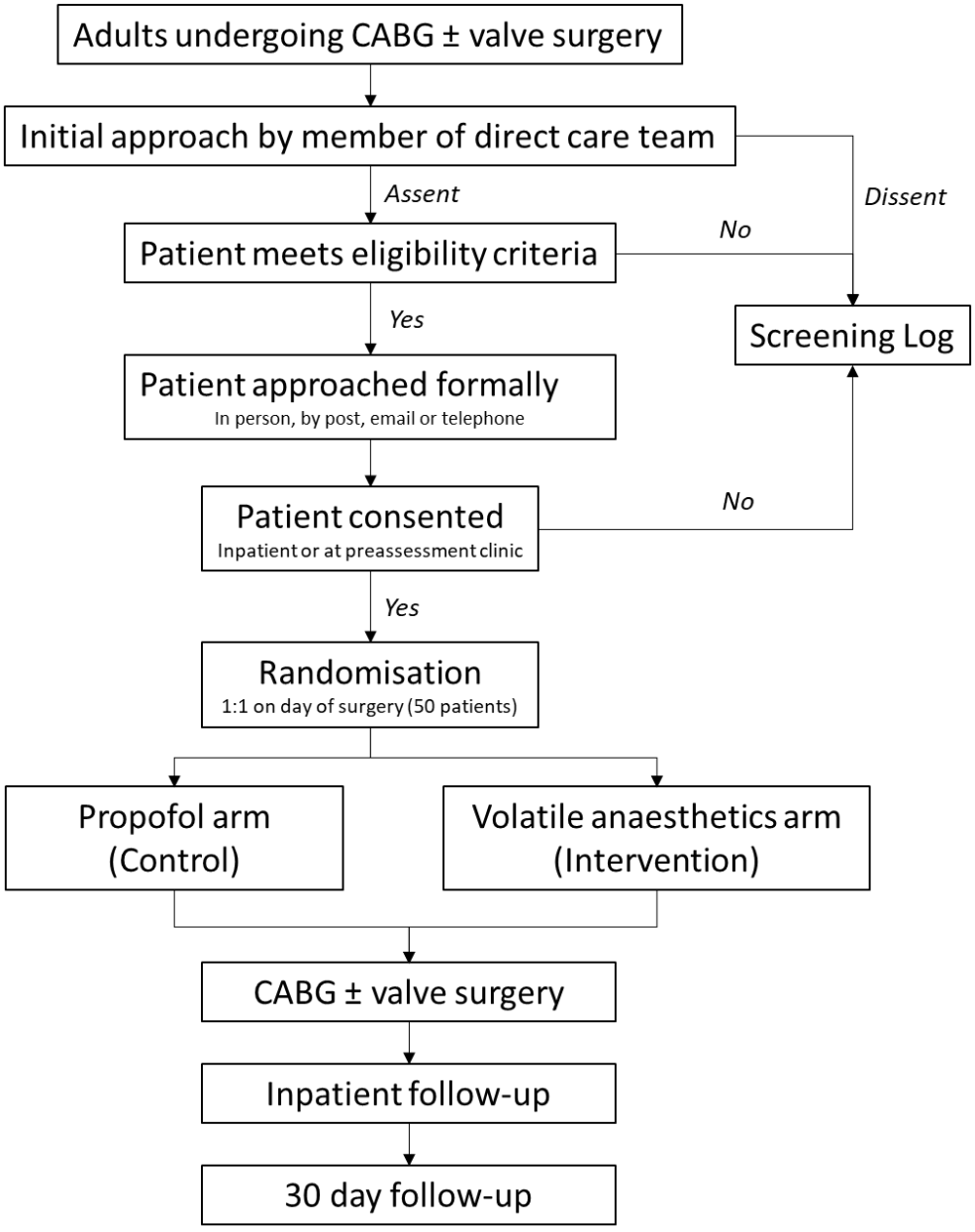
7.2. Randomisation

On the morning of surgery, patients will be randomised to one of two groups:

1. **Volatile anaesthetics**
2. **Propofol**

Randomisation will be 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.

7.3. Trial flowchart



8. Trial procedures

8.1. 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**		
Myocardial Injury			**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.

8.2. Data collection

8.2.1. Before Surgery

- Assessment of rate of recruitment (trial feasibility)
- Eligibility review
- Informed consent
- Demographics:
  Age (month and year of birth), ethnic origin, gender
- 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 is taking prior to surgery including beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE-) inhibitors, angiotensin receptor blockers, (ARBs), aldosterone antagonists, 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

8.2.2.Day of Surgery

- Randomisation
- Study drug administration
- Assessment of adherence to treatment allocation (feasibility)
- Surgery details;

  Including surgery time, bypass time, cross clamp time, temperature during CPB, type of myocardial protection (cardioplegia, cross clamp-fibrillation), number of grafts and type of operation, type and highest/lowest dose of volatile agent /propofol before, during and after CPB, 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

  All administered drugs during the general anaesthesia will be collected
- LCOS
- serum hsTnT, MyC levels (pre-operatively and 6hrs after the end of surgery)
- MACCE (death, stroke, MI) including cause of death
- Adverse Events

8.2.3.Postoperative day 1

- Concomitant medications

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

8.2.4.Postoperative day 2

- Concomitant medications

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

8.2.5. Postoperative day 3

- Concomitant medications

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

8.2.6. Discharge from Hospital

- Concomitant medications

  Following surgery the inotropes will be recorded for each individual patient until discharge from the high dependency unit (HDU). No other medication will be recorded.
- Assessment of MACCE (death, stroke, MI) including cause of death.
- Adverse events
- ECG*
- Length of ICU stay
- Length of hospital stay

*An ECG to be performed in hospital on postoperative day 9 if the patient has not been discharged before then.

8.2.7. 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 is 30 days after randomisation. This can take place up to 14 days after the 30 day period.

8.3. Storage of samples

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

8.4. Definition of end of trial

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

9. Statistical considerations

9.1. Power calculations and sample size determination

50 patients are to be recruited from two centres allocated in a ratio of 1:1.
As this is a feasibility trial, power calculations are not appropriate.

9.2. Trial statistician

Statistical analysis will be coordinated by the CTU at LSHTM.

9.3. Statistical analysis

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

Descriptive summaries of baseline data by arm will be performed, but no significance tests will be performed at baseline. Descriptive statistics for continuous variables will include the mean, standard deviation, median, range and the number of observations. Categorical variables will be presented as numbers and percentages. Exploratory analysis for the main trial outcomes will be 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 will include assessment of rates of missing data.

10. Ethics

10.1. Declaration of Helsinki and Good Clinical Practice

The trial will conform to the spirit and the letter of the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

10.2. Withdrawal of patients

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, cure, administrative reasons or other reasons. It is understood by all concerned that an excessive rate of withdrawals

can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a patient withdraw from study drug only, efforts will be made to continue to obtain follow-up data, with the permission of the patient. A patient may decide to withdraw from the trial at any time without prejudice to their future care.

10.2.1. Evaluation of patient withdrawal

An evaluation of withdrawals, including rate and reason for withdrawal, is a key secondary outcome for this feasibility trial, and will inform the design of the proposed full RCT.

10.2.2. Opt out of follow-up only

If a patient requests to withdraw from the trial they will be offered the option of opting out of further active follow-up (including visits, telephone calls and contact by email or post) and for MACCE and clinical event data to be gathered from their medical notes.

10.2.3. Follow up of patients withdrawing from the trial

Patients who withdraw from the trial will undergo standard clinical care. Patients will be encouraged to allow data and samples that have been collected before withdrawal to be used in the analyses. If consent to use data is also withdrawn, then these will be discarded. Appropriate handover of patients withdrawing from the trial will occur so their local clinical team can arrange their ongoing treatment.

10.2.4. Reporting withdrawal of patients

The research team should inform the CTU at LSHTM by email if a patient has opted out of active follow-up or has decided to withdraw from the trial (using only the study ID of this patient).

10.2.5. Loss of capacity

Patients are followed up only at 30 days, but as stroke is an expected complication of CABG surgery there is a risk that patients may lose the capacity to give their continued consent in the trial. In order to avoid bias it is essential that loss of capacity should not restrict gathering of MACCE and clinical event data, which can be gathered from hospital notes. WHODAS and EQ-5D-5L will not be collected in these cases.

10.3. Regulatory approvals

10.3.1. Ethical approval

The trial was granted ethical approval by the London Chelsea Research Ethics Committee on the add date.

The Chief Investigator will submit a final report at conclusion of the trial to the King's Health Partners Clinical Trials Office (KHP-CTO) on behalf of the Sponsor, the REC and the MHRA within the timelines defined in the Regulations.

10.3.2. MHRA approval

This protocol and related documents will be submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation.

11. Assessment of safety

11.1. Specification, timing and recording of safety parameters

Patients will undergo a pre-operative assessment by trained healthcare professionals. All safety requirements in place for CABG surgery will be applied in this study. Any patient deemed unfit or unsafe to participate, or meets any exclusion criteria, will not be included in the study.

Safety reporting for each patient should commence from time of randomisation to completion of follow up at 30 days after randomisation.

11.2. Procedures for recording and reporting adverse events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for that product (for products with a marketing authorisation).

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Requires hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

11.2.1. Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.
Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

11.2.2. Reporting Responsibilities

King's College Hospital NHS Foundation Trust has delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).
All SAEs, SARs and SUSARs will be reported immediately (and certainly no later than 24hrs) to the KHP-CTO and Chief Investigator in accordance with the current Pharmacovigilance Policy.
The KHP-CTO will report SUSARs to the regulatory authorities (MHRA).
The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP-CTO (on behalf of the sponsor), will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

In cardiac surgery, post-operative transient complications are not unexpected and are not infrequent. The centres will only notify fatal and 'unexpected' non-fatal serious adverse events (SAEs) to the Trial Sponsor. Unexpected events are those not listed in the trial protocol or on the CRF. The sponsor will inform CTU if an event needs to be reported to the REC (usually only events that are both related to the intervention and unexpected). Centres will follow-up unexpected events to their conclusion or until the Trial Sponsor agrees that no further follow-up is necessary.

11.2.3. Adverse events that do not require reporting as an SAE

The following events are 'expected' following cardiac surgery and where they are relevant to the trial will be gathered in the CRF. There is no need for them to be reported as an AE or SAE:

- Cardiac arrest, requiring:
  - Resuscitation involving ventricular defibrillation/DC shock,
  - Chest reopening

  - External/internal cardiac massage
- Haemodynamic support, including use of:
  - Any inotropes
  - Intra-aortic balloon pump (IABP)
  - Pulmonary artery catheter
  - Vasodilator
- Low cardiac output, requiring management with a Swan-Ganz catheter, IABP, or left ventricular assist device
- Arrhythmias, including:
  - Supraventricular tachycardia or atrial fibrillation requiring treatment
  - VF/VT requiring intervention
  - Pacing
- Pulmonary complications, including:
  - Re-intubation and ventilation
  - Tracheostomy
  - Initiation of mask CPAP ventilation after weaning from ventilation
  - ARDS
  - Pneumothorax or effusion requiring drainage
- Renal complications, including:
  - New haemofiltration/dialysis
  - Acute kidney injury
- Infective complications, including:
  - Wound infection
  - Respiratory infection
  - Sepsis (defined as antibiotic treatment for suspected infection, and the presence of systemic inflammatory response syndrome (SIRS) within 24 hours prior to start of antibiotic treatment)
- Thromboembolic complications, including:
  - Deep vein thrombosis
  - Pulmonary embolus
- GI complications:
  - Peptic ulcer/GI bleed/perforation
  - Pancreatic (amylase >1500iu)
  - Other (e.g. laparotomy, obstruction)
- Neurological complications:
  - Stroke
  - Transient ischaemic attack (TIA)
- Bleeding requiring reoperation
- Mediastinitis requiring reoperation
- Wound dehiscence requiring rewiring or treatment

11.3. Treatment stopping rules

The trial may be prematurely discontinued by the Sponsor, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the DMC, regulatory authority or ethics committee concerned.
If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

12. Blinding and unblinding

Staff at each site, and at the LSHTM CTU, will be arranged into blinded and unblinded teams. This will be recorded in the delegation log at each organisation.
For the duration of the trial, staff may move from the blinded team to the unblinded team, but not from the unblinded team to the blinded team.
The unblinded teams will look after the patient in theatres, and include the anaesthetist and the research nurse collecting intraoperative data. The blinded teams include medical teams looking after the patient from arrival at the postoperative cardiac recovery onwards and research nurse teams collecting postoperative follow-up data.

12.1. Blinded staff

Patients and the research nurse collecting the follow-up data, and the assessor of clinical outcomes will be blinded to the treatment allocation for the duration of the trial.
At the LSHTM CTU the trial manager, senior manager and senior statistician will be blinded to treatment allocation until after database lock.

12.2. Unblinded staff

The treatment allocation will be known by the anaesthetic team (anaesthetist or anaesthetic practitioner) at the randomising site as well as members of the research team delegated to support in randomisation and trial treatment.
These unblinded site staff will not be involved with the follow up or data collection other than those relating to the randomisation and the delivery of the randomised treatment allocation.
At the LSHTM CTU the data manager and unblinded statistician will have access to treatment allocation.

12.3. Record of treatment allocation in patient notes

After intraoperative anaesthetic and relevant haemodynamic data collection on the CRF, the anaesthetic chart will be put into a sealed envelope, which will be left in the notes of the patient after the surgery until discharge. The concealment of the anaesthetic chart after surgery due to blinding reasons has been successfully applied in the multicentre randomised controlled ENIGMAII trial (nitrous oxide anaesthesia and cardiac morbidity after major surgery) in the UK [6]. After discharge of the patient, the envelope will be

kept in a confidential locked cabinet in the hospital until completion of the last patient's last visit.

12.4. Emergency unblinding

The sealed envelope containing the anaesthetic chart may be opened by clinical staff included in the treatment of the patient, if there is an appropriate clinical indication. If emergency unblinding has occurred the site must report this to the LSHTM CTU.

13. Data Management and Quality Assurance

13.1. Confidentiality

All data will be handled in accordance with the UK Data Protection Act 2018.
The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's date of birth (month and year only) and trial identification number will be used for identification.

13.2. Data Management

Data will be entered at each local site using an electronic data capture (EDC) system and will be managed at the LSHTM CTU by the data manager. The data analysis will be performed by the trial statistician based at LSHTM CTU.

13.3. Trial database

A trial database that is compliant with all required regulations will be developed prior to the start of the recruitment period.
Trial data will be transmitted securely, via password/PIN protected online data entry over an encrypted internet connection (SSL). This transfer and storage of data will be in accordance with the Data Protection Act 2018, KCL Information Security Policy and the Trust Information Governance Policy.

13.4. Direct access to source data and documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s) and regulatory bodies direct access to source data and other documents (e.g. patients' case sheets). Patients will be asked to confirm that they understand and agree to this on the consent form.

13.1. Data handling and record keeping

Data will be kept for 15 years following completion of the trial. The data controller for the trial is King's College Hospital (Sponsor) and the data processor is LSHTM. They are both based in the United Kingdom.
Patient data will be kept confidential and managed in accordance with the General Data Protection Regulations 2018, NHS Caldecott principles, The Research Governance

Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.
Patients' rights to access, change or move their information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If patients withdraw from the study, we will keep the information that we have already obtained and we will use the minimum personally-identifiable information possible. Further information about this can be found here:
https://www.kch.nhs.uk/about/corporate/ data-protection

13.2. Monitoring and Auditing

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

14. Trial Committees

14.1. Trial Steering Committee (TSC)

The TSC will meet periodically, at least twice a year. The TSC will be responsible for drafting the final report and submission for publication. A TSC charter will be agreed at the first meeting.
TSC membership to be confirmed

14.2. Trial Management Group (TMG)

The TMG will meet on a monthly basis during the recruitment period, and approximately once every 6-8 weeks after recruitment ends. The TMG will be responsible for the day to day running of the trial.

Dr Gudrun Kunst (King's College Hospital)

Dr Martin John (St Thomas' Hospital)

Professor Michael Marber (St Thomas' Hospital and King's College London)

Mr Richard Evans (London School of Hygiene and Tropical Medicine)

Mr Tim Clayton (London School of Hygiene and Tropical Medicine)

Ms Kimberley Potter (London School of Hygiene and Tropical Medicine)

Mr Steven Robertson (London School of Hygiene and Tropical Medicine)

Professor Gavin Murphy (Leicester University)

Mr Max Baghai (King's College Hospital)

14.3. Data Monitoring Committee (DMC)

The DMC membership will include an independent statistician (Tim Morris). The other independent members will be confirmed before the recruitment period starts.
The Data Monitoring Committee will meet periodically, 6-monthly, to carefully monitor safety of the study. A DMC charter will be agreed at the first meeting.

15. Finance

The COPIA Feasibility Trial funding was awarded by the National Institute for Academic Anaesthesia and funded by the Association of Anaesthetists of Great Britain and Ireland and the Association for Cardiothoracic Anaesthesia and Critical Care.

16. Insurance / Indemnity

16.1. Sponsorship

The trial is sponsored by King's College Hospital NHS Foundation Trust.

16.2. Insurance

Staff will be covered by NHS indemnity for negligent harm, providing researchers hold a contract of employment with the NHS, including honorary contracts held by academic staff.

17. Publication policy and dissemination of research findings

17.1. Publication policy

It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.
Publications will follow CONSORT guidelines, and authorship will follow international guidelines.
All proposed publications will be discussed with sponsor prior to publishing, other than those presented at scientific forums/meetings. We will also follow the guidelines from the funders with regards to their publication policy.

17.2. Dissemination of results to trial participants

Locally, the results of the study will be published in the hospitals research and development newsletter. Patients involved in the study will be indirectly informed of the results through these means.

18. References

1. Kunst G, Klein AA. Peri-operative anaesthetic myocardial preconditioning and protection - cellular mechanisms and clinical relevance in cardiac anaesthesia. Anaesthesia 2015;**70**(4):467-82 .
2. Symons JA, Myles PS. Myocardial protection with volatile anaesthetic agents during coronary artery bypass surgery: a meta-analysis. British Journal of Anaesthesia 2006;**97**(2):127-36
3. Kunst G. From coronary steal to myocardial, renal, and cerebral protection: more questions than answers in anaesthetic preconditioning? Br J Anaesth 2014;**112**(6):958-60.
4. Hausenloy DJ, Candilio L, Evans R, et al. Remote Ischemic Preconditioning and Outcomes of Cardiac Surgery. N Engl J Med 2015;**373**(15):1408-17.
5. Biancari F, Kangasniemi OP, Aliasim Mahar M, et al. Changing risk of patients undergoing coronary artery bypass surgery. Interactive cardiovascular and thoracic surgery 2009;**8**(1):40-4.
6. Landoni G, Guarracino F, Cariello C, et al. Volatile compared with total intravenous anaesthesia in patients undergoing high-risk cardiac surgery: a randomized multicentre study. Br J Anaesth 2014.
7. Uhlig C, Bluth T, Schwarz K, et al. Effects of Volatile Anesthetics on Mortality and Postoperative Pulmonary and Other Complications in Patients Undergoing Surgery: A Systematic Review and Meta-analysis. Anesthesiology 2016;**124**(6):1230-45.
8. Bignami E, Guarnieri M, Pieri M, et al. Volatile anaesthetics added to cardiopulmonary bypass are associated with reduced cardiac troponin. Perfusion 2017;**32**(7):547-53.
9. Ansley DM, Raedschelders K, Choi PT, et al. Propofol cardioprotection for on-pump aortocoronary bypass surgery in patients with type 2 diabetes mellitus (PRO-TECT II): a phase 2 randomized-controlled trial. Can J Anaesth 2016;**63**(4):442-53.
10. Zuurbier CJ, Koeman A, Houten SM, et al. Optimizing anesthetic regimen for surgery in mice through minimization of hemodynamic, metabolic, and inflammatory perturbations. Experimental biology and medicine 2014;**239**(6):737-46.
11. De Hert SG, ten Broecke PW, Mertens E, et al. Sevoflurane but not propofol preserves myocardial function in coronary surgery patients. Anesthesiology 2002;**97**(1):42-9
12. De Hert SG, Van der Linden PJ, Cromheecke S, et al. Cardioprotective properties of sevoflurane in patients undergoing coronary surgery with cardiopulmonary bypass are related to the modalities of its administration. Anesthesiology 2004;**101**(2):299-310
13. Ng KT, Alston RP, Just G, et al. Assessing the depth of isoflurane anaesthesia during cardiopulmonary bypass. Perfusion 2018;**33**(2):148-55.
14. Meroni R, Gianni S, Guarnieri M, et al. Feasibility of Anesthesia Maintenance With Sevoflurane During Cardiopulmonary Bypass: A Pilot Pharmacokinetics Study. J Cardiothorac Vasc Anesth 2017;**31**(4):1210-17.

15. Nigro Neto C, De Simone F, Cassara L, et al. Tricks, tips, and literature review on the adapted vaporize system to deliver volatile agents during cardiopulmonary bypass. Annals of cardiac anaesthesia 2016;**19**(2):240-4.
16. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Annals of internal medicine 1990;**113**(12):941-8
17. Shulman MA, Myles PS, Chan MT, et al. Measurement of disability-free survival after surgery. Anesthesiology 2015;**122**(3):524-36.
18. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). European heart journal 2018.
19. Kellum JA, Lameire N, Group KAGW. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Critical care 2013;**17**(1):204.
20. Thielmann M, Sharma V, Al-Attar N, et al. ESC Joint Working Groups on Cardiovascular Surgery and the Cellular Biology of the Heart Position Paper: Perioperative myocardial injury and infarction in patients undergoing coronary artery bypass graft surgery. European heart journal 2017;**38**(31):2392-407.
21. Myles PS, Leslie K, Chan MT, et al. The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet 2014.

Appendix 1: EQ-5D-5L questionnaire

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

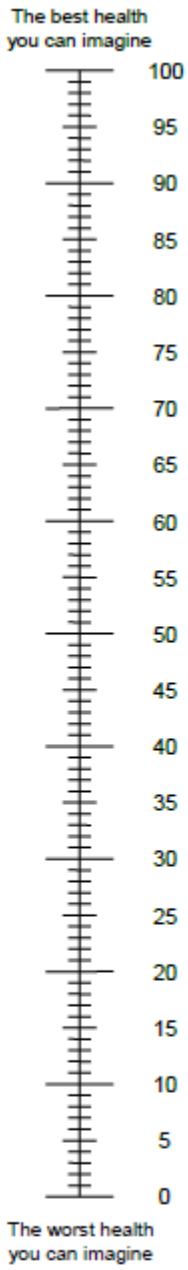
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 2: WHODAS questionnaire

PLEASE NOTE: When scoring WHODAS, the following numbers are assigned to responses:

0 = No Difficulty
1 = Mild Difficulty
2 = Moderate Difficulty
3 = Severe Difficulty
4 = Extreme Difficulty or Cannot Do

		Score
S1	Standing for long periods such as 30 minutes?	
S2	Taking care of your household responsibilities?	
S3	Learning a new task, for example, learning how to get to a new place?	
S4	How much of a problem did you have in joining in community activities (for example, festivities, religious or other activities) in the same way as anyone else can?	
S5	How much have you been emotionally affected by your health problems?	
S6	Concentrating on doing something for ten minutes?	
S7	Walking a long distance such as a kilometre [or equivalent]?	
S8	Washing your whole body?	
S9	Getting dressed?	
S10	Dealing with people you do not know?	
S11	Maintaining a friendship?	
S12	Your day-to-day work/school?	
	Overall Score	0.00%
H1	Overall, in the past 30 days, how many days were these difficulties present?	
H2	In the past 30 days, for how many days were you totally unable to carry out your usual activities or work because of any health condition?	
H3	In the past 30 days, not counting the days that you were totally unable, for how many days did you cut back or reduce your usual activities or work because of any health condition?	