



Clinical trial results:

Phase II mechanistic, randomised controlled trial of Stopping Perioperative Angiotensin II Converting Enzyme inhibitors and/or receptor blockers in major noncardiac surgery

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2016-004141-90 |
| Trial protocol | GB |
| Global end of trial date | 15 March 2022 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 22 October 2023 |
| First version publication date | 08 April 2023 |
| Version creation reason | • New data added to full data set Addition information to be added regarding tertiary endpoints |
| Summary attachment (see zip file) | SPACE Tertiary exploratory analyses (SPACE tertiary exploratory analyses FINAL.pdf) |

Trial information

Trial identification

| | |
|-----------------------|-----|
| Sponsor protocol code | 8.0 |
|-----------------------|-----|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN17251494 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Queen Mary University of London |
| Sponsor organisation address | Dept W Mile End Road, London, United Kingdom, E1 4UJ |
| Public contact | Salma Begum, Queen Mary University of London, admin@spacetrial.org |
| Scientific contact | Professor Gareth Ackland, Queen Mary University of London, g.ackland@qmul.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 18 October 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 October 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 March 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether continuing ACE-I and/or ARB treatment perioperatively reduces the risk of perioperative myocardial injury in patients undergoing major surgery. This assessment will be based on plasma troponin levels measured in the first 48 hours postoperatively.

Protection of trial subjects:

This trial was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. All subjects provided written informed consent before undergoing any trial related procedures. The trial was reviewed and approved by a Research Ethics Committee (REC) and the Medicines & Healthcare products Regulatory Agency (MHRA).

Background therapy:

N/A

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 02 January 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 260 |
| Worldwide total number of subjects | 260 |
| EEA total number of subjects | 260 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 243 |

| | |
|-------------------|----|
| 85 years and over | 17 |
|-------------------|----|

Subject disposition

Recruitment

Recruitment details:

Recruitment began in January 2017 and ended in October 2021. Patients were recruited from 5 sites in the United Kingdom and were screened from preoperative assessment outpatient clinics and/or referring surgeons according to the eligibility criteria.

Pre-assignment

Screening details:

1110 patients were assessed for eligibility for the study. 262 patients were randomised and 848 patients were excluded. One patient withdrew consent from each arm.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open-label trial. Trial participants and staff were not blinded to treatment group allocation. Only the primary outcome (Troponin-T) assessment was blinded.

Arms

| | |
|------------------------------|---------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Stopping ACE-I and/or ARB |

Arm description:

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. One patient withdrew consent.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | ACE-I and/or ARB |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

As prescribed by patient's responsible clinician

| | |
|------------------|-----------------------------|
| Arm title | Continuing ACE-I and/or ARB |
|------------------|-----------------------------|

Arm description:

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. One patient withdrew consent.

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | ACE-I and/or ARB |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

As prescribed by patients' responsible clinician

| Number of subjects in period 1 | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB |
|---------------------------------------|------------------------------|--------------------------------|
| Started | 129 | 131 |
| Completed | 129 | 131 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------------------------|
| Reporting group title | Stopping ACE-I and/or ARB |
|-----------------------|---------------------------|

Reporting group description:

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. One patient withdrew consent.

| | |
|-----------------------|-----------------------------|
| Reporting group title | Continuing ACE-I and/or ARB |
|-----------------------|-----------------------------|

Reporting group description:

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. One patient withdrew consent.

| Reporting group values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | Total |
|------------------------|---------------------------|-----------------------------|-------|
| Number of subjects | 129 | 131 | 260 |
| Age categorical | | | |
| Units: Subjects | | | |
| From 60-64 years | 22 | 24 | 46 |
| From 65-84 years | 104 | 99 | 203 |
| 85 years and over | 3 | 8 | 11 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 72.1 | 71.5 | |
| standard deviation | ± 7.1 | ± 7.2 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 63 | 63 | 126 |
| Male | 66 | 68 | 134 |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | Stopping ACE-I and/or ARB |
| Reporting group description: | |
| 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. One patient withdrew consent. | |
| Reporting group title | Continuing ACE-I and/or ARB |
| Reporting group description: | |
| 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. One patient withdrew consent. | |

Primary: Myocardial injury

| | |
|---|-------------------|
| End point title | Myocardial injury |
| End point description: | |
| In the stop arm 9 patients had missing primary outcomes | |
| In the continue arm 10 patients had missing primary outcomes | |
| 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: 1. Troponin-T ≥15 ng/L within 48 hours after surgery with a pre-operative value <15 ng/L OR 2. Troponin-T increase ≥5 ng/L within 48 hours after surgery with a pre-operative value ≥15ng/L | |
| End point type | Primary |
| End point timeframe: | |
| within 48 hours after surgery | |

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 121 | | |
| Units: number of patients | 58 | 50 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Myocardial injury |
| Statistical analysis description: | |
| The primary outcome, myocardial injury within 48 hours after surgery, was analysed using a mixed effect logistic regression model, with a random intercept for the minimisation variable trial centre. The model was 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). | |
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[1] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Notes:

[1] - Model taking into account clustering by site did not converge and hence a logistic regression model was fitted ignoring clustering

Secondary: Peak level Troponin-T

| | |
|-----------------|-----------------------|
| End point title | Peak level Troponin-T |
|-----------------|-----------------------|

End point description:

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.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 48 hours after surgery

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 120 | 121 | | |
| Units: ng/L | 18 | 17 | | |

Statistical analyses

| | |
|----------------------------|-----------------------|
| Statistical analysis title | Peak level Troponin-T |
|----------------------------|-----------------------|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |
| Number of subjects included in analysis | 241 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[2] |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Notes:

[2] - 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

Secondary: Infection

| | |
|---------------------------|-----------|
| End point title | Infection |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Within 30 days of surgery | |

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 123 | | |
| Units: number of patients | 26 | 24 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Infection |
| Statistical analysis description: | |
| Infection within 30 days of surgery was analysed using a mixed-effect logistic regression model with a random intercept for the minimisation variable trial centre. The model was 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). | |
| Comparison groups | Continuing ACE-I and/or ARB v Stopping ACE-I and/or ARB |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Notes:

[3] - Model taking into account clustering by site did not converge and hence a logistic regression model was fitted ignoring clustering

Secondary: Myocardial infarction

| | |
|------------------------|-----------------------|
| End point title | Myocardial infarction |
| End point description: | |

| | |
|---------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Within 30 days of surgery | |

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 123 | | |
| Units: proportion | 3 | 0 | | |

Statistical analyses

| Statistical analysis title | Myocardial infarction |
|----------------------------|-----------------------|
|----------------------------|-----------------------|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Secondary: Acute heart failure

| | |
|-----------------|---------------------|
| End point title | Acute heart failure |
|-----------------|---------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 30 days of surgery

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 123 | | |
| Units: Number of patients | 2 | 0 | | |

Statistical analyses

| Statistical analysis title | Acute heart failure |
|----------------------------|---------------------|
|----------------------------|---------------------|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Secondary: Stroke

| | |
|-----------------|--------|
| End point title | Stroke |
|-----------------|--------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 30 days of surgery

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 123 | | |
| Units: number of patients | 1 | 0 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Stroke |
| Statistical analysis description: The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events. | |
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Secondary: Death

| | |
|---|-----------|
| End point title | Death |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Within 30 days of surgery | |

| End point values | Stopping ACE-I and/or ARB | Continuing ACE-I and/or ARB | | |
|-----------------------------|---------------------------|-----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 123 | | |
| Units: number of patients | 1 | 2 | | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Death |
| Statistical analysis description: The number (%) was presented in each treatment group. An exact unadjusted logistic regression was performed if 10 or more events were reported. No statistical analysis will be performed if there are fewer than 10 events. . | |
| Comparison groups | Stopping ACE-I and/or ARB v Continuing ACE-I and/or ARB |

| | |
|---|----------------------|
| Number of subjects included in analysis | 247 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.05 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to 30 days post surgery

Adverse event reporting additional description:

1. Systolic BP>180mmHg from randomisation until 48 hours after surgery
2. Diastolic BP> 100mmHg from randomisation until 48 hours after surgery
3. Hypotension requiring pressor via central venous access from randomisation until 48 hours after surgery
4. Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO grades 1-4) within 30 days

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|-----|
| Dictionary name | n/a |
|-----------------|-----|

| | |
|--------------------|-----|
| Dictionary version | n/a |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Continuing ACE-I/ARB |
|-----------------------|----------------------|

Reporting group description:

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.

| | |
|-----------------------|--------------------|
| Reporting group title | Stopping ACE-I/ARB |
|-----------------------|--------------------|

Reporting group description:

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.

| Serious adverse events | Continuing ACE-I/ARB | Stopping ACE-I/ARB | |
|---|----------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 131 (3.05%) | 8 / 129 (6.20%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 3 / 129 (2.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 0 / 129 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac arrest | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 129 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | 0 / 129 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 131 (0.00%) | 1 / 129 (0.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 131 (1.53%) | 0 / 129 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 131 (0.76%) | 1 / 129 (0.78%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Continuing ACE-I/ARB | Stopping ACE-I/ARB | |
|---|--|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 29 / 131 (22.14%) | 40 / 129 (31.01%) | |
| Vascular disorders | | | |
| Hypertension | Additional description: 1) Systolic BP>180mmHg from randomisation until 48 hours after surgery 2) Diastolic BP> 100mmHg from randomisation until 48 hours after surgery. As verified on measurement by study investigators. This is a pre-specified adverse event. | | |
| subjects affected / exposed | 8 / 131 (6.11%) | 15 / 129 (11.63%) | |
| occurrences (all) | 8 | 15 | |
| Hypotension | Additional description: Hypotension requiring pressor via central venous access from randomisation until 48 hours after surgery. This is a pre-specified adverse event. | | |

| | | | |
|--|---|-------------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 131 (7.63%) 10 | 12 / 129 (9.30%) 12 | |
| Renal and urinary disorders Acute kidney injury | Additional description: Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO grades 1-4) within 30 days after surgery. This is a pre-specified adverse event. | | |
| subjects affected / exposed occurrences (all) | 11 / 131 (8.40%) 11 | 13 / 129 (10.08%) 13 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 14 December 2016 | <p>Substantial amendment 1</p> <p>Changes to IRAS Form (v5.3.2): The study category has been changed to Clinical Trial of an Investigational Medicinal Product (CTIMP). The subsequent MHRA form has been completed via IRAS.</p> <p>Changes to Protocol: Format change on the table of contents in accordance to sponsor requirements.</p> <p>Specified this will be a phase III CTIMP clinical trial.</p> <p>Change in the number of patients recruited from 248 to 260.</p> <p>Further information has been added to the protocol on the pre-clinical and clinical data to support the trial. Immune function has been added as a tertiary end point.</p> <p>New section on the IMP including the list of drugs being investigated, formulation, supply, prescription. Informed consent can also be done by the principal investigator or medically qualified person. Section on schedule of treatment for each visit. Laboratory assessments detailing the procedures used, sample analysis and storage.</p> <p>Detailed section on safety reporting and notification of SAE/SUSAR. Section on quality control and assurance.</p> <p>Patient Information Sheet: Patients will receive advice letters confirming their trial allocation to stopping or continuing their medication. We will also provide reminders by telephone, text message or in person if they are in hospital.</p> <p>Additional information on the time frame the drugs will be restarted.</p> <p>Informed consent form: Only the principal investigator or medically qualified person can take consent.</p> <p>Minor Corrections following HRA review:</p> <p>Changes to Protocol:</p> <p>Change in the flow diagram in Section 2.3 to include 'to provide there is no change in creatinine, as >30% of patients on ACE/ARB and undergoing an operation may have underlying CKD, so from the protocol the ACEi would not be restarted'</p> <p>Patient Information Sheet: Changes to accommodate the following conditions set by the original REC letter dated 15 September 2016.</p> <p>Informed consent form: Changes to the title to ensure consistency cross the documentation.</p> |

| | |
|------------------|--|
| 27 November 2017 | <p>Substantial amendment 2</p> <p>Changes to Protocol</p> <ul style="list-style-type: none"> - Change in trial title. - Clarification on the trial objectives and design. - Clarifications on the study procedures for screening, randomisation patient follow-ups and the schedule of assessment. - Updated the time line on the end of study definition. - Updated the Laboratories and all samples will be measured using a central lab. <p>Specified the time lines for the adverse event reporting</p> <ul style="list-style-type: none"> - Updated the statistical considerations section. - Updated the data handling and record keeping section. - Updated the data management section. - Updated the trial steering committee and data monitoring and ethics committee section. - Updated appendix 2 detailing the perioperative morbidity definitions. <p>Patient Information Sheet</p> <ul style="list-style-type: none"> - Change in the study title and added a sentence that patients will be contacted at 30 days to check on their wellbeing. <p>Informed Consent Form</p> <ul style="list-style-type: none"> - Change in the study title. - Added nurse to the list of people taking consent. - Changed which copy of the signed consent form goes into the investigator file and the medical notes. <p>Patient invitation letter</p> <ul style="list-style-type: none"> - Letter to inform patients of the SPACE trial to give them more time to consider whether they want to take part in the trial. <p>Patient Advice Letters - treatment continuation</p> <ul style="list-style-type: none"> - Spelling mistake. - Updated the information for the co-ordinating centre. <p>Patient Advice Letters - treatment discontinuation</p> <ul style="list-style-type: none"> - Spelling mistake. - Updated the information for the co-ordinating centre. |
| 21 May 2019 | <p>Substantial amendment 3</p> <p>Changes in conduct or management of the trial</p> <p>Previous and new wording:(tracked) Page 2: Statistician Name: Tahanah Ahmad New wording: Page 2: Statistician Name: Akshaykumar Patel</p> <p>Comments/ explanation/ reasons for substantial amendment: We have added 'regional anaesthesia with sedation' to the inclusion criteria. This change has been made for clarity/consistency. Regional anaesthesia is a common anaesthetic technique used in combination with general anaesthesia or heavy sedation for patients undergoing orthopaedic surgery. We want to ensure that this patient group is not excluded from the study. This has been updated in all the necessary sections of the protocol.</p> <p>Other minor clarifications to the protocol regarding patient follow up, the addition of the TMG committee and participation in other trials.</p> |
| 11 March 2020 | <p>Substantial amendment 4</p> <p>1. Clarification to the Patient information sheet to section: What will happen to me if I take part?</p> <p>2. Clarification to the following sections of the protocol: 2.1 Trial objectives, 2.2 Safety outcomes, 2.4 Assessment of primary and secondary outcomes, 3.1 Number of subjects and subject selection, 5.3 Randomisation procedures, 5.6 Schedule of assessment in diagrammatic format, 5.8 Laboratory assessments, 6.1 Central/ local laboratories, 6.2 Sample collection/labelling/logging, 7.1.3 Serious Adverse Event or Serious Adverse Reaction, 9.1 Statistical Primary Endpoint Efficacy Analysis and 10.2 Case Report Form.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|---|--------------|
| 17 March 2020 | Recruitment suspension/pause due to the Covid-19 pandemic. The trial restarted on 25/06/2020. | 25 June 2020 |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

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| Further endpoint plasma samples has been analysed for NT-pro BNP and mediators of the Renin-angiotensin system. An addendum detailing these findings has been attached as a PDF document to version 2 of this report. |
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Notes: