Phase III mechanistic, randomised controlled trial of *S*topping *P*erioperative *A*ngiotensin II *C*onverting *E*nzyme inhibitors and/or receptor blockers in major noncardiac surgery

Short title:	SPACE trial
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REC reference:	16/LO/1495
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SIGNATURE PAGE

Chief Investigator Agreement Page

The clinical study as detailed within this research protocol (version 2.0, 14/12/2016), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), 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 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Chief Investigator Name: Dr Gareth Ackland

Chief Investigator Site: Queen Mary University of London

Signature and Date:  **14-December-2016**

Statistician Agreement Page

The clinical study as detailed within this research protocol (version 2.0, 14/12/2016), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), 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 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Statistician Name: Tahania Ahmad

Site: Queen Mary University of London

Signature and Date:  **14-December-2016**

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol (version 2.0, 14/12/2016), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), 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 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name:

Principal Investigator Site:

Signature and Date:

SUMMARY

TITLE	Mechanistic randomised controlled trial of ***S***topping ***P***erioperative ***A***ngiotensin II ***C***onverting ***E***nzyme inhibitors and/or receptor blockers in major noncardiac surgery.
SHORT TITLE	SPACE
Protocol Version & Date	version 3.0, 12/05/2017
Methodology	Randomised controlled interventional trial.
Study Duration	24 months
Study Centre	Barts Health NHS Trust
Objectives	To determine whether continuing perioperatively reduces the risk of perioperative myocardial surgery.
Phase of the Trial	Phase III
Number of Patients	260 patients (130 per arm)
Main Inclusion Criteria	Patients aged 60 years and over receiving chronic angiotensin II converting enzyme inhibitors and/or receptor blockers and undergoing major surgery requiring general anaesthesia.
Statistical Analysis	The analysis will be conducted on an intention-to-treat basis; all participants with a recorded outcome will be analysed according to the treatment group to which they were randomised.

GLOSSARY OF TERMS AND ABBREVIATIONS

ACE-I	Angiotensin-Converting-Enzyme Inhibitor
AE	Adverse Event
AR	Adverse Reaction
ARB	Angiotensin-II Receptor Blocker
BP	Blood Pressure
CI	Chief Investigator
CRF	Case Report Form
CT	Computed tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DSUR	Development Safety Update Report
ECG	Electrocardiograms
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GCP	Good Clinical Practice
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JRMO	Joint Research Management Office
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial Infarction
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Patient Information Sheet
PSF	Pharmacy Site File
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SSI	Surgical Site Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

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1 INTRODUCTION

1.1 Background

A triad of myocardial injury,[1] immunosuppression[2, 3] and persistent autonomic dysfunction[4, 5] is observed in high-risk patients following major surgery, leading to infection, organ failure, delayed recovery and/or death. Prolonged activation of neurohormones such as angiotensin-II correlates with tissue injury.[6, 7] Around 40% of surgical patients most at risk of postoperative complications are prescribed angiotensin-converting-enzyme inhibitors (ACE-I) or angiotensin-II receptor blockers (ARB).[8] These drugs are first-line therapy for improving outcomes from several chronic diseases, including hypertension, chronic kidney disease and cardiac failure. The use of ACE-I and/or ARB is set to rise dramatically, with the recent publication of the landmark SPRINT trial, which shows that lowering blood pressure (BP) control targets to systolic ≤120mmHg reduces mortality.[9] ACE-I and/or ARB are frequently stopped before surgery in the widely-held belief that this prevents intraoperative hypotension, although robust evidence for this is lacking.

1.2 Investigational Medicinal Product

ACE-I and/or ARB are orally administered drugs prescribed for hypertension, chronic kidney disease and cardiac failure the dose. The choice of ACE-I and/or ARB drugs is already established by the responsible clinician and are not described within this protocol. The responsible clinician can use any other antihypertensive medication for optimal patient care, in addition to the ACE-I and/or ARB, to achieve target BP in those cases which remain difficult to control and if the clinician decides it is required. All investigational medicinal products (IMP) used in this study will be within its UK licenced indication.

1.3 Preclinical Data

ACE-I and/or ARB are established treatments for patients with hypertension, chronic kidney disease and cardiac failure. Drug metabolism, pharmacokinetics and toxicological data are well established for these indications; in the SPACE trial, these drugs will be continued or stopped as per normal clinical practice. The decision to restart ACE-I and/or ARB in SPACE will be confirmed by the PI at each site. There may be a delay in restarting the drugs (for patients in whom they have been stopped preoperatively) on postoperative day 2, if BP is low and/or the presence of acute kidney injury, according to the protocol criteria.

1.4 Clinical Data

UK practice and international guidelines reflect clinical uncertainty regarding ACE-I and/or ARB withdrawal.[1, 2] However, a strong association exists between stopping ACE-I and/or ARB and an increased risk of mortality.[3, 4] These epidemiologic data suggest that acute withdrawal of ACE-I and/or ARB, coupled with upregulation of the angiotensin receptor as a result of chronic ACE-I and/or ARB therapy and substantial elevations in angiotensin-2, could be directly injurious, leading to excess postoperative morbidity and mortality. This hypothesis is highly plausible since the use of ACE-I and/or ARB reduces cardiovascular morbidity,[5] [6] and inflammation,[7] particularly in patients with established cardiovascular and chronic kidney disease.

1.5 Rationale and Risks/ Benefits

We do not currently know whether ACE-I and/or ARB should be stopped or continued in major surgery. Furthermore, our current mechanistic understanding suggests that ACE-I and/or ARB may confer organ protection in the perioperative period. There may be benefits of administering these drugs throughout the perioperative period, by counteracting the harmful effects of high levels of angiotensin-II following the stress of surgery. There may also be harm, as a result of lowering BP, which can affect kidney function and the heart. There is an acceptable risk-benefit ratio, exemplified by the fact that some clinicians continue these drugs while others stop them prior to surgery, in the absence of interventional trial data.

2 TRIAL OBJECTIVES AND DESIGN

2.1 Trial Objectives

Primary Objective – To determine whether continuing ACE-I and/or ARB perioperatively reduce the risk of perioperative myocardial injury.

Secondary Objective – To determine whether ACE-I and/or ARB cessation is linked to postoperative morbidity.

Primary Endpoint – high-sensitivity plasma troponin levels, a marker of perioperative myocardial injury, in the first 48 hours postoperatively.

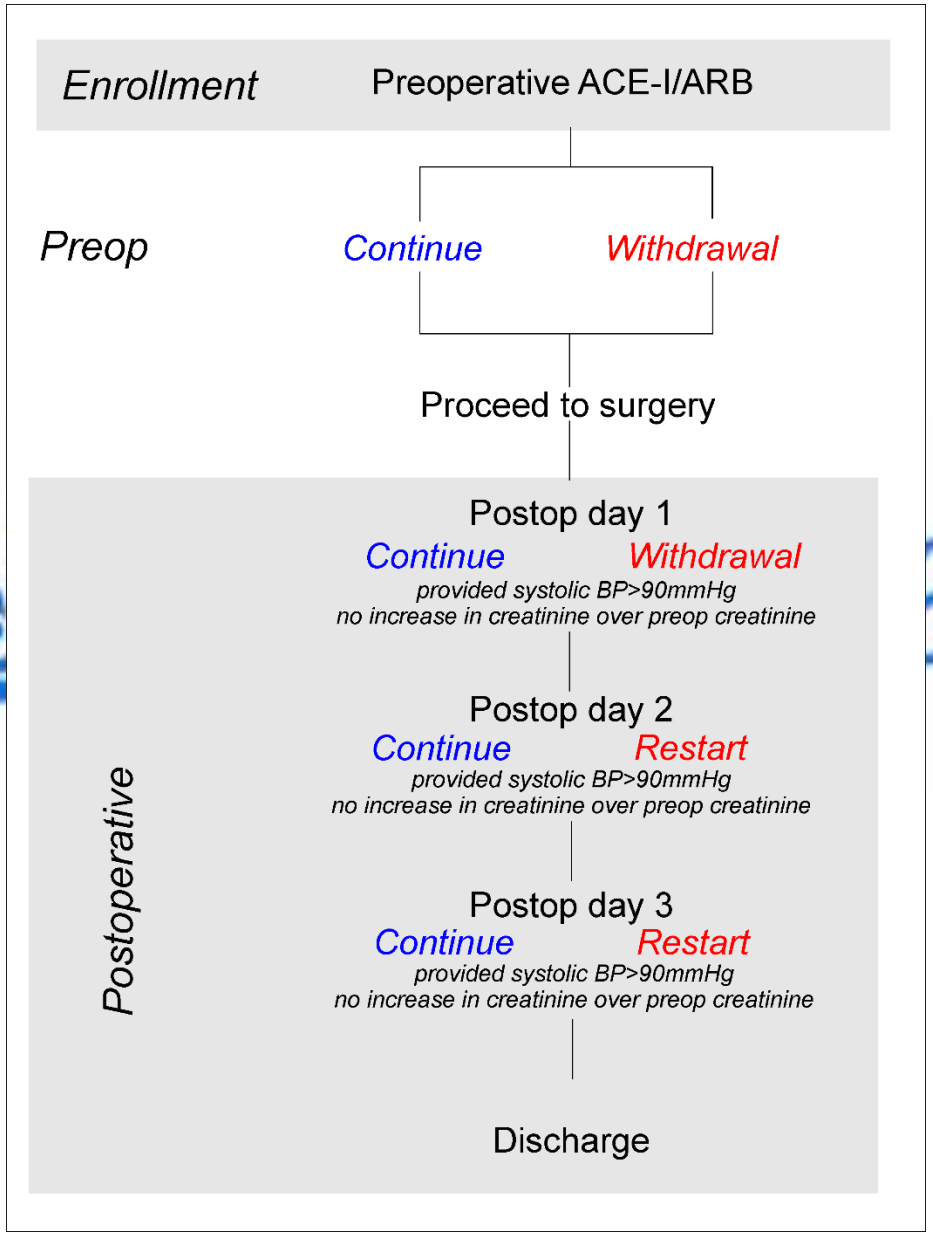
Secondary Endpoint – related to, and selected based on, the secondary objectives of the study- postoperative morbidity, length of hospital stay.

Tertiary Endpoint – changes in heart rate, blood pressure and tests of immune function.

2.2 Trial Design

National (UK only) open, multi-centre randomised controlled trial and blinded primary outcome.

2.3 Study Scheme Diagram



3 SUBJECT SELECTION

3.1 Number of Subjects and Subject Selection

Target accrual for the study is 260 patients over 24 months. Patients aged 60 years and over, on chronic ACE-I and/or ARB therapy and undergoing joint replacement/ vascular/ gastrointestinal surgery lasting more than 120 minutes requiring general anaesthesia. Patients will be selected for the study from preoperative assessment outpatient clinics and/or referring surgeons (no use of advertisements). Patients will be contacted during their preoperative hospital visit; vulnerable groups will not be included.

3.2 Inclusion Criteria

- Informed consent (no incapacitated or vulnerable adult or minors will be included).
- Age 60 years and over.
- Undergoing major surgery (major joint replacement/ vascular/ gastrointestinal) requiring general anaesthesia.
- Currently taking ACE-I, ARB or combined ACE-I and ARB therapy.
- Duration of surgery longer than 120 minutes.
- ASA grade 3 or above.
- All female subjects must be postmenopausal, as demonstrated by clinical history or demonstrated not to be pregnant though a preoperative pregnancy test.

3.3 Exclusion Criteria

- Current participation in any other trials.
- 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.

3.4 Criteria for Premature Withdrawal

Systematic incompliance (i.e. not stopping ACE-I and/or ARB on randomization to that arm, or failure to restart the drug) may culminate in a patient's withdrawal from the study. Once withdrawn no further data collection will be conducted with regards to these patients.

4 INVESTIGATIONAL MEDICINAL PRODUCT

4.1 List and Definition of Each IMP, Including Placebos

Any ACE-I and ARB licensed for use in the treatment of hypertension, heart failure, chronic kidney disease and/or diabetes mellitus within the UK. Patients will be taking their usual prescribed ACE-I and/or ARB therapy.

As detailed in the British National Formulary the following ACE-I and ARB medications are currently available and will be discontinued in those participants randomised to the cessation arm of the SPACE trial.

Candesartan	Perindopril Erbumine
Lisinopril	Perindopril Arginine
Irbesartan	Quinapril
Enalapril Maleate	Trandolapril
Telmisartan	Imidapril Hydrochloride
Ramipril	
Eprosartan	
Captopril	
Losartan	
Cilazopril	
Olmesartan	
Fosinopril Sodium	
Valsartan	
Moexipril Hydrochloride	
Azilsartan	

Any new ACE-I or ARB licenced within the study treatment period will also be accepted.

4.2 Formulation of IMP

There will be no IMP to source or label in either arm. Participants are randomised to either continue or stop ACE-I and/or ARB preoperatively. Participating hospital pharmacies will be responsible for the continued supply of medication for participants in each arm throughout the trial as per routine local clinical practice. The medication will be from a commercial stock in standard packaging. As the medication is a continuation of the participant's standard treatment from the local pharmacy's own stock it will not be labelled as an IMP.

4.3 IMP Supply

Regulation 46 of The Medicines for Human Use (Clinical Trial) Regulations 2004 allows for a particular situation where specific trial labelling is not required. This applies to trials of marketed products being (a) used within the terms of their marketing authorisation, (b) dispensed to a subject in accordance with a prescription given by an authorised health care professional and (c) labelled in accordance with the regulations that apply to dispensed relevant medicinal products. IMP in the SPACE trial are marketed products being used within the terms of their marketing authorisation. They will be dispensed to the participant in accordance with a prescription given by an authorised health care professional (the participant's responsible clinician) and will be labelled in accordance with the regulations that apply to dispensed relevant medical products. The medication will be commercial stock in standard packaging. Therefore, specific trial labelling is not required. The IMP to be used in the SPACE trial can be labelled with a standard pharmacy dispensing label under the exemption described above and participants issued with trial information cards. This is clearly documented in the submission in support of the Clinical Trials Authorisation (CTA) application.

4.4 Prescription of IMP

There will be no prescription of IMP by the study team as participants will already be taking the IMP on admission to the study. The study team will only suspend the IMP the participant is usually taking when randomized to withdraw, according to the half-life of the drug to ensure it has been stopped for an adequate period of time to allow "washout".

4.5 Preparation and Administration of IMP

IMP in the SPACE trial are marketed products being used within the terms of their marketing authorisation. The medication will be commercial stock in standard packaging. Specific trial labelling is not required. No changes from local NHS trust standard procedure will occur.

4.6 Prior and Concomitant Therapies

All prior and concomitant treatments that the subjects take can continue whilst on treatment on the study (this may also include non-medicinal products). The case reporting forms (CRF) will capture data on any prior or concomitant therapies.

4.7 Dose Modification/ Reduction/ Delay

Resumption or continuation of ACE-I and/or ARB in SPACE will not require dose modifications. There may be a delay in restarting the drugs (for patients in whom they have been stopped preoperatively) on postoperative day 2, if BP is low and/or the presence of acute kidney injury, according to the protocol criteria. The decision to restart ACE-I and/or ARB in SPACE will be confirmed by the PI at each site.

4.8 Return/ Recall or Destruction of IMP

There will be no IMP returns or destructions as part of this study. Drug recall will be though the standard local NHS dispensing pharmacy recall process.

5 STUDY PROCEDURES

5.1 Informed Consent Procedures

It is the responsibility of the site Principal Investigator (PI), or appropriately Good Clinical Practice (GCP) trained medically qualified person as specified in the delegated log by the PI to obtain written informed consent from (ICF).

If for some reason, a sub-investigator is not accessible in person or by phone and the participant wishes to speak with them, a second consent visit should be arranged. The PI (or medically qualified person) must explain to the potential participant that they are free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

As stipulated by GCP, the patient should be given ample time to consider giving their consent for the study. It is felt that 24 hours gives sufficient time for the patient to consider their participation within the study and give informed consent. If for any reason, less than 24 hours is to be given, this will be clearly documented in the medical notes along with justification for this decision. The date that the Patient Information Sheet (PIS) is given to the patient must be documented within the patient's notes to ensure that sufficient time is given (minimum 24 hours).

If there is any further safety information which may result in significant changes in the risk/benefit analysis, the PIS and ICF must be reviewed and if applicable updated accordingly.

5.2 Screening Procedures

Screening will take place in the preoperative assessment clinics and surgical wards where patients are admitted prior to surgery for other investigations to assess whether patients who receive ACE-I and/or ARB may be eligible, prior to their entry/eligibility into the study. All patients that undergo screening will be logged into a study screening log.

5.3 Randomisation Procedures

Once a medically qualified member of the research team has confirmed the patient's eligibility, the process of randomisation can commence. Randomisation will occur after the participant has provided informed consent but before the surgical procedure is due to start. Randomisation parameters will ensure that participants will be centrally allocated to treatment groups (1:1) by a computer generated dynamic procedure (minimisation) with a random component.

Minimisation will be performed on trial centre, surgical procedure and ACE-I and/or ARB category. Each participant will be allocated to their surgical group that minimises between group differences in these factors among all participants recruited to the trial to date.

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. Generation of randomisation codes (automated process) will be provided by the Perioperative Trials group. Patients will receive a patient advice letter confirming their trial allocation to stopping or continuing their ACE-I and/or ARB. In addition, patients will be told in person or by telephone together with a daily reminder via text message before hospital admission.

The randomization system is a customized bespoke system developed In–house; research staff will document randomization allocation on the CRF. This randomisation system has been validated for use by statistician Tahania Ahmed, Queen Mary University of London.

Once the patient has been successfully randomised onto the study, the enrolment of this patient will be documented within an enrolment log.

5.4 Schedule of Treatment for Each Visit

The trial intervention period will commence 48 hours before surgery and continue for at least 48 hours after surgery. After having received the patient advice letter confirming their trial allocation to stopping or continuing their ACE-I and/or ARB, patients will also be reminded by telephone call and text message, or in person if they are in hospital. If the patients are not in hospital, they will receive another telephone call and text message, or in person, the day before surgery. ACE-I and/or ARB will be continued or discontinued as per randomization and this allocation will continue until 48 hours after the end of surgery. Because ACE-I and ARB have differing durations of action, patients will receive drug-specific instructions as to when to stop. When the ACE-I and/or ARB duration of action is equal to, or more than, 24 hours, the drug will be stopped 48 hours prior to surgery. All other ACE-I and/or ARB will be stopped on the day before surgery (see appendix for specific drugs' half-life and duration of action).

5.5 Schedule of Assessment in Diagrammatic Format

Event/Visit	Screening	Preop 48 hrs ± 6 hrs	Postop 24 hrs ± 6 hrs	Postop 48 hrs ± 6 hrs	Postop 72 hrs ± 6 hrs	Within 1 week of Hospital discharge
Inclusion/exclusion criteria	x					
Informed consent	x					
Demographic information		x				
Medical history		x				
Height and weight		x				
Telephone contact		x				
Randomisation		x				
Intraoperative information			x			
Restart drug				x		
Review of medical notes			x	x	x	x
Blood samples		x	x	x		
Blood pressure/heart rate		x	x	x		x
Review for adverse events		x	x	x	x	
End of trial form						x

5.6 Follow-up Procedures

Participants will be followed up on 24, 48 and 72 hours post-operating. The end of study visit will take place on the day of discharge from the hospital following the operation. This may be

combined with the 72 hour visit should this also be the day of discharge. To minimise bias, follow-up data will be collected by a study team member who is blinded to the primary outcome result. Similarly, investigators will review a participant's medical record (paper or electronic) after surgery, unaware of the primary outcome result (which is measured after the end of the trial).

5.7 Laboratory Assessments

Troponin T (5th generation assay, Roche Elecsys) will be measured preoperatively, on postoperative 24 and 48 hours at local site NHS labs pathology labs, but the results will not be made available to the study team until the last study patient sample has been seen on postoperative day 3. Non-study clinicians and patients will remain blinded to the troponin T results throughout the study. Mechanistic studies for tertiary exploratory outcomes requiring assays of immune, neurohormonal function, electrocardiograms (ECG) and BP will be undertaken in laboratories at the Institute for Translational Medicine and Therapeutics, William Harvey Research Institute, Queen Mary University of London.

5.8 End of Study Definition

The end of the study is defined as the point when the last patient has completed their hospital stay.

5.9 Procedures for Unblinding

Only the primary outcome of the study is blinded; therefore, treatment allocation is not blinded so no un-blinding procedures are required.

5.10 Subject Withdrawal

All study participants are free to withdraw from the study at any time. All randomised patients will be included in the final analysis on an intention to treat basis, unless a participant specifically asks for their data not to be included.

5.11 Data Collection and Follow-up for Withdrawn Subjects

Patients that withdraw consent or drop out pre-randomisation will be replaced; the withdrawal will be documented in the CRF and medical records. Although participants are not obliged to give the reason for withdrawing their consent, we will attempt to ascertain trends if possible relating to trial procedures, in case this results in a protocol amendment.

6 LABORATORIES

6.1 Central/ Local Laboratories

Troponin T (5th generation assay) will be measured from samples at local NHS site pathology labs. Tertiary outcome measures and mechanistic studies requiring laboratory assays for immune, neurohormonal, ECG and BP function will be undertaken in laboratories at the at the Institute for Translational Medicine and Therapeutics, William Harvey Research Institute, Queen Mary University London.

6.2 Sample Collection/ Labelling/ Logging

All troponin samples will be pseudo-anonymised. Samples remaining within the Site NHS system will be labelled/ collected and transferred as per local NHS procedure. All samples leaving the originating NHS will be pseudo-anonymised. These samples will be logged with regards to the date sent to the Laboratory and the temperature/conditions at which it was sent to ensure the integrity and viability not compromised. The full sample, collection, labelling, logging and transfer procedure will be document in the study laboratory manual

6.3 Sample Receipt/ Chain of Custody/ Accountability

Please see study laboratory manual for details. Handling of the samples upon arrival at the laboratory will be documented. Upon receipt of the samples, the laboratory will ensure that the physical integrity of these samples have not been compromised in transit. If compromise has occurred, the study team, as well as the sponsor, will be informed of this. Upon receipt of samples, laboratory staff will ensure that all samples are accounted as per the labelling. All samples received will be logged in an sample log.

6.4 Sample Analysis Procedures

For high sensitivity troponin analysis methodology standard measurement protocol will be undertaken.

6.5 Sample Storage Procedures

For the purposes of tertiary and exploratory outcome studies, leukocyte samples will be stored at -80°C (unless they are tested immediately) in a dedicated research sample freezer at the

Institute for Translational Medicine and Therapeutics, William Harvey Research Institute, John Vane Science Centre, Charterhouse Square, London, United Kingdom, EC1M 6BQ.

6.6 Data Recording/ Reporting

Troponin data will be recorded within local laboratory sites and shared by secure electronic communication after the last patient sample has been obtained.

7 PHARMACOVIGILANCE

7.1 General Definitions

7.1.1 Adverse Event

An Adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an IMP, whether or not considered related to the IMP.

All cardiovascular events will be reported as AEs, adverse reaction (AR), Serious Adverse Event (SAE), Serious Adverse Reaction (SAR), or Suspected Unexpected Serious Adverse Reaction (SUSAR), as appropriate. AEs that may be expected from acute perioperative discontinuation of ACE-I or ARB (or combination of both) are listed below. Cardiovascular events such as myocardial infarction (MI), stroke and heart failure could potentially be expected from ACE-I and/or ARB withdrawal but may equally be expected from undergoing major surgery in higher-risk patients who require ACE-I and/or ARB therapy. Note that each of these events are frequently observed in higher-risk surgical patients in normal practice, so also serve as secondary outcome measures for postoperative morbidity, as applicable:

1. Systolic BP>180mmHg pre and/or postop (as verified on measurement by study investigators)
2. Diastolic BP> 100mmHg pre and/or postop (as verified on measurement by study investigators)
3. Hypokalaemia (serum potassium <3.0mmol.L^{-1})
4. Hypotension within the first 24h postoperatively requiring pressor via central venous access

5. Clinically diagnosed myocardial infarction (NOT defined by clinician-ordered, incidental troponin measurement)
6. Acute coronary syndrome
7. Cardiac arrhythmia
8. Cerebrovascular accident/stroke
9. Acute kidney injury, in the absence of haemorrhage/sepsis (KDIGO criteria)

7.1.2 Adverse Reaction

An AR is any untoward and unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

7.1.3 Serious Adverse Event or Serious Adverse Reaction

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

For the purposes of this study, prolonged hospitalisation is defined by more than 2 standard deviations from normal length of stay at each hospital for that specific procedure.

An SAR is an AR that is classed as serious and which is consistent with the information about the medicinal product as set out in the Summary of Product Characteristics (SmPC) for that product.

7.1.4 Suspected Unexpected Serious Adverse Reaction

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the SmPC for that product.

7.2 Investigators Assessment

7.2.1 Seriousness

The PI responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 7.1.

7.2.2 Causality

The PI must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

7.2.3 Expectedness

The Chief Investigator (CI)/PI must assess the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR.

7.2.4 Severity

The CI/PI must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

7.3 Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

7.4 Notification and Reporting of Serious Adverse Events/ Sudden Unexpected Serious Adverse Reaction

All SAEs will be recorded in the subjects' notes, the CRF, the sponsor SAE form and reported to the Joint Research Management Office (JRMO) within 24 hours of the PI or co-investigators becoming aware of the event. Nominated co-investigators will be authorised to sign the SAE forms in the absence of the CI at the co-ordinating site or the PI at the participating sites.

All SUSARs that occur during the trial will be reported to the JRMO within 24 hours of the PI or co-investigator becoming aware of the event. SUSARs should be reported to the sponsor (JRMO) within 24 hours as the sponsor has a legal obligation to report this to the Medicines and Healthcare products Regulatory Agency (MHRA) within 7 days (for fatal or life-threatening SUSARs) or 15 days for all other SUSARs. In the case of multicentre studies, the PI or the co-investigators at the participating site must inform the CI within 24 hours of the event. The CI or co-investigators at the co-ordinating site must inform the sponsor (JRMO) immediately to allow reporting to the MHRA within the allocated timelines.

The original and any subsequent follow up of SAE Forms, together with the fax confirmation sheet must be kept with the trial master file (TMF) at the study site.

7.5 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor, Research Ethics Committee (REC) (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event **immediately**.

The CI has an obligation to inform both the MHRA and REC in writing within 3 days, in the form of a substantial amendment as per sponsor standard operating procedures.

7.6 Annual Safety Reporting

The Development Safety Update Report (DSUR) will be sent by the CI to the sponsor, the Research Ethics Committee (REC) and MHRA. The CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial. The DSUR will be sent on the anniversary of the “notice of acceptance letter” from the MHRA. A copy of the DSUR and any associated correspondence with the MHRA will also be sent to participating sites.

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the REC “favourable opinion” letter from the REC) and to the sponsor.

7.7 Overview of the Safety Reporting Process

The CI has the overall pharmacovigilance oversight responsibility. The CI has a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.

8 REFERENCE SAFETY INFORMATION

Captopril- The reference safety information for this study for the ACE-I group will be Section 4.8 of the Captopril 50 mg tablets.

Losartan- The reference safety information for this study for the ARB group will be Section 4.8 of the Losartan Potassium 50 mg tablets (45.8mg of Losartan).

9 STATISTICAL CONSIDERATIONS

9.1 Primary Endpoint Efficacy Analysis

The primary outcome measure is plasma troponin release within the first 48h after surgery. The incidence of the primary outcome will be compared between the intervention and usual care groups using a multivariable logistic regression model, allowing the inclusion of baseline risk factors such as age, gender, co-morbid disease and surgical procedure. Adjusted odds ratios will be reported with 95% confidence intervals. The proportion of troponin-positive patients and those free of myocardial injury will be compared between groups with the Chi-square test. Both relative effects (measured with the Risk Ratio and 95% CI) and absolute effects (measured with the Risk Difference and the Number Needed to Treat, NNT, with 95% CI) will be estimated. Baseline demographic and clinical data for the two groups will be summarised but not subjected to statistical testing. Significance will be set at $p<0.05$. Clinical outcomes are defined in appendix 1.

9.2 Secondary Endpoint Efficacy Analysis

Secondary analyses will be performed according to protocol adherence on "as treated" populations, with explorative and/or explicative purposes only. The secondary outcomes will be postoperative morbidity and duration of hospital stay. A Kaplan-Meier curve will be plotted for hospital stay following surgery. Cox regression analysis will take into account ACE-I and/or ARB type and other cardiovascular drugs, type of surgery, cardiometabolic comorbidity and

regional analgesia. For binary outcomes, differences between groups will be tested using Fisher's exact test. For continuous outcomes, differences will be tested using independent samples t-tests or non-parametric equivalents. Significance will be set at $p<0.05$.

9.3 Sample Size

The primary outcome is plasma troponin within the first 48h after surgery. The incidence of postoperative troponin release in previous trials was ~40.0% in similar patients undergoing major surgery. An absolute decrease in the number of patients with troponin >99th centile of 20% (from 50% in the 'cessation' group to 30% in the 'continuation' group), with a built-in loss to follow up rate of 5% after surgery, would require a total sample size of **260 patients** (130 per group). This sample size will allow us to detect a 20% absolute risk reduction in the primary outcome measure, with a power of 90% and an overall type I error rate of 5%. Sample size calculations were performed using STATA 13.1 (StataCorp, College Station, TX). This will be conducted on an intention-to-treat basis i.e. all patients randomised during the study period will be included, and considered exposed to the intervention according to randomisation regardless of when the intervention was actually implemented.

9.4 Statistical Analysis

No interim analyses is planned. All randomised subjects will be analysed. All comparisons are two-tailed with the level of significance set at <0.05. Adjusted analyses undertaken will account for covariates: ACE-I and/or ARB type and other cardiovascular drugs, operation type, cardiometabolic comorbidity and regional analgesia.

10 DATA HANDLING & RECORD KEEPING

10.1 Confidentiality

The CI has a responsibility to ensure that patient confidentiality is protected and maintained. They must also ensure that participant identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and REC Approval.

The PI as well as the study team must adhere to these parameters to ensure that the patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, each patient, at time of consent must be allocated an unique screening number

by either the PI or a member of the study team before undergoing any screening procedures. The patients initials (the first letter of their first name and the first letter of their last name) should be used as a means of pseudo-anonymising parameters. This information should be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled onto the study, the patient will be allocated a randomisation number.

No identifiable information will be collected from the subjects. The CI is the 'Custodian' of the data, and maintains access to the data. No patient identifiable details will be transferred outside the EU. Subjects maintain their right to revoke their authorisation for the use of their PID. The patients will be anonymised with regards to any future publications relating to this study.

10.2 Case Report Form

On data collection times illustrated in section 5.5, research study nurse will be responsible for the completion of the electronic CRF throughout the life cycle of the study. The electronic CRF will be hosted on a secure, custom-designed trial Queen Mary University of London bespoke clinical trial database.

10.3 Record Retention and Archiving

At the end of the trial, as defined by GCP all documentation should be stored by each individual site's archiving facility, for 20 years or until notification, for destruction, from the Sponsor.

A 'close out' visit will be conducted where all trial documentation will be prepared for archiving by that site. Records will be retained at each individual site. All records relating to the trial should be stored together, including the Investigator Site File (ISF), Pharmacy Site File (PSF) and CRF. It is the responsibility of the PI to ensure a full set of records is collated and documented.

In addition, source documentation (medical notes, images, results etc.) should be retained, as per local policy, for the duration of the archiving period.

These will be stored for a minimum of 20 years or the maximum period required by the Institution in which the trial will be conducted, whichever is longer. The sponsor should be contacted prior to destruction.

10.4 Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, and all subsequent amendments, Trust and sponsor policies and procedures and any subsequent amendments.

In addition, sponsor auditors and Competent Authority inspectors will be allowed access to CRFs, source documents and other trial files to evaluate the trial. Audit reports will be kept confidential.

10.5 Ethical Considerations

This protocol and any subsequent amendments, along with any accompanying material provided to the patient in addition to any advertising material will be submitted by the Investigator to an Independent Research Ethics Committee. Written Approval from the Committee must be obtained and subsequently submitted to the JRMO to obtain Declaration of Sponsorships and approval.

10.6 Quality Control and Quality Assurance

10.6.1 Summary Monitoring Plan

Monitoring will involve a review of the ISF and PSF as well as a proportion of source data verification. This will involve direct access to patient notes at the participating hospital sites which will include the review of consent forms and other relevant investigational reports. Missing data will be sought, unless confirmed as not available.

A summary of all monitoring activity for this study will be provided to the sponsor at least every three months. All sites will undergo an on-site site initiation visit. On site monitoring visits will then occur within one month of the first patient being enrolled at a site and subsequently as per monitoring plan. At the end of the trial all sites will undergo an on-site close out visit.

Non-commercial central facilities will be monitored during their participating in the trial, as detailed in the monitoring plan.

Refer to the study Monitoring Plan for full detail Monitoring will involve a review of the ISF and PSF as well as a proportion of SDV. This will involve direct access to patient notes at the participating hospital sites which will include the review of consent forms and other relevant investigational reports. Missing data will be sought, unless confirmed as not available.

A summary of all monitoring activity for this study will be provided to the Sponsor at least every three six months.

All sites will undergo an on-site site initiation visit. On site monitoring visits will then occur within one month of the first patient being enrolled at a site and subsequently every 6 months, or 10 patients, whichever is sooner. At the end of the trial all sites will undergo an on-site close out visit.

Non-commercial central facilities will be monitored during their participating in the trial, as detailed in the monitoring plan.

10.6.2 Audit and Inspection

This study may be audited by representatives from the coordinating centre and the sponsor or its delegate. The investigator and institution will be informed of the audit outcome. Investigators are obliged to cooperate in any audit allowing the auditor direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor to discuss any findings or issues. An audit may occur at any time during or after completion of the study.

Inspections may be carried out by the Competent Authority at any time and the investigator should notify the sponsor immediately if there are any such plans for an inspection.

10.7 Serious Breaches in GCP or the Trial Protocol

The sponsor of the Clinical Trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to the trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

For the purposes of this regulation, a 'serious breach', is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trials; or
- The scientific value of the trial.

The CI is responsible for reporting any serious breaches to the sponsor (JRMO) **within 24 hours**. The sponsor will notify and report to the MHRA within 7 working days of becoming aware of the serious breach.

11 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be convened and chaired by and clinician independent to the study team and sponsor. Other members of the committee will be the CI, all PIs and at least 6 suitably qualified members. At least 3 of these will be independent.

12 STUDY FINANCES

12.1 Funding sources

The study is British Oxygen Company research chair award in Anaesthesia, administered by the National Institute for Academic Anaesthesia.

12.2 Patient expenses/ payment

There are no participant study payments or travel expenses available for this study.

13 SPONSORSHIP AND INDEMNITY

Dr Gareth Ackland of Queen Mary University of London the CI. Queen Mary University of London is also sponsoring the study.

14 PUBLICATION POLICY

This is an investigator-led study sponsored by the CI's substantive employer, Queen Mary University of London. The data collected will not be used to license/register any pharmaceuticals. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the design, TSC, accrual of eligible patients and

statistical analysis. Contributing centres (and participating investigators) will be acknowledged in the final manuscript.

No participant may present data from his/her centre separately from the rest of the study results unless approved by the TSC and the sponsor.

15 REFERENCES

1 Sear JW. Perioperative renin-angiotensin blockade: to continue or discontinue, that is the question! *Anesth Analg* 2014;**118**:909-11

2 Mets B. To stop or not? *Anesth Analg* 2015;**120**:1413-9

3 Lee SM, Takemoto S, Wallace AW. Association between Withholding Angiotensin Receptor Blockers in the Early Postoperative Period and 30-day Mortality: A Cohort Study of the Veterans Affairs Healthcare System. *Anesthesiology* 2015;**123**:288-306

4 Mudumbai SC, Takemoto S, Cason BA, Au S, Upadhyay A, Wallace AW. Thirty-day mortality risk associated with the postoperative nonresumption of angiotensin-converting enzyme inhibitors: a retrospective study of the Veterans Affairs Healthcare System. *J Hosp Med* 2014;**9**:289-96

5 Marott SC, Nielsen SF, Benn M, Nordestgaard BG. Antihypertensive treatment and risk of atrial fibrillation: a nationwide study. *Eur Heart J* 2014;**35**:1205-14

6 Chae YK, Khemasuwan D, Dimou A, et al. Inhibition of renin angiotensin axis may be associated with reduced risk of developing venous thromboembolism in patients with atherosclerotic disease. *PLoS One* 2014;**9**:e87813

7 Benigni A, Cassis P, Remuzzi G. Angiotensin II revisited: new roles in inflammation, immunology and aging. *EMBO Mol Med* 2010;**2**:247-57

16 APPENDICES

Appendix 1: Duration of preoperative cessation required for SPACE trial.

Drug	Time required to stop drug preop (days)
Candesartan	2
Lisinopril	1
Irbesartan	2
Enalapril Maleate	1
Telmisartan	2

Ramipril	1
Eprosartan	2
Captopril	1
Losartan	1
Cilazopril	1
Olmesartan	2
Fosinopril Sodium	1
Valsartan	2
Moexipril Hydrochloride	1
Azilsartan	2
Perindopril	1
Quinapril	1
Trandolapril	5
Imidapril Hydrochloride	1

Appendix 2: Perioperative morbidity definitions for SPACE trial.

Respiratory events

Nosocomial pneumonia

Care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia. Nosocomial pneumonia will be characterized as early or late onset ie before or after first 4 days of hospitalization. Where repeated episodes of nosocomial pneumonia are suspected, a combination of new signs and symptoms and radiographic evidence or other diagnostic testing will be required to distinguish a new episode from a previous one. This category includes ventilator- associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or endotracheal tube), however care will be taken to distinguish between tracheal colonization, upper respiratory tract infections and early onset pneumonia.

Nosocomial pneumonia must meet the following criteria:

Two or more serial chest radiographs with at least one of the following:

i) new or progressive and persistent infiltrate

ii) consolidation

iii) cavitation

And at least one of the following:

i) fever (>38°C) with no other recognized cause

ii) leucopaenia (<4, 000 WBC mm3) or leucocytosis (>12, 000 WBC mm3)

iii) for adults >70 years old, altered mental status with no other recognized cause

And at least two of the following:

i) new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements

ii) new onset or worsening cough, or dyspnoea, or tachypnoea

iii) rales or bronchial breath sounds

iv) worsening gas exchange

v) need for invasive or non-invasive mechanical ventilation

Cardiovascular events

Hypotension: systolic blood pressure <90mHg either intraoperatively, or postoperatively within 72h of surgery.

Myocardial ischaemia or infarction: Acute ECG changes with appropriate clinical findings and changes in cardiac troponins ordered by attending clinicians.

Arrhythmia: ECG evidence of rhythm disturbance resulting in a fall in mean arterial pressure of greater than 20% and considered by clinical staff to be severe enough to require treatment (anti-arrhythmic agents, vasoactive agents, intra venous fluid, etc).

Cardiac or respiratory arrest: Clinical criteria according to UK Resuscitation Council Guidelines.

Cardiogenic pulmonary oedema: Appropriate clinical history and examination with consistent chest radiograph.

Kidney injury

Acute kidney injury

A >26ϒmol.L^{-1} increase in serum creatinine or sustained oliguria of <0.5 ml.kg^{-1} hour^{-1} for twelve hours (KDIGO consensus definition).

Infective complications

Infection, source uncertain

Two more of the following associated with strong clinical suspicion of infection (sufficient to require intra-venous antibiotic therapy):

i) core temperature <36ºC or >38ºC

ii) white cell count >12 x 109 l-1 or <4 x 109 l-1

iii) respiratory rate >20 breaths per minute or PaCO2 < 4.5 kPa

iv) pulse rate >90 bpm

v) radiological investigation for suspected sepsis

vi) specimen/ blood samples sent for microbiological culture.

Urinary tract infection

A symptomatic urinary tract infection must meet at least one of the following criteria:

i) Patient has at least one of the following signs or symptoms with no other recognized cause: fever (>38oC), urgency, frequency, dysuria, or suprapubic tenderness and patient has a

positive urine culture, that is, >105 microorganisms per cm3 of urine with no more than two species of microorganisms.

ii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38^{o}C), urgency, frequency, dysuria, or supra- pubic tenderness and at least one of the following:

a. positive dipstick for leucocyte esterase and/or nitrate;

b. pyuria (urine specimen with >10 WBC mm-3);

c. organisms seen on Gram stain of unspun urine;

d. at least two urine cultures with repeated isolation of the same uropathogen with >102 colonies/ mL in non-voided specimens;

e. >105 colonies/mL of a single uropathogen in a patient being treated with an effective antimicrobial agent for a urinary tract infection;

f. physician diagnosis of a urinary tract infection;

g. physician institutes appropriate therapy for a urinary tract infection.

Other infections of the urinary tract (kidney, ureter, bladder, urethra, etc.)

Other infections of the urinary tract must meet at least one of the following criteria:

i) patient has organisms isolated from culture of fluid (other than urine) or tissue from affected site.

ii) Patient has an abscess or other evidence of infection seen on direct examination, during a surgical operation or during a histopathologic examination.

iii) Patient has at least two of the following signs or symptoms with no other recognized cause: fever (>38^{o}C), localized pain, or localized tenderness at the involved site and at least one of the following:

iv) purulent drainage from affected site;

v) organisms cultured from blood that are compatible with suspected site of infection

vi) radiographic evidence of infection, for example, abnormal ultrasound, computed tomography or magnetic resonance imaging;

vii) physician diagnosis of infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space;

viii) physician institutes appropriate therapy for an infection of the kidney, ureter, bladder, urethra, or tissues surrounding the retroperitoneal or perinephric space.

Surgical site infection SSI (superficial incisional)

A superficial SSI must meet the following criteria:

i) infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following:

a. purulent drainage from the superficial incision.

b. organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.

c. at least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.

d. diagnosis of superficial incisional SSI by the surgeon or attending physician.

Surgical site infection (deep incisional)

A deep incisional SSI must meet the following criteria:

i) infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle layers) of the incision and patient has at least one of the following.

ii) purulent drainage from the deep incision but not from the organ/ space component of the surgical site.

iii) a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38ºC) or localized pain or tenderness, unless incision is culture-negative.

iv) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

v) diagnosis of a deep incisional SSI by a surgeon or attending physician. An infection that involves both superficial and deep incision sites should be classified as a deep incisional SSI.

Surgical site infection (organ/space)

An organ/space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers that is opened or manipulated during the operative procedure. Specific sites are assigned to organ/space SSI to further identify the location of the infection. Listed later are the specific sites that must be used to differentiate organ/space SSI. An example is appendectomy with subsequent sub-diaphragmatic abscess, which would be reported as an organ/space SSI at the intra-abdominal specific site. An organ/space SSI must meet the following criteria:

Infection occurs within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure and infection involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure and patient has at least one of the following:

i) purulent drainage from a drain that is placed through a stab wound into the organ/space.

ii) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space.

iii) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.

iv) diagnosis of an organ/space SSI by a surgeon or attending physician.

Laboratory - confirmed bloodstream infection

Laboratory - confirmed bloodstream infection must meet at least one of the following criteria:

i) Patient has a recognized pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.

ii) Patient has a fever (>38oC), chills, or hypotension and at least one of the following:

a. common skin contaminant is cultured from two or more blood cultures drawn on separate occasions.

b. common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy.

c. positive antigen test on blood. And signs and symptoms and positive laboratory results are not related to an infection at another site.

Other defined postoperative complications

Postoperative haemorrhage

Overt blood loss requiring transfusion of two or more units of blood in two hours.

Stroke

Clinical diagnosis with confirmation by CT scan.

Limb or digital ischaemia

Sustained loss of arterial pulse (as determined by palpation or Doppler) or obvious gangrene.

Multi-organ dysfunction syndrome

A life threatening but potentially reversible physiologic derangement involving failure of two or more organ systems not involved in the primary underlying disease process.

Acute psychosis

Acute episode of severe confusion or personality change, which may result in hallucinations or delusional beliefs in the absence of a pre-existing diagnosis which may account for the clinical symptoms and signs.

Pulmonary embolism

Computed tomography (CT) pulmonary angiogram with appropriate clinical history.

Acute respiratory distress syndrome

According to consensus criteria:

i) suitable precipitating condition (many causes exist).

ii) acute onset diffuse bilateral pulmonary infiltrates on chest radiograph.

iii) no evidence of cardiac failure or fluid overload (PAOP < 18 mmHg);

iv) Either: PaO_2:FiO2 < 40 kPa = Acute Lung Injury

PaO_2:FiO_2 < 27 kPa = Acute Respiratory Distress Syndrome.

Gastro-intestinal bleed

Unambiguous clinical evidence or endoscopy showing blood in gastro-intestinal tract.

Bowel infarction

Demonstrated at laparotomy.

Anastamotic breakdown

Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan.

Paralytic ileus

Persistent clinical evidence of intestinal ileus and failure to tolerate enteral fluid or feed associated with valid cause.