APPENDIX 4 to the PROTECT Platform Master Protocol

This appendix must be read with the accompanying PROTECT Platform Master Protocol IRAS 353122. This appendix describes only the additional details relevant to the conduct of this randomised comparison within the context of the overarching master protocol.

Full Title	Stopping or continuing RAS-inhibitor drugs before major elective non-cardiac surgery: SPACE II trial.
Short Title	PROTECT-SPACE II
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Participating locations	For a list of participating locations please refer to the combined review application

Comparison contributors

The trial sponsor and trial funder have not played, nor will play a role in the study design, conduct, data analysis and interpretation, manuscript writing, and/or dissemination of results.

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1. Contents

1. Contents 5
2. Glossary of comparison specific terms and abbreviations 6
3. Signature page 8
4. Synopsis 9
5. Introduction 10
6. Trial objectives 12
7. Patient evaluability and replacement 15
8. Informed consent procedures 15
9. Participant randomisation and study group allocation 16
10. Participant eligibility criteria 16
11 Study schedule 17
12 Participant, study and site discontinuation 20
13 Study medication 20
14 Pharmacovigilance 23
15 References 30

2. Glossary of comparison specific terms and abbreviations

ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse event
AKI	Acute kidney injury
ARB	Angiotensin Receptor Blocker
BP	Blood pressure
CKD	Chronic Kidney Disease
CMG	Comparison Management Group
CSC	Comparison Steering Committee
cTn	Cardiac Troponin
DAH30	Days Alive and at Home within 30 days after surgery
eCRF	electronic Case Report Form
EQ-5D-5L	EuroQol 5-Dimension Questionnaire (five-level version)
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
GP	General Practitioner
IDMC	Independent Data Monitoring Committee
IMP	Investigational medicinal product
JRMO	Joint Research Management Office (QMUL)
KDIGO	Kidney Disease: Improving Global Outcomes definition of AKI
MACE	Major cardiovascular events
MHRA	Medicines and Healthcare products Regulatory Agency
NHS	UK National Health Service
NIHR-HTA	National Institute for Health Research Health Technology Assessment programme
NT-proBNP	N-terminal pro-B-type naturietic peptide (biomarker of heart failure)
OR	Odds ratio
PPI	Patient & Public Involvement
PROTECT	UK trial platform for surgical and perioperative research
QMUL	Queen Mary University of London
RAS-inhibitor	Renin-Angiotensin System inhibitor (i.e. ACEi or ARB)
RSI	Reference Safety Information
SAE	Serious adverse event
SAR	Serious Adverse Reactions
SUSAR	Suspected Unexpected Serious Adverse Reactions

SmPC	Summary of Product Characteristics
SMS	Short Message Service (i.e. mobile phone text message)
SOP	Standard Operating Procedure
SPACE II	Stopping or continuing RAS-inhibitor drugs before major elective non-cardiac surgery trial
SD	Standard deviation
TnI	Troponin-I (biomarker of myocardial injury)
TnT	Troponin-T (biomarker of myocardial injury)
URL	Upper Reference Limit
ZINB	Zero-inflated negative binomial distribution

3. Signature page

Chief Investigator Agreement
The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2025 (UK S.I. 2025/538) and all subsequent modifications. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

PROTECT Platform Chief Investigator: Dr Tom Abbott

Signature: Tom Abbott

Date: Digitally signed by Tom Abbott Date: 2026.09.11 08:41:17 +01'00'

PROTECT-SPACE II Lead Investigator: Prof Rupert Pearse

Signature: Rupert Pearse

Date: Digitally signed by Rupert Pearse Date: 2026.09.11 08:56:16 +01'00'

Statistician's Agreement
The study as detailed within this research protocol plan will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2025 (UK S.I. 2025/538) and all subsequent modifications, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups.
I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician name: Jo Haviland

Signature: Jo Haviland

Date: Digitally signed by Jo Haviland Date: 2026.09.14 11:46:05 +01'00'

Principal Investigator Agreement
The clinical study as detailed within this research protocol **(version 1.0, dated 30.04.2026)**, or any subsequent modifications, involves the use of an investigational medicinal product and will be conducted in accordance with the UK Policy Framework for Health and Social Care Research , the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2025 (UK S.I. 2025/538) and any subsequent modifications of the clinical trial regulations.

Principal Investigator:

Location:

Signature:

Date:

4. Synopsis

Full title	Stopping or continuing RAS-inhibitor drugs before major elective non-cardiac surgery
Short title	PROTECT-SPACE II
Sponsor	Queen Mary University of London
MHRA risk level	Full MHRA authorisation
Phase of the trial	IV
Medical condition or disease under investigation	Adult patients undergoing major elective non-cardiac surgery
Study design and methodology	Multi-centre individual patient randomised clinical trial
Planned number of participants	2214 patients
Objectives	1. To establish the clinical and cost effectiveness of continuing or stopping RAS-inhibitors for patients undergoing major elective non-cardiac surgery. 2. To describe treatment benefit for patients with and without NT-proBNP ≥100 pg/ml (risk of heart failure). 3. To describe treatment benefit for patients with and without chronic kidney disease (≥G3a).
Inclusion and exclusion criteria	*Inclusion criteria:* Participants aged ≥50 years, awaiting major elective non-cardiac surgery, and taking a RAS-inhibitor (ACEi or ARB). *Exclusion criteria:* Participant refusal, Clinician refusal.
Investigational Medicinal Product	Any RAS-inhibitor (ACEi or ARB) prescribed to a trial participant as part of their routine cardiovascular treatment
Treatment duration	Seven days
Follow-up duration	180 days
End of study definition	180-day follow-up completed for all participants

5. Introduction

5.1 Background

Renin-angiotensin system (RAS) inhibitors are important and widely used drugs

RAS-inhibitors, which include Angiotensin Converting Enzyme inhibitors (ACEi) and Angiotensin-II Receptor Blockers (ARB), are some of the most important medicines available to the NHS. They are widely used to treat high blood pressure, heart failure, and chronic kidney disease (CKD). Common ACEi include ramipril, lisinopril, and perindopril, while angiotensin-II blockers include valsartan, losartan and candesartan. ACEi work by blocking the enzyme which converts angiotensin-I to angiotensin-II, a hormone that narrows blood vessels. This reduces blood pressure and improves cardiac output. For patients with heart failure, ACEi reduce the amount of fluid retained in the body through the renin-angiotensin-aldosterone system. This mechanism also reduces ultrafiltration pressure in the renal glomeruli, slowing disease progression for patients with CKD. Angiotensin-II blockers have similar actions but at a different point in the hormonal pathway. 3.9 million people take RAS-inhibitors in the UK [1], with 65 million NHS prescriptions in 2021 [2]. RAS-inhibitors have transformed survival and quality of life for people with cardiovascular and kidney disease. Once a patient is stable on a RAS-inhibitor, doctors are reluctant to make sudden changes because poorly controlled blood pressure may cause myocardial injury and kidney injury. This can be a problem when patients require surgical treatments.

Major surgery presents a common problem for people taking RAS-inhibitors

Each year, 500,000 NHS patients taking RAS-inhibitors undergo major surgery [3-5]. This is a problem because RAS-inhibitors often interact with anaesthetic drugs to cause severe low blood pressure events during and after surgery. This problem can be serious, resulting in myocardial injury, and requiring admission to critical care for intra-venous vasopressor therapy. Perioperative myocardial injury leads to poor long-term patient outcomes with a four-fold increase in one-year mortality [6]. Many anaesthetists ask patients to stop their RAS-inhibitors before surgery. However, sudden cessation of RAS-inhibitors coupled with the physiological stress of surgery may lead to heart failure, severe high blood pressure, myocardial injury and stroke. The patient population taking RAS-inhibitors are already at high long-term risk of cardiovascular morbidity and mortality regardless of risks associated with surgical treatment [7]. Both stopping and continuing RAS-inhibitors may cause significant additional harm for surgical patients. We need to know which of these risks is greatest, and in which patients.

New evidence suggests stopping RAS-inhibitors may be more harmful than continuing them

We recently completed a phase IIb trial where we randomised patients to stop or continue their RAS-inhibitors before, during and after major non-cardiac surgery (SPACE-I; n=262) [8]. The primary outcome of myocardial injury was more frequent amongst patients who stopped RAS-inhibitors although this did not reach statistical significance (Continued: 50 (41.3%) patients vs Stopped: 58 (48.3%) patients; OR 0.77 [0.45-1.31]). High blood pressure adverse events were more frequent when RAS-inhibitors were stopped but low blood pressure event rates were similar in the two groups. The less frequently used approach, i.e. continuing RAS-inhibitors, appeared to offer the best outcomes for patients but we cannot be certain of this.

Effects of stopping RAS-inhibitors differ for patients at risk of heart failure

Importantly in the SPACE-I trial, the benefits of continuing RAS-inhibitors were different for patients with heart failure [9]. Using an established threshold for pre-operative NT-proBNP of ≥100 pg/ml to identify patients at risk of heart failure [10], myocardial injury rates were similar regardless of stopping or continuing RAS-inhibitors (Continued: 35/56 [62.5%] patients vs Stopped: 28/45 [62.2%] patients; OR 0.98 [0.44-2.22]) [9]. However, patients not at risk of heart failure were much more likely to experience myocardial injury if they stopped their RAS-inhibitor (Continued: 15/65 [23.1%] patients vs Stopped: 30/75 [40.0%] patients; OR: 2.22 [1.06-4.65]). These findings suggest patients without heart failure are likely to develop myocardial injury because of high blood pressure during surgery, and benefit from continuing their RAS-inhibitor. Patients with heart failure are prone to both low and high blood pressure and the benefit/harm of RAS-inhibitors may be more equivocal.

RAS-inhibitors are also used to treat chronic kidney disease (CKD)

Patients with significant CKD are also commonly prescribed RAS-inhibitors. This is partly because cardiovascular disease is the most frequent mode of death for this population, but also because RAS-inhibitors have important benefits for kidney disease itself. By decreasing the ultrafiltration pressure within the renal glomeruli, RAS-inhibitors can prevent further kidney damage and disease progression. There is considerable overlap between the CKD, hypertension and heart failure indications for RAS-inhibitors among CKD patients. In addition to myocardial injury, acute kidney injury (AKI) is also an important risk affecting 30% of patients with CKD G3a and above when they have surgery [11]. The decision to stop/continue RAS-inhibitors for patients with CKD must therefore include consideration of the risks of AKI, which may be more likely when RAS-inhibitors are continued, and is common cause of CKD progression. In SPACE-I, 30% of patients had CKD ≥G3a [8], but a conservative estimate is ~20% of RAS-inhibitor users presenting for major surgery.

Systematic review

We undertook a systematic review of randomised trials comparing stopping vs continuing RAS-inhibitors among patients undergoing major non-cardiac surgery published between January 2000 and October 2024 [12]. The primary outcome was a composite of mortality up to 30 days and major cardiovascular events (MACE). Secondary outcomes were hypertension and hypotension adverse events. We identified five trials including 2848 patients but only three trials reported our primary outcome. Stopping RAS-inhibitors was not associated with a significant increase in mortality and MACE (three trials; OR 1.21 [0.60-2.42]); p=0.59; I^2=19%). Stopping RAS-inhibitors was associated with more hypertension events (four trials; OR 1.90 [1.20-3.02]; p=0.007; I^2=8%) but fewer hypotension events (five trials; OR 0.62 [0.42-0.90]; p=0.01; I^2=38%). There was a low risk of bias, but a low or very low certainty of evidence for all outcomes except hypotension, where there was a moderate certainty of evidence.

5.2 Rationale for trial design

During and after major surgery, patients who take RAS-inhibitors commonly experience important high and low blood pressure events, leading to increased post-operative mortality and prolonged hospital stay. Continuing RAS-inhibitors during major surgery may offer important health benefits to some patients but not others. Existing clinical evidence cannot resolve this uncertainty. A large clinical effectiveness trial is needed to address the overarching question, including patient groups with heart failure and CKD.

5.3 Assessment and management of risk

The trial is categorised as Condition A, IMP authorised in UK, unmodified, used normally (no placebos). The risk is no higher than the standard medical care.

6. Trial objectives

a. Primary objective

- To establish the clinical and cost effectiveness of continuing or stopping RAS-inhibitors for patients aged ≥50 years, awaiting major elective non-cardiac surgery.

b. Secondary objectives

- To describe treatment benefit for patients with and without NT-proBNP ≥100 pg/ml (risk of heart failure).
- To describe treatment benefit for patients with and without chronic kidney disease (≥G3a).

6.1. Outcome measures

a. Primary outcome measure

- Days Alive and at Home within 30 days after surgery (DAH30)

b. Secondary outcome measures

- Myocardial injury within three days after surgery (see definition below)
- Acute kidney injury within seven days after surgery (KDIGO creatinine criteria) [13]
- High blood pressure events (systolic BP ≥160 mmHg) within seven days after surgery
- Low blood pressure events (systolic BP ≤90 mmHg) within seven days after surgery
- Stroke within 30 days after surgery
- Other post-operative complications within 30 days after surgery (predefined in eCRF)
- Mortality at 180 days after surgery
- Hospital in-patient re-admission within 180 days after surgery
- Health-related quality of life at 30 and 180 days after surgery (EQ-5D-5L)
- Hospital care costs within 180 days after surgery

6.2 Study design

Multi-centre, open-label, individual patient randomised trial.

6.3 Study setting

Surgical services of NHS hospitals.

6.4 Estimand framework

The estimand for the primary outcome (DAH30) is the difference in mean days alive and at home within 30 days of randomisation between continuing versus stopping RAS-inhibitors, regardless of adherence, in participants aged ≥50 years taking a RAS-inhibitor and awaiting major elective non-cardiac surgery. Details of the analytical strategy underlying this approach are shown in the table below.

Aspect	Definition
Target population	Patients aged ≥50 years, awaiting major elective non-cardiac surgery, and taking a RAS-inhibitor.
Variable / endpoint	Days alive and at home within 30 days of randomisation [DAH30; where DAH30=0 if participant dies within 30 days, and DAH=30-(days in hospital within 30 days of randomisation) if participant alive 30 days after randomisation]
Treatment conditions	**Continuing RAS-inhibitor group** Participants continue their RAS-inhibitors during the perioperative period. **Stopping RAS-inhibitor group** Participants stop their RAS-inhibitors for a total of seven days (from Day -3 to Day 3 inclusive, where Day 0 = day of surgery).
Population-level summary measure	Difference in means (continuing versus stopping)
Intercurrent events	**Strategy**
Surgery not received (applies to both treatment arms)	Principal stratum (of participants who would undergo surgery regardless of randomised treatment allocation)
RAS-inhibitors stopped (continuing group only)	Treatment policy
RAS-inhibitors continued (stopping group only)	Treatment policy
RAS-inhibitors continued but dosing altered (continuing group only)	Treatment policy
RAS-inhibitors stopped but timing deviates from protocol (stopping group only)	Treatment policy

Table. Estimand framework for primary outcome analysis

7. Patient evaluability and replacement

7.1 Target accrual

2214 participants.

7.2 Participant identification and recruitment

7.2.1 Pre-screening

SPACE II pre-screening involves medical record review only and there are no formal screening tests or procedures. Potential participants will be pre-screened by the direct care team to identify patients who may be suitable to be invited to participate, in accordance with the corresponding section of the PROTECT master protocol. A medically qualified investigator (any doctor on the delegation log) will assess the potential eligibility of patients identified by the pre-screening process, and document this in the patient record. Patients who wish to participate in the trial will be asked to give informed consent (electronic or on paper). Informed consent will be obtained before any other trial-related procedures take place. The pre-screening period is defined as up to 365 days before surgery, where Day 0 is the planned day of surgery at the time of pre-screening.

7.2.2 Eligibility

Eligibility will be confirmed within eight weeks before randomisation (not surgery) and documented in the patient record by a medically qualified investigator. This will allow pre-randomisation blood tests to be performed during routine patient visits to hospital. Randomisation is best performed between five and ten days before the planned date of surgery (see section 9 below for details). Immediately prior to randomisation, a site investigator will check there have been no changes that may affect the participant's eligibility. The eligibility criteria are very simple and any changes will be obvious e.g. cancellation of surgery, withdrawal of consent. If the date of surgery is postponed *after* the participant has been randomised, eligibility may still need to be re-confirmed depending on the length of the delay.

8. Informed consent procedures

Consent procedures are documented in the PROTECT master protocol. Ideally, 24 hours should be left between providing the participant information sheet and obtaining consent. All other trial procedures will commence after informed consent has been obtained. All consented participants will be recorded on the study enrolment log with their trial ID.

8.1 Vulnerable participant considerations and participants lacking capacity

The trial will not involve vulnerable participant groups or patients lacking capacity to consent.

9. Participant randomisation and study group allocation

Randomisation is best performed between five and ten days before the date of surgery, allowing adequate time to communicate study group allocation to the trial participant while minimising problems caused by cancellation of surgery. Following informed consent and immediately prior to randomisation, a site investigator will check that the date of the participant's surgery has not changed, and that there have been no changes that may affect the participant's eligibility. The eligibility criteria are very simple and any changes will be obvious e.g. cancellation of surgery, withdrawal of consent. If there have been changes that might affect eligibility, then this must be re-confirmed and documented in the patient record by a medically qualified investigator (as described in section 7.2.2).

10. Participant eligibility criteria

10.1 Inclusion criteria

- Patients aged ≥50 years, awaiting major elective non-cardiac surgery, and taking a RAS-inhibitor (ACEi and/or ARB with a single active ingredient formulation).

10.2 Exclusion criteria

- Inability or refusal to provide informed consent
- Clinician refusal to allow a patient to participate

Please see section 13 for further information regarding RAS-inhibitor formulations that are eligible for the trial.

11 Study schedule

11.1 Schedule for each visit

Visit	Pre-screening *(up to 365 days before surgery)*	Before randomisation	Randomisation *(between five and ten days before surgery)*	Intervention period *(where Day 0 is day of surgery)*							Hospital discharge	30-day follow-up after surgery *(± 3 days)*	180-day follow-up after surgery *(± 7 days)*
				Day -3	Day -2	Day -1	Day 0*	Day 1	Day 2	Day 3			
Eligibility confirmation		x											
Informed consent	x												
Demographics		x											
Review of patient record	x	x		x	x	x	x	x	x	x	x	x[α]	x
CRF completion			x	x	x	x	x	x	x	x	x	x[α]	x
Randomisation			x										
Intervention				x	x	x	x	x	x	x			
NT-proBNP measurement		x**											
Cardiac troponin measurement		x**						x	x	x			
Blood pressure measurement							x	x	x	x			
Concomitant medication review		x					x	x	x	x			
Pharmacovigilance		x	x	x	x	x	x	x	x	x	x	x	
Post-operative follow-up								x	x	x	x	x	

*Day of surgery is defined as Day 0 and the three calendar days before surgery as Day -1, Day -2 and Day -3
**Performed no more than eight weeks before randomisation
[α]Performed as part of PROTECT master protocol

11.2 Randomisation method

Randomisation will be performed through the PROTECT REDCap database using an application programme interface system, which will interact with bespoke randomisation software after the participant has given informed consent. Participants will be randomised 1:1 to stop or continue their RAS-inhibitor during the perioperative period stratified by hospital, type of RAS-inhibitor (ACEi or ARB) and CKD (≥G3a).

11.3 Randomisation procedure

The code creating the randomisation sequence will be approved and validated by the lead trial statistician for the SPACE II comparison.

11.4 Study assessments

The study data will include the items listed below which will be collected in addition to those in the common dataset listed in the PROTECT master protocol.

Pre-screening

- Checklist to ensure the patient meets the eligibility criteria

Baseline data

- Cardiovascular medications
- Preoperative NT-proBNP measurement (no more than eight weeks before randomisation)
- Preoperative cardiac troponin measurement (no more than eight weeks before randomisation)

Adherence to study group allocation during the intervention period

- Continuing or stopping RAS-inhibitor medication

Day of surgery

- Treatment of severe high or low blood pressure
- Intravenous fluids and blood products

Post-operative follow-up

- Cardiovascular medication (e.g. RAS-inhibitors)
- Treatment of severe high or low blood pressure
- Cardiac troponin measurements (post-operative days 1, 2 and 3)
- Creatinine measurements (post-operative days 1, 2 and 3)

- Mortality at 180 days after surgery
- Health-related quality of life at 180 days after surgery
- Hospital readmission within 180 days after surgery

11.5 Trial procedures

Continuing RAS-inhibitor group

Participants will continue their RAS-inhibitors during the perioperative period except when they need vasopressor treatment for low blood pressure, or where a decision is made by the responsible physician for appropriate medical reasons.

Stopping RAS-inhibitor group

Participants will stop their RAS-inhibitors for a total of seven days. The last dose before surgery will be taken on Day -4 where the day of surgery is Day 0. RAS-inhibitors will be withheld for the three days before surgery i.e. from Day -3 onwards, and re-started on Day 4 after surgery. The duration for stopping before surgery is defined by the typical half-life of RAS-inhibitors.

Ensuring adherence to allocated study group

Investigators will work with treating clinicians in out-patient and in-patient periods of patient care, ensuring they are aware of participants in SPACE II, and their trial group allocation. We will offer participants options for reminders e.g. phone call, SMS (Short Message Service i.e. mobile phone text message), carer involvement, etc, which can be tailored to their specific circumstances. If a participant chooses the SMS option, the investigators will use an approved SMS provider to send reminders regarding their treatment allocation.

Procedures for postponed or cancelled surgery

Some participants may be randomised into the trial but then have their surgery postponed or cancelled. The consequent steps to be taken will vary depending on the cause and length of the delay. A Standard Operating Procedure (SOP) for surgery delay and cancellation will outline the necessary steps to be taken in these circumstances. Where a participant's surgery is cancelled permanently, they will be withdrawn from the trial and not included in the analysis. This is in keeping with the estimand framework (Section 6.4).

Blood sampling

Blood samples will be taken before randomisation for measurement of NT-proBNP and cardiac troponin. These assays may be performed either on plasma using samples collected in a

lithium heparin blood tube (typically with a green top), or on serum using samples collected in a serum separator blood tube (typically with a yellow top). Wherever possible these assays will be performed on the routine blood samples taken as part of the participants' usual clinical care. If this is not possible, additional blood samples of approximately 5ml will be collected for each test. Samples may be taken using the routine NHS blood sampling services at the hospital site but must be sent to the NHS laboratory for that hospital. Point-of-care assays will not be used in SPACE II as it is not possible to ensure quality control of the testing procedures.

Assays will be performed on preoperative blood samples taken no more than eight weeks before randomisation. If the date of surgery is postponed to more than eight weeks after the date of blood sampling, then new blood samples should be taken and the assays repeated. This is because some patients may experience a deterioration in cardiac function that could affect the test results. Where it is not possible to repeat the blood samples before randomisation, the site principal investigator should be consulted and advice taken from the comparison management group. In some cases, the best course of action will be to keep the participant enrolled on the trial, but in others it may be preferable to withdraw them. Post-operative blood samples will be taken for cardiac troponin measurement on Days 1, 2 and 3 after surgery during the hospital admission (where Day 0 is the day surgery is performed).

11.6 Follow-up procedures

Investigators will review participants' patient records and contact them to conduct brief interviews to collect follow-up data. To minimise bias, follow-up data will be collected by an investigator who is unaware of the study group allocation wherever possible.

12 Participant, study and location discontinuation

It is always within the remit of the responsible physician to withdraw the participant from the trial for appropriate medical reasons. This can be due (but is not limited) to adverse events or toxicities, new information about a treatment, or if it is felt to be in the participant's best interest. Please follow the procedures in the corresponding section of the PROTECT master protocol.

13 Study medication

13.1 Study drug

RAS-inhibitor (ACEi and/or ARB).

13.2 Name and description of Investigational Medicinal Products (IMP)

Any ACEi and/or ARB with a single active ingredient formulation* licensed for use in the UK.

*Combination drugs such as Hyzaar (a combination of Losartan Potassium and Hydrochlorothiazide) and Triapin (a combination of Felodipine and Ramipril) are not considered study IMP. Patients taking a combination drug are not eligible for the trial.

13.3 Name and description of Non-Investigational Medicinal Product (NIMP)

Not applicable.

13.4 Reference Safety Information (RSI)

RSI is the information used for assessing whether an adverse reaction is expected. Expectedness will be evaluated against the trial RSI in use at the time the reaction occurred. For the purposes for this trial, the Summary of Product Characteristics (SmPC) for Ramipril provided by Sandoz Limited will be used as an example for all ACEi. The SmPC for Losartan provided by Accord Healthcare Limited will be used as an example for all ARBs. Participating hospitals can use any generic hospital stock for both ACEi and ARBs used within the trial. The applicable RSI (section 4.8 of the SmPC) for the specific RAS inhibitor received by a participant will be used as the RSI during safety review. The version and date of the specific approved SmPC used for review will be documented in the safety reporting form. Updates to the RSI within the SmPC will be reviewed annually on the Electronic Medicines Compendium by the Lead Investigator/s for the comparison. Changes to the RSI will be submitted as a trial modification and locations will be notified accordingly.

13.5 Drug manufacturer and supply arrangements

Prior to surgery (i.e. Days -3 to Day 0), participants will use their own IMP supply prescribed by their GP. During their hospital stay, IMP may be sourced from hospital stock or the participant's own supply, in accordance with local hospital policies.

13.6 Drug accountability

Local hospital policies will be followed for drug accountability. There will be no trial specific prescription, IMP accountability, IMP trial specific labelling required other than details of what is taken in the participant record.

13.7 Assessment of compliance

Compliance will be assessed by interviewing the participant, and by review of their drug chart, patient record and the trial database.

13.8 Prescription and dispensing of drug

On Days -3, -2 and -1 prior to surgery, and the day of surgery, participants in the continue group will be using their personal supply of medication. For Days 1, 2 and 3 after surgery, participants in the continue group will have their medication dispensed in accordance with their in-patient drug chart and those in the stop group will have their RAS-inhibitor prescription suspended. Only the principal investigator (doctor in charge of trial at the recruiting location) or medical delegate (i.e. doctor on the delegation log) is responsible for the participant's prescription.

13.9 Administration of drug

For post-operative days 1, 2 and 3, the study drug will be administered to the participant by a healthcare practitioner who is a member of the direct care team as per local hospital policies and procedures for administration and recording. The task of administering the trial drug(s) will NOT be listed on the delegation log and staff undertaking these tasks do NOT need to be listed on the delegation log unless they are undertaking other trial duties.

13.10 Dosage schedules

Resumption or continuation of RAS-inhibitors will not require dose modifications and any changes will be made at the discretion of the doctor in overall charge of the participant's care.

13.11 Destruction, return, and recall of IMP

Not applicable.

13.12 Management of IMP specific adverse events

RAS-inhibitors are widely used in the NHS and have been for many years. The adverse event profile is well documented. Any adverse events should be managed according to clinical need.

13.13 Arrangements for post-trial access to IMP and care

Patients are only eligible if they are taking a RAS-inhibitor as part of their usual treatment before surgery. If for any reason a participant requires a supply of their usual cardiac medication at the point of hospital discharge, these will be provided through the usual hospital pharmacy ('To Take Away') service for to the participant to self-administer at home.

13.14 Known drug reactions and interventions with other therapies

To be eligible for the trial, patients must be routinely taking a RAS inhibitor which will or will not be stopped before their surgery. The only difference with SPACE II is this decision will be

made at random. Any safety events are incremental to routine care. Please refer to the SmPC for known drug reactions and interaction with other therapies.

13.15 Recommended concurrent treatment

No concurrent treatment is necessary.

13.16 Prohibited medication

Please refer to 'Interactions with other medicinal products and other forms of interaction' of the SmPC for further information.

13.17 Concomitant medication

By definition, patients are only eligible to participate in SPACE II if they take a RAS-inhibitor as a routine medication. When undergoing surgery, all patients must either stop or continue their RAS-inhibitor according to the clinical advice they receive. In SPACE II, a medically qualified investigator will be responsible for prescribing the study drug (i.e. the patient's usual RAS-inhibitor at the usual dose) when they are admitted to hospital. Their concomitant medications will be reviewed at this point.

13.18 Study restrictions

There are no study restrictions.

14 Pharmacovigilance

Please refer to the corresponding section of the PROTECT master protocol for the overall safety reporting concept and general definitions. RAS-inhibitors are widely used in the NHS and have been for many years. The RAS-inhibitor adverse event profile is well described and those most relevant to the perioperative period are included as predefined outcome measures. Participant contact is not required solely for adverse event screening alone. This procedure need only be undertaken alongside other procedures involving participant contact. Adverse events should be managed according to clinical need. Pharmacovigilance reporting will start from the completion of informed consent until post-operative day 30.

14.1 Adverse events (AEs) and Serious Adverse Events (SAEs) exempt from reporting

Medical complications are common after surgery for this patient population, and an expected part of routine perioperative care. Data describing post-operative complications will be reported in the electronic Case Report Form (eCRF) and reviewed regularly by the

Independent Data Monitoring Committee (IDMC). Predefined complications listed in the eCRF are exempt from routine safety reporting as AEs and/or SAEs, unless the principal investigator and/or medical delegate believes they are possibly or definitely related to the trial intervention. Please see the SPACE II Pharmacovigilance SOP for the list of pre-defined complications that are exempt from reporting.

14.2 Notification and reporting of Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

The following safety events will be reported for SPACE II:

- All SAEs except those specified in the SPACE II pharmacovigilance SOP.
- SAEs which the principal investigator and/or medical delegate believe are possibly or definitely related to the trial intervention (i.e. SAR or SUSAR)

Please refer to the PROTECT master protocol section “Procedure for immediate reporting of SAEs, SARs and SUSARs” for further details on the reporting procedure. The completed form will be signed and submitted to the SPACE II e-mail address (space2-admin@qmul.ac.uk) within 24 hours of the investigator becoming aware of the event.

14.3 Pregnancy

As part of routine clinical practice, pregnant or breastfeeding participants taking RAS inhibitors would either continue or temporarily discontinue treatment during the perioperative period, irrespective of their participation in the trial. Therefore, trial participation does not introduce any additional exposure beyond current routine patient care.

The trial population is by definition ≥50 years of age with significant cardiovascular disease. It is very unlikely that any patient will be pregnant when approached to participate. The trial intervention itself lasts for only seven days, which includes a period in hospital for major surgery, so pregnancy during the course of participation is not a practical concern. The trial definition for menopause is having no periods for 12 consecutive months. Any woman who does not meet the definition of menopause will be defined as a woman of child-bearing potential. For women of child-bearing potential, a pregnancy test will be performed before randomisation.

Potential participants will not be excluded simply because they are pregnant, as this is considered poor research practice. However, in the very unlikely event that a potential

participant is pregnant, this would be confirmed prior to randomisation and the participant would have the opportunity to withdraw from the trial.

If a participant becomes pregnant during the trial, they will continue to be followed up according to the standard trial procedures. They will also have the opportunity to withdraw at any time. Regardless of pregnancy status, all patients who take RAS-inhibitors must either stop or continue these during the perioperative period. All trial interventions reflect current versions of routine patient care.

Please refer to the corresponding section of the PROTECT master protocol for further details.

15. Statistical and data analysis

15.1 Sample size

We will recruit **2214 participants** (1107 per group). DAH30 tends to follow a zero-inflated negative binomial distribution (ZINB) in this patient population, exhibiting an excess of zeros and overdispersion [14]. Parameters from the DAH30 distribution in the SPACE-I stop group were used to inform simulations (mean 21, SD 8.4, 11% zeros [including one death]). These simulations indicated that 2000 participants would provide 95% power (with two-sided α=0.05) to detect a Minimum Clinically Important Difference in DAH30 of 1.0 day, representing the smallest meaningful difference for high-risk surgical patients. Our recent trials in this population have <1% loss to follow-up [8, 15, 16]. Attrition in SPACE II is expected to be low as outcome data will be obtained from electronic health records and routine datasets. Allowing for a 2% attrition rate gives 2040 patients, and further inflating for 2% non-adherence in each group (experience from SPACE-I) gives 2214 participants. Use of the ZINB distribution to estimate sample size for DAH30 is more efficient than a t-test which has <80% power for this sample size and treatment difference.

A large power for the trial overall (95%) has been used, to facilitate pre-specified sub-group analyses according to risk of heart failure, and CKD. In SPACE-I we found a large treatment effect in the group without risk of heart failure and no effect in the group at risk of heart failure. SPACE-II would have similar power to detect this size of interaction as for the overall treatment effect [17] . The sample size provides >90% power for testing this interaction, assuming a similar prevalence of heart failure risk (defined as NT-proBNP ≥100 pg/mL, see section 15.3) to SPACE-I (~40%). Power for the CKD sub-group analysis will be lower, with ~20% of participants anticipated to have CKD. In the absence of data on anticipated treatment effects

in the no-CKD/CKD sub-groups to inform an estimate of power for the interaction test, we calculate that an analysis of the ~400 participants with CKD would have 73% power to detect a larger difference in DAH30 (1.5 days), and 80% power to detect an increase in AKI from 30% (stopping) to 44% (continuing) [18]. For key secondary outcomes overall, we will have 99% power to detect a reduction in myocardial injury from 50% to 40% [8], and 80% power to detect an increase in AKI from 20% to 25% (stopping vs continuing) [18].

15.2 Statistical analysis

Participant flow throughout the trial will be presented in a CONSORT flow chart. Baseline characteristics will be summarised by randomised treatment group. Participants will be analysed according to the treatment group to which they were randomised and all eligible participants for whom an outcome is available will be included in the analysis except (i) those randomised in error (i.e. were ineligible at the time of randomisation) and (ii) those who were eligible and randomised but did not undergo surgery as per the principal stratum strategy (Section 6.4). The former exclusion (participants randomised in error) is based on pre-randomisation information (i.e. failure to meet the eligibility criteria) and as such will be unbiased. The latter exclusion (participants who did not undergo surgery) will be unbiased for the principal stratum effect under the assumption that treatment group allocation does not affect whether participants undergo surgery or not (i.e. a participant in the continuing group who does not undergo surgery would also not receive surgery had they been allocated to the stopping group, and vice versa).

The distribution of the DAH30 primary outcome will be examined graphically and described using appropriate summary statistics. DAH30 will be compared between randomised treatment groups using appropriate regression models for the distribution, anticipated to be ZINB regression which accounts for the composite nature of the DAH30 outcome. The logit part of the model captures effects with respect to 30-day mortality, and the count part addresses length of stay in hospital for 30-day survivors. The estimand for the primary outcome (DAH30) will be estimated using a mixed-effects regression model, with a random intercept for centre and adjusting for CKD; the treatment effect will be summarised as mean difference with 95% confidence intervals. Sensitivity analyses will assess the impact of missing data and distribution assumptions for DAH30, in addition to those described in section 15.4. The estimands for the secondary outcomes will be estimated using mixed effects regression models as appropriate for the type of data, with covariates and random effect specification as above and the same principal stratum strategy applied (participants who receive surgery).

15.3 Definitions for blood-based cardiac biomarkers

Myocardial injury

The trial secondary outcome measure of post-operative myocardial injury will be defined as any increase in cTn concentration greater than or equal to the sex and assay-specific 99th percentile upper reference limit (URL) on one or more of post-operative days 1, 2 or 3 after surgery (where day 0 is the day surgery is performed). Patients presenting for surgery with chronic myocardial injury will be identified with a cardiac troponin assay performed on a blood sample taken no more than eight weeks before randomisation. Chronic myocardial injury will be defined as a *pre-operative* cTn concentration greater than or equal to the sex and assay-specific 99th percentile URL, and in these patients, *post-operative* myocardial injury will be defined as a post-operative cTn concentration of greater than or equal to a 30% increase from the pre-operative value on one or more of post-operative days 1, 2 or 3 after surgery. Blood samples may be taken using the routine NHS blood sampling services at the hospital site but must be sent to the NHS laboratory for that hospital. Point-of-care assays will not be used in SPACE II as it is not possible to ensure quality control of the testing procedures. As there are a variety of commercially available cardiac troponin assays, the team at each site will be asked to confirm the assay used in their hospital to ensure the correct assay-specific reference range is used. The training package for staff at each hospital site will include details on how to ensure cardiac troponin blood test data are measured and recorded correctly. The trial statistician will confirm the assay-specific diagnosis of myocardial injury for each patient.

Heart failure

Patients at risk of heart failure will be identified with an NT-proBNP assay performed on a blood sample taken no more than eight weeks before randomisation. Patients with an NT-proBNP ≥100 pg/mL will be defined as being at risk of heart failure. Patients with an NT-proBNP ≥400 pg/mL will be defined as having overt heart failure. Commercially available NT-proBNP assays are all very similar and assay-specific definitions are not required. An exploratory analysis of cut-points for NT-proBNP will also be performed.

15.4 Sub-group and sensitivity analyses

To fully inform individualised patient care, we will include pre-specified sub-group analyses for patients with NT-proBNP ≥100 pg/ml (at risk of heart failure), patients with NT-proBNP ≥400 pg/ml (overt heart failure), and chronic kidney disease (≥G3a). To ensure our findings are not sensitive to biological differences in the troponin assay, we will include a pre-specified sensitivity analysis of the myocardial injury outcome comparing hospitals that use the two main categories of cardiac troponin assay (cTnI versus cTnT). Sub-group effects will be

summarised using group-specific treatment effects and tested by including interaction terms in the regression models, using the same analysis strategy as described for the primary estimand (Section 6.4).

15.5 Statistical analysis plan

A full statistical analysis plan will be developed and signed off prior to data unblinding and final analysis of this comparison.

15.6 End of trial definition

The end of the SPACE II trial comparison is defined as the time point when the last 180-day participant visit has been completed.

16. Annual reporting

Please refer to the corresponding section of the PROTECT master protocol.

17. Data handling and record keeping

Please refer to the corresponding section of the PROTECT master protocol.

18. Confidentiality

Please refer to the corresponding section of the PROTECT master protocol.

19. Monitoring, audit and inspection

Please refer to the corresponding section of the PROTECT master protocol.

20. Compliance

Please refer to the corresponding section of the PROTECT master protocol.

21. Declaration of interests

Please refer to the corresponding section of the PROTECT master protocol.

22. Peer review

This research was funded in open competition by NIHR-HTA (NIHR171124). The proposal underwent extensive peer review during the funding process. Since securing the award, the protocol has been reviewed further during the study design process.

23. Public and Patient Involvement (PPI)

During SPACE II, our patient researchers will be included as specific experts on patient views and experience, with equal standing to experts in patient care, trial methodology, and trial management, etc. We recognise that participants may not feel comfortable speaking up during large trial committee meetings. To tackle this, our patient researchers will lead a diverse advisory group of people who take RAS-inhibitors, which will meet on a regular basis. Our patient researchers will join the CMG and PSC and ensure patient views expressed in the advisory group are represented in trial leadership meetings. Similarly, they will take questions from the trial leadership team back to the Patient Advisory Group for them to offer guidance on. Among other contributions, the group will review the trial protocol and patient facing documents, advise on patient participation and safety, and co-produce dissemination materials ensuring the trial has maximum impact on NHS practice.

24. Indemnity/ Insurance

Please refer to the corresponding section of the PROTECT master protocol.

25. Study committees

25.1 Comparison Management Group (CMG)

Please refer to the corresponding section of the PROTECT master protocol.

25.2 Comparison Steering Committee (CSC)

Please refer to the corresponding section of the PROTECT master protocol.

25.3 Independent Data Monitoring Committee (IDMC)

Please refer to the corresponding section of the PROTECT master protocol.

26. Publication and dissemination policy

Please refer to the corresponding section of the PROTECT master protocol.

27. Archiving

Please refer to the corresponding section of the PROTECT master protocol.

This protocol is based on JRMO Protocol template for MHRA Regulated Studies; SOP 11a Associated Document 2 v8.0 07.04.2022 FINAL

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