Queen Mary University of London

SPACE

Stopping Perioperative Angiotensin II Converting Enzyme inhibitors and/or receptor blockers in major non-cardiac surgery (SPACE): a phase II, explanatory, randomised controlled trial

Statistical Analysis Plan

Version 1.0
Date: 13/10/2021

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1. Administrative information

Trial Information

REC number:	16/LO/1495
Trial Sponsor:	Queen Mary University of London
Trial Sponsor reference:	011368
Trial Funder:	British Oxygen Company research chair award in Anaesthesia, administered by the National Institute for Academic Anaesthesia
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Protocol version (date):	Version 7.0 (14/12/2020)

SAP revision history

Protocol version	Updated SAP version no.	Section number changed	List of changes from previous version/protocol	Author of change	Date

Members of the writing committee
Akshaykumar Patel (AP) wrote the statistical analysis plan, with input from Gareth Ackland (GA).

Timing of the SAP
Version 1.0 of the SAP was written after AP had access to unblinded data (i.e. trial dataset with the variables for treatment allocation included). Note that all contributors are blinded to the primary outcome as samples will be processed by an independent laboratory at the end of the trial (defined as when the last patient leaves hospital).

Remit of the SAP
The purpose of this document is to provide details of the statistical analyses and presentation of results to be reported within the principal paper(s) of the SPACE trial. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data derived decisions in the analysis are avoided. Any exploratory, post hoc or unplanned analysis will be clearly identified as such in the respective study analysis report. This SAP does not include in its remit the health economic analysis which will be planned in a separate document.

2. Background and trial design

Study objectives	**Primary Objective** To determine whether continuing perioperative Angiotensin converting enzyme inhibitor (ACE-I) and/or Angiotensin II receptor blockers (ARB) reduces the risk of myocardial injury, identified using high-sensitivity plasma troponin measurement during the first 48 hours after surgery **Secondary Objectives** To determine whether continuing perioperative ACE-I and/or ARB reduces the risk of postoperative morbidity
Study design	Phase II, multi-centre, two-arm, parallel group randomised controlled trial
Setting	Surgical services of hospitals undertaking major elective surgery
Participants	**Inclusion criteria** • Informed consent (no incapacitated or vulnerable adult or minors will be included) • Age 60 years and over • Undergoing major surgery (e.g. major joint replacement or vascular or gastrointestinal) requiring general and/or regional anaesthesia with sedation • Currently taking ACE-I or combined ACE-I and ARB therapy or combination therapy where medication includes ACE-I or ARB • Expected duration of surgery longer than 120 minutes • American Society of Anaesthesiologists physical status grade 3 or above • All female subjects must be postmenopausal, as demonstrated by clinical history, or demonstrated not to be pregnant through a preoperative pregnancy test **Exclusion criteria** • Current participation in any other trials where care or treatment is being altered • Recent myocardial infarction (within 3 months) • Any condition, which in the opinion of the treating clinician, would result in the patient being harmed by the cessation of the ACE-I and/or ARB therapy.
Interventions	**Continue Group** Patients in the continue group will continue with their ACE-I and/or ARB 72 hours prior to the day of surgery and continue for at least 48 hours after surgery. **Stop Group** Patients in the stop group will stop their ACE-I and/or ARB [according to half-life of each individual drug] prior to the day of surgery through to at least 48 hours after surgery.

Primary outcome measure	The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours. The primary outcome is met under the following conditions: • Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L *OR* • Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L

3. Outcome measures

Primary outcome measure

The primary outcome is myocardial injury, a binary variable based on plasma high sensitivity Troponin-T) measured in blood samples collected immediately before the induction of anaesthesia, and then postoperative day 1± 6 hours and day 2 ± 6 hours after surgery. The primary outcome is met under the following conditions:

- Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L *OR*
- Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L

Secondary outcome measures

- Peak level of Troponin-T measured within 48 hours of surgery. Peak Troponin-T level (ng/L) will be calculated as the highest Troponin-T from the blood samples collected at 24 hours and 48 hours after surgery.
- Infection within 30 days of surgery
- Myocardial infarction within 30 days of surgery
- Acute heart failure within 30 days of surgery
- Stroke within 30 days of surgery

Full definitions of secondary outcome measures can be found in the SPACE protocol.

4. Sample size and randomisation

Sample size calculation

Assuming incidence of postoperative myocardial injury of 50% in patients undergoing major surgery in the cessation group, a sample size of 248 patients will provide 90% power to detect as statistically significant ($p<0.05$) an 20% absolute risk reduction to 30% [1, 2]. Allowing for 5% withdrawal/loss to follow up, we will aim to recruit a total of 260 patients.

Randomisation procedure

Randomisation will occur after the participant has provided informed consent 72 hours before the surgical procedure is due to start. Participants are randomised to a treatment group in a 1:1 ratio using a computer-generated dynamic procedure (minimisation) with a random component. Minimisation variables are trial centre, surgical procedure category (surgery involving the gut and all other surgery) and ACE-I and/or ARB category. Each participant will be allocated with 80% probability to the treatment group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To enter a patient into the SPACE trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. A patient's treatment group allocation will only be revealed to the person performing randomisation.

5. Analysis methods

General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis and analysed according to the treatment to which they were randomised [3, 4]. Patients will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol. Definitions of what constitutes a recorded outcome for each outcome can be found in Appendix 1. Patients with missing outcome data will be excluded from the analysis. Missing data for baseline covariates to be included in the analysis model will be accounted for using mean imputation for continuous variables and the missing indicator approach will be used for missing data for categorical variables [5, 6].

For the analysis of the primary outcome, each secondary outcome, and all process measures, we will present the following information:

- The number of patients included in each analysis, by treatment group
- A summary statistic of the outcome (e.g. mean (SD), number (%)), by treatment group
- The estimated treatment effect
- A 95% confidence interval for the estimated treatment effect
- A two-sided p-value

For all analyses, a significance level of 5% will be used.

Representativeness of patients

All participating sites have been asked to keep a log of eligible patients not recruited to the trial. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram [7].

Baseline characteristics

Baseline characteristics will be summarised for each treatment group by the mean and standard deviation or median and interquartile range for continuous variables, and the number and percent for categorical variables. The following baseline characteristics will be summarised by treatment group:

- Demographic: age (years), gender (male/female)
- Co-morbid disease: (a) COPD; (b) asthma; (c) interstitial lung disease or pulmonary fibrosis; (d) ischaemic heart disease; (e) diabetes mellitus; (f) heart failure; (g) liver cirrhosis; (h) active cancer; (i) previous stoke or TIA; (j) peripheral vascular disease; (k) Hypertension; (l) any treated infections within the previous month
- Current smoker
- ASA grade (III/IV)
- Pre-operative blood test results (within 4 weeks before surgery or most recent): (a) haemoglobin (g/L); (b) creatinine (µmol/L)
- Minimisation criteria:
    - Planned surgical procedure: (a) surgery involving the gut; (b) all other surgery
    - Class of drug routinely taken: (a) ACE-I; (b) ARB
    - Trial centre: (a) County Durham and Darlington NHS foundation trust; (b) Plymouth hospitals NHS trust; (c) Barts Health NHS trust; (d) University college London hospitals; (e) University hospitals Bristol NHS foundation trust
- Surgical procedure performed: (a) surgery involving the gut; (b) all other surgery
- Cardiovascular medication: (a) beta-blocker; (b) calcium channel antagonist; (c) Doxazosin; (d) Diuretic; (e) Statin; (f) Nitrate; (g) Anti-platelet agents (h) ACE-I/ARB drugs

Analysis software

All analyses will be conducted in Stata Version 14 (StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP).

Analysis of primary outcome

Primary analysis

The primary outcome, myocardial injury within 48 hours after surgery, will be analysed using a mixed-effect logistic regression model, with a random intercept for the minimisation variable trial centre [8]. The model will be adjusted for minimisation variables as fixed factors which are planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB) [9]. The model will also be adjusted for the following pre-specified baseline covariates [10-12]: age, gender (M/F), and the revised Cardiac Risk Index for pre-operative Risk [13] (0-1 vs 2-6). All covariates will be entered into the model as fixed factors. Age will be included as a continuous variable, assuming a linear association with the outcome [14].

When participants are randomised according to incorrect baseline information, under the ITT principle they should be analysed in their allocated treatment group, irrespective of the fact that their allocation was based on incorrect information. The incorrect baseline information should be kept in the randomisation record, as this reflects how the randomisation was performed, and the correct information documented for use in an adjusted analysis [15].

Analysis of secondary outcomes

Peak level of Troponin-T measured within 48 hours of surgery

The mean (SD) peak level of Troponin-T measured within 48 hours of surgery will be reported within each treatment group. Differences between the groups in the mean peak level troponin-t will be analysed using multilevel linear regression – adjusted for the same baseline variables as the adjusted analysis of the primary outcome. We will also adjust for baseline pre-operative Troponin-T as a continuous variable.

Infection within 30 days of surgery

Infection within 30 days of surgery will be analysed using a mixed-effect logistic regression model with a random intercept for the minimisation variable trial centre. The model will be adjusted for minimisation variables planned surgical procedure ((a) surgery involving the gut; (b) all other surgery) and class of drug routinely taken ((a) ACE-I; (b) ARB).

The expected event rate for this outcome is low, and as such we have reduced the number of covariates included in the model to avoid over-stratification.

Myocardial infarction within 30 days of surgery

The number (%) will be presented in each treatment group. An exact unadjusted logistic regression will be performed if 10 or more events are reported. No statistical analysis will be performed if there are fewer than 10 events.

Acute heart failure within 30 days of surgery

The number (%) will be presented in each treatment group. An exact unadjusted logistic regression will be performed if 10 or more events are reported. No statistical analysis will be performed if there are fewer than 10 events.

Stroke within 30 days of surgery

The number (%) will be presented in each treatment group. An exact unadjusted logistic regression will be performed if 10 or more events are reported. No statistical analysis will be performed if there are fewer than 10 events.

Death within 30 days of surgery

The number (%) will be presented in each treatment group. An exact unadjusted logistic regression will be performed if 10 or more events are reported. No statistical analysis will be performed if there are fewer than 10 events.

Strategy for analysis of primary and secondary outcomes if model fails to converge

If the statistical models for any of the primary or secondary outcomes do not converge, then the following steps will be taken:

1. The model will be fitted without a random intercept for trial centre
2. As above, but excluding any additional covariates apart from minimisation variables
3. As above, but also excluding minimisation variables.

Plan in case of over-stratification

When adjusting for covariates in the primary analysis or secondary analysis models where the outcome is binary, if there is a category within that covariate where no events have occurred in either of the treatment groups, the statistical model will exclude all patients within this category. To overcome this, this category will be merged with another category; this will be decided by the chief investigator who will be blinded to results. This will apply to covariates with three or more categories. However, if all but one category within that covariate have no events recorded in one of the treatment groups then we will exclude this covariate from the model.

Sensitivity analysis

The amount of missing primary outcome data is anticipated to be minimal but will be accounted for in a sensitivity analysis if missing data is greater than 5%. The primary analysis will be repeated once assuming that all patients in the continue group with missing outcomes did not experience myocardial injury, and all patients in the stop group with missing outcomes experienced myocardial injury. The analysis will then be repeated again with the opposite assumptions. This will then give the absolute range of how much the results could change if the data were complete. This will also assess the robustness of our analysis of the primary outcome under the assumption that data is missing-not-at-random (MNAR).

6. Other analyses, data summaries and graphs

Clinical management

Clinical management for the continue group and stop group will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The continue and stop groups will be compared for the following clinical management characteristics:

- Surgical technique
- Anaesthetic technique
- Planned level of care on the first night after surgery
- Blood pressure during surgery
- Intravenous fluids during surgery

Process measures

Summary measures will be presented separately for each treatment group. All patients with recorded data will be included in the summary. Formal statistical analysis will not be performed. Duration of hospital stay after surgery (days) and total duration of critical care stay within 30 days of surgery (days) will be summarised using mean (SD) and median (IQR).

Safety analyses

Adverse events and serious adverse events will be presented as a number (%) by treatment group. All patients with a recorded outcome will be included in the summary. In addition to this, 'other' adverse events will be reported separately if prevalence is more than 5% across all participants in the trial.

Protocol deviations

Numbers and percentages of protocol deviations will be reported. The following protocol deviations will be reported: (a) Patient in the stop group did receive ACE-I and/or ARB; (b) Patient in the continue group did not receive ACE-I and/or ARB; (c) other deviation. We will report the number of patients in each treatment group with at least one of the above protocol deviations. In addition to this, 'other' protocol deviations will be reported separately of prevalence is more than 5% in the trial.

Complications within 30 days after surgery

The number and percentage of patients experiencing each of the following complications will be presented by treatment allocation. These summaries will not be subjected to any statistical testing. These complications are as follows:

- Cardiac complications
- Respiratory complications
- Infective complications
- Other complications
- Acute kidney injury

References

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Appendix 1: Derived outcomes and variables

Variables

Revised cardiac risk index for pre-operative risk (RCRI)
RCRI is the sum of the following 6 components of the score:

- Elevated-risk surgery (Intraperitoneal; intrathoracic; suprainguinal vascular): 0=No; 1=Yes
- Ischaemic heart disease: 0=No; 1=Yes
- Heart failure: 0=No; 1=Yes
- Cerebrovascular disease (Prior TIA or stroke): 0=No; 1=Yes
- Pre-operative treatment with insulin (diabetes mellitus): 0=No; 1=Yes
- Pre-operative creatinine >2 mg/dL / 176.8 μmol/L: 0=No; 1=Yes

RCRI Score will range from 0-6. The total score will be set to missing if any items are missing.

Primary outcome

Myocardial injury within 48 hours of surgery

- Equal to 1 (Event) if:
    - Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L or
    - Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L
- Equal to 0 (No Event) if:
    - If the above definition of an 'event' is not satisfied and data collected on T-troponin pre-operative and post-operative day 1 or 2 is complete
- Equal to missing if:
    - Data is missing for T-troponin pre-operative and post-operative day 1 & 2
    - Data is missing for T-troponin pre-operative and T-troponin post-operative day 1 & 2 is complete

Secondary outcomes

Peak level of Troponin-T measured within 48 hours of surgery
This is defined as the highest troponin-t value measured within 48 hours of surgery which is collected on post-op day 1 or day 2. If only one troponin-T value is available on post-op day 1 or day 2 then this will be used as the peak. If troponin-T data is missing for both post-operative day 1 & 2, then the outcome will be set to missing.

Infection within 30 days of surgery
This is defined as one or more of the following infections (more detail on the definition of each type of infection is available in the SPACE protocol):

- Superficial surgical site infection
- Deep surgical site infection
- Organ space surgical site infection
- Urinary tract infection
- Infection, source uncertain
- Laboratory confirmed blood stream infection

Equal to 1 if:

- At least one of the components of infection is listed as occurring (i.e. listed under Clavien-Dindo grade I-V)

Equal to 0 if:

- All of the components of postoperative infection are “None”

Missing if:

- All components are missing
- OR one or more of the components of postoperative infection is missing and all other components are “None”

Myocardial infarction within 30 days of surgery

Equal to 1 if:

- Myocardial infarction is marked under Clavien-Dindo grade I-V

Equal to 0 if:

- Myocardial infarction is marked as “None”

Missing if:

- Myocardial infarction is missing

Acute heart failure within 30 days of surgery

Note in the CRF acute heart failure is known as Cardiogenic pulmonary oedema

Equal to 1 if:

- Cardiogenic pulmonary oedema is marked under Clavien-Dindo grade I-V

Equal to 0 if:

- Cardiogenic pulmonary oedema is marked as “None”

Missing if:

- Cardiogenic pulmonary oedema is missing

Stroke within 30 days of surgery

Equal to 1 if:

- Stroke is marked under Clavien-Dindo grade I-V

Equal to 0 if:

- Stroke is marked as “None”

Missing if:

- Stroke is missing

Death within 30 days of surgery

Equal to 1 if:

- Patient status at 30-day follow-up is dead
- AND date of death is within 30 days of surgery

Equal to 0 if:

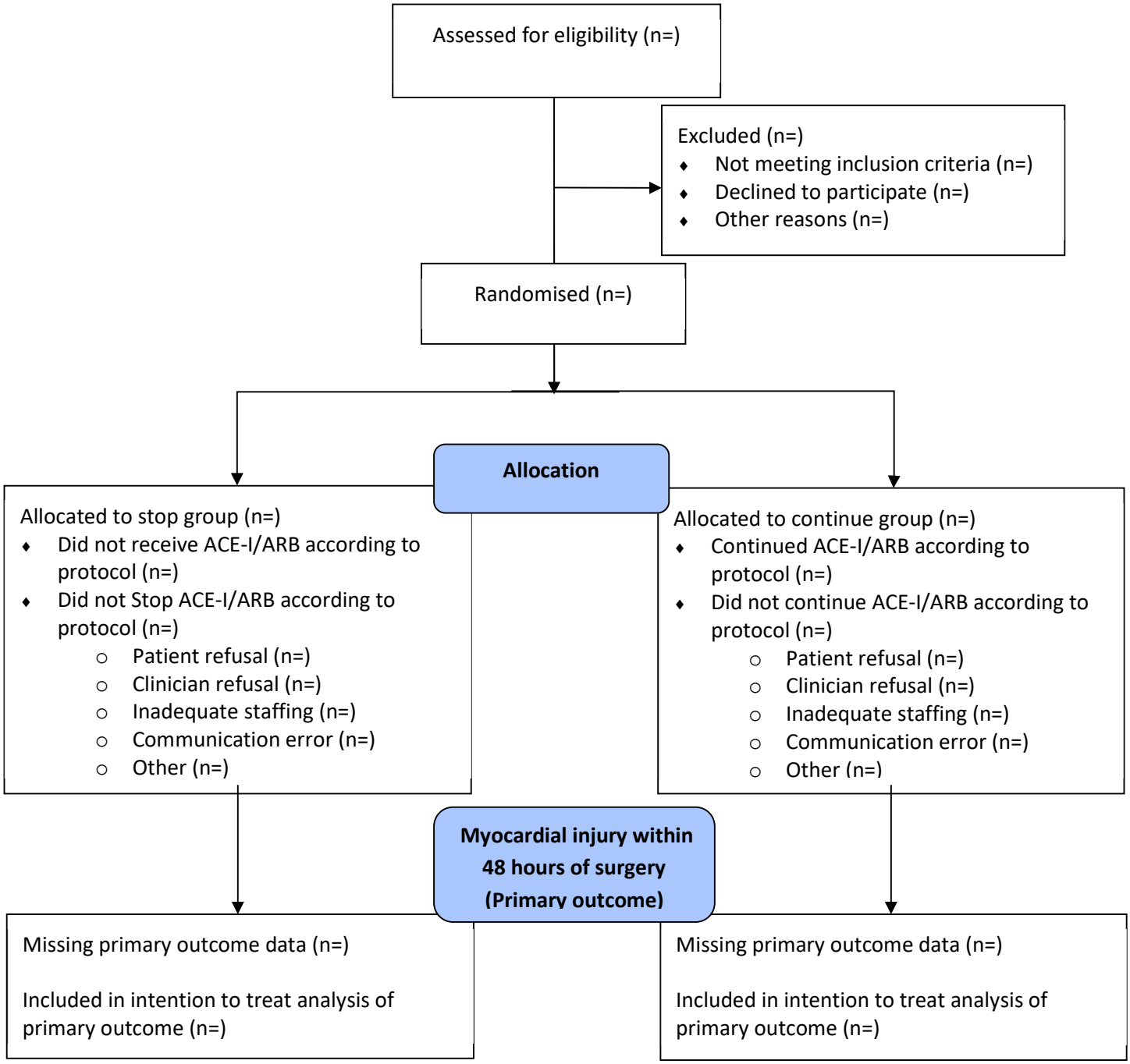
- Patient status at 30-day follow-up is alive
- OR patient status at 30-day follow-up is marked as ‘dead’ and date of death is not within 30 days of surgery

Missing if:

- Patient status at 30-day follow-up is missing
- Patient status at 30-day follow-up is marked as ‘dead’ and missing date of death

Appendix 2: Information for CONSORT flow diagram

The following information will be provided in the CONSORT flow diagram:



Appendix 3: Dummy tables

Table 1: Baseline Characteristics

Baseline Characteristics	Number of patients with available data - no. (%)		Summary measure	
	Stop (n=XXX)	Continue (n=XXX)	Stop	Continue
Gender - no. (%)				
Male				
Female				
Age (years)				
Mean (SD)				
Median (IQR)				
Current Smoker - no. (%)				
American Society of Anaesthesiology grade - no. (%)				
III				
IV				
Chronic comorbid disease - no. (%)				
COPD				
Asthma				
Interstitial lung disease or pulmonary disease				
Ischaemic heart disease				
Diabetes mellitus				
Heart failure				
Liver cirrhosis				
Active cancer				
Stroke or transient ischaemic attack (TIA)				
Peripheral vascular disease				
Hypertension				
Any treated infections within the previous month				
Planned surgical procedure - no. (%)				
Surgery involving the gut				
All other surgery				
Class of drug routinely taken - no. (%)				
ACE-I				
ARB				
Trial Centre - no. (%)				
County Durham and Darlington NHS Foundation Trust				
Plymouth Hospitals NHS Trust				
Barts Health NHS Trust				
University College London Hospitals				
University Hospitals Bristol NHS Foundation Trust				
Surgical procedure performed - no. (%)				
Surgery involving the gut				
All other surgery				
Pre-operative blood tests results				
Haemoglobin (d/DL)				
Mean (SD)				
Median (IQR)				
Creatinine (µmol/L)				
Mean (SD)				

Median (IQR)				
Cardiovascular medication - no. (%)				
Beta-blocker				
Calcium channel antagonist				
Doxazosin				
Diuretic				
Statin				
Nitrate				
Anti-platelet agents				
ACE-I/ARB drugs				

Abbreviations: SD, standard deviation; IQR, Interquartile range; COPD, chronic obstructive pulmonary disease.

Table 2: Clinical management

Clinical management characteristics	Number of patients with available data - no. (%)		Summary measure	
	Stop (n=XXX)	Continue (n=XXX)	Stop	Continue
Surgical technique - no. (%)				
Open surgical technique used during surgery				
Laparoscopic or laparoscopic assisted technique				
Laparoscopic converted to open				
Anaesthetic technique - no. (%)				
General anaesthesia alone				
General anaesthesia + epidural				
General anaesthesia + spinal				
General anaesthesia + other regional				
Regional anaesthesia + sedation				
Endotracheal tube inserted				
Planned level of care on the first night after surgery - no. (%)				
Critical care unit level 3				
Critical care unit level 2				
Post-anaesthesia care unit				
Surgical ward				
Blood pressure during surgery				
Systolic blood pressure <90 mmHg - no. (%)				
Phenylephrine, total dose during surgery (mcg)				
Median (IQR)				
Ephedrine, total dose during surgery (mg)				
Median (IQR)				
Metaraminol, total dose during surgery (mg)				
Median (IQR)				
Other pressor support - no. (%)				
Arrhythmias - no. (%)				
Intravenous fluids during surgery				
Total volume of intravenous fluid administered excl. blood products (Ml/kg/h)				

Median (IQR)				
Total volume of blood products administered (mL)				
Median (IQR)				
Lactate end of surgery mmol/L				
Median (IQR)				

Abbreviations: SD, standard deviation; IQR, Interquartile range

Table 3: Adherence and contamination

Adherence and contamination - no. (%)	Stop (n=XXX)	Continue (n=XXX)
Patients with ≥1 treatment deviation		
Total number of deviations		
Number of treatment deviations per patient		
0		
1		
2		
Patient in the stop group did receive ACE-I and/or ARB		N/A
Patient in the continue group did not receive ACE-I and/or ARB	N/A	
Other deviation		

Table 4: Primary and secondary outcomes.

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Treatment effect (95% CI)	P-value
	Stop (n=XXX)	Continue (n=XXX)	Stop	Continue		
Primary outcome						
Myocardial injury[a]						
Secondary outcomes						
Peak hsTnT[a]						
Infection[b]						
Myocardial infarction[b]						
Acute heart failure[b]						
Stroke[b]						
Death[b]						

[a] Within 48 hours of surgery
[b] Within 30 days of surgery

Table 5: Complications within 30 days of surgery

Complication	Number of patients with available data - no. (%)		Summary measure	
	Stop (n=XXX)	Continue (n=XXX)	Stop	Continue
Cardiac - no. (%)				
Arrhythmia				
Cardiac arrest with resuscitation				
Respiratory - no. (%)				
Pneumonia				
Pleural effusion				
Pneumothorax				
Bronchospasm				
Aspiration pneumonitis				
Acute lung injury				
Acute respiratory distress syndrome				
Infection - no. (%)				
Surgical site infection (superficial)				
Surgical site infection (deep)				
Surgical site infection (organ space)				
Urinary tract infection				
Infection, source uncertain				
Laboratory confirmed blood stream infection				
Other - no. (%)				
Pulmonary embolism				
Acute psychosis or delirium				
Bowel infarction				
Anastomotic leak				
Perforation of viscus				
Gastro-intestinal bleed				
Other postoperative haemorrhage				
Any other complication				
Acute kidney Injury - no. (%)				

Table 6: Process measures

Process measures	Number of patients with available data - no. (%)		Summary measure	
	Stop (n=XXX)	Continue (n=XXX)	Stop	Continue
Duration of hospital stay after surgery (days)				
Mean (SD)				
Median (IQR)				
Number of patients admitted to a critical care unit - no. (%)				
Total duration of critical care stay within 30 days of surgery (days)				
Mean (SD)				
Median (IQR)				

Table 7:Adverse events

Adverse Events - no. (%)	Stop (n=XXX)	Continue (n=XXX)
Patients with ≥ 1 adverse event		
Total number of adverse events		
Number of adverse events per patient		
0		
1		
2		
3		
Type of adverse event		
Hypertension[a]		
Hypotension[b]		
Acute kidney injury[c]		
Other		

[a] Defined as Systolic BP>180mmHg from randomisation until 48 hours after surgery, Diastolic BP> 100mmHg from randomisation until 48 hours after surgery

[b] Defined as requiring pressor via central venous access from randomisation until 48 hours after surgery

[c] Defined as in the absence of haemorrhage/sepsis (KIDIGO grades 1-4) within 30 days after surgery

Table 8: Serious Adverse Events

Serious Adverse Events	Stop (n=XXX)	Continue (n=XXX)
Patients with ≥1 SAE		
Total number of SAEs		
Type of SAE		
Death		
Life-threatening complication		
Prolonged existing hospital stay or required re-admission		
Significant disability or incapacity		
Other important medical event		