Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome

Trial Protocol Version 4.0
1st December 2011

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**Trial description**

Open, multi-centre, randomised controlled trial of stroke volume guided fluid therapy and low dose dopexamine infusion compared to usual care in patients undergoing major abdominal surgery involving the gastrointestinal tract.

**Chief Investigator**

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Trial Statistician: Dr David Harrison, ICNARC
## Trial Summary

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<th><strong>Title</strong></th>
<th>Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome</th>
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<tr>
<td><strong>Short title</strong></td>
<td>Optimise</td>
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<tr>
<td><strong>Protocol version</strong></td>
<td>Version 4.0, 1st December 2011</td>
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<tr>
<td><strong>Methodology</strong></td>
<td>Open, multi-centre, randomised controlled trial</td>
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<tr>
<td><strong>Trial duration</strong></td>
<td>2 years</td>
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<td><strong>Trial Sites</strong></td>
<td>17</td>
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<tr>
<td><strong>Primary objective</strong></td>
<td>To establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid, combined with low dose dopexamine infusion will reduce the number of patients who experience complications within 30 days following major surgery involving the gastro-intestinal tract.</td>
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<tr>
<td><strong>Number of patients</strong></td>
<td>734</td>
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<td><strong>Inclusion criteria</strong></td>
<td>Adult patients undergoing major abdominal surgery involving the gastrointestinal tract that is expected to take longer than 90 minutes will be eligible for recruitment provided they satisfy one of the following criteria:</td>
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<td>Age 65 years and over</td>
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<td>Or…</td>
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<td></td>
<td>Age 50-64 plus, one or more of:</td>
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<td></td>
<td>- non-elective surgery;</td>
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<td></td>
<td>- acute or chronic renal impairment (serum creatinine $\geq 130 , \mu\text{mol/l}$);</td>
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<td>- diabetes mellitus;</td>
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<td>- presence of a risk factor for cardiac or respiratory disease.</td>
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<td><strong>Statistical methodology</strong></td>
<td>Primary analyses will be unadjusted by Fisher’s exact test for binary outcomes and t-tests, or non-parametric alternatives, for continuous outcomes. Logistic and linear regression will be used to perform analyses adjusted for baseline data. Outcomes will be analysed on an intention to treat basis. Significance will be set at p&lt;0.05.</td>
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**Abstract**

Complications following major surgery are an important cause of death and disability. A high-risk population of surgical patients accounts for over 80% of deaths but only 12.5% of in-patient surgical procedures. There are approximately 170,000 high-risk surgical procedures each year in the UK. Around 12% of this population die and as many as 70% develop complications.

A number of small single centre studies suggest that the use of cardiac output monitoring to guide the administration of intra-venous fluids and inotropes may improve outcome for patients undergoing high-risk surgery. However, this approach to peri-operative care has yet to be incorporated into routine practice. The most notable reason for this is the doubt surrounding the wider applicability of the findings of previous clinical trials.

The aim of this multi-centre trial is to evaluate the effects of the use of cardiac output monitoring to guide peri-operative haemodynamic therapy on the number of patients who develop complications following major abdominal surgery in high-risk patients. In addition, economic analysis will be performed to provide the data necessary for widespread implementation of this treatment approach should our hypothesis prove correct.
## Schedule of abbreviations

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>AE</td>
<td>Adverse Event</td>
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<td>AR</td>
<td>Adverse Reaction</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists</td>
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<tr>
<td>CI</td>
<td>Chief Investigator</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<tr>
<td>DMEC</td>
<td>Data Monitoring and Ethics Committee</td>
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<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
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<tr>
<td>GDHT</td>
<td>Goal Directed Haemodynamic Therapy</td>
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<tr>
<td>GMP</td>
<td>Good Manufacturing Practice</td>
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<tr>
<td>HR</td>
<td>Hazard Ratio</td>
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<tr>
<td>ICNARC</td>
<td>Intensive Care National Audit &amp; Research Centre</td>
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<tr>
<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<tr>
<td>MAOI</td>
<td>Monoamine Oxidase Inhibitors</td>
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<td>MHRA</td>
<td>Medical and Healthcare products Regulatory Agency</td>
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<tr>
<td>MET</td>
<td>Metabolic Equivalent</td>
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<td>NCEPOD</td>
<td>National Confidential Enquiry into Peri-Operative Death</td>
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<td>OR</td>
<td>Odds Ratio</td>
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<tr>
<td>PI</td>
<td>Principal Investigator</td>
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<tr>
<td>POMS</td>
<td>Post-Operative Morbidity Survey</td>
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<tr>
<td>POSSUM</td>
<td>Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Years</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SAR</td>
<td>Serious Adverse Reaction</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<tr>
<td>SUSAR</td>
<td>Serious Unexpected Suspected Adverse Reaction</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>SSAR</td>
<td>Suspected Serious Adverse Reaction</td>
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<td>SSI</td>
<td>Surgical Site Infection</td>
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<tr>
<td>TMG</td>
<td>Trial Management Group</td>
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<tr>
<td>TSC</td>
<td>Trial Steering Committee</td>
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<tr>
<td>WMD</td>
<td>Weighted Mean Difference</td>
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Background

Complications following major surgery are an important cause of death and disability. High-risk surgical patients account for over 80% of post-operative deaths but only 12.5% of in-patient procedures.\(^1\)\(^2\) Over 170,000 high-risk surgical procedures are performed each year in the UK, following which more than 100,000 patients will develop complications resulting in over 25,000 deaths.\(^1\)-\(^4\) Patients who develop complications but survive, remain on hospital wards for many days until well enough to be discharged.\(^1\)-\(^4\) In the long term, such patients suffer a reduction in functional independence and a substantially decreased life expectancy.\(^5\) There is an urgent need to develop interventions which will improve outcome for high-risk surgical patients, regardless of the availability of critical care resources.

The findings of a number of studies indicate that derangements in cardiac output, global oxygen delivery and related variables are strongly associated with post-operative complications and death.\(^6\)-\(^11\) These observations led to the suggestion that cardiac output and oxygen delivery could be used as haemodynamic end-points to which the doses of intra-venous fluid and inotropic therapy could be carefully titrated during the peri-operative period. This approach, sometimes termed Goal Directed Haemodynamic Therapy (GDHT), is believed to improve outcome by augmenting oxygen delivery to the tissues. Although GDHT has been evaluated in many clinical trials, the evidence base for this approach is problematic and inconclusive. The findings of trials have proved inconsistent because of important methodological variations including differences in patient group, timing and duration of interventions, treatment end-points, therapies used to achieve end-points and choice of monitoring technology. In surgical patients, some trials identified reductions in morbidity\(^12\)-\(^19\) and mortality.\(^20\)-\(^22\) Others, however failed to show any benefit,\(^23\)-\(^28\) particularly in the case of vascular surgery.\(^24\)-\(^27\) Concern has been expressed that harmful effects, in particular myocardial ischaemia, may result from the high doses of inotropic therapy administered to some patients who receive GDHT. Most importantly, there have been no large multi-centre clinical trials to evaluate the effect of haemodynamic therapy, guided by cardiac output, on outcomes after surgery.
In recent investigations, GDHT protocols have been refined to address key issues of safety and practicality, whilst remaining as effective as those used in earlier trials.\textsuperscript{16, 17} These indicate an approach to peri-operative GDHT which maximises patient benefit and safety whilst minimising the requirement for additional resources, in particular the need to routinely admit patients to a critical care unit. If effective, this intervention could therefore be rapidly introduced into all NHS hospitals after a short period of training. Retrospective economic analyses suggest the minimal capital investment and running costs would be more than offset by reductions in duration of hospital stay.\textsuperscript{29, 30}

A meta-analysis of four studies of oesophageal Doppler guided intra-operative fluid therapy in patients undergoing major abdominal surgery identified a significant reduction in post-operative complications (OR 0.32 [0.19–0.52]; p<0.0001) and duration of hospital stay (WMD 1.68 days [2.39–0.98]; p<0.0001) for patients receiving Doppler guided fluid therapy, although there was no significant reduction in mortality (OR 0.32 [0.03–3.14]; p=0.33).\textsuperscript{31} A further meta-analysis of cardiac output monitoring guided intra-operative fluid therapy in patients undergoing major abdominal surgery identified very similar reductions in post-operative complications (OR 0.28 [0.17-0.46]; p<0.0001) and duration of hospital stay (WMD 1.60 days [0.62-2.58]; p=0.001) but again no reduction in mortality (OR 0.62 [0.16-2.45]; p=0.50).\textsuperscript{32} The findings of a meta-regression analysis of clinical trials of peri-operative dopexamine infusion (agent most commonly used to increase global oxygen delivery in this setting) suggest that low dose dopexamine (≤1 µg/kg/min) is associated with a 50% reduction in 28 day mortality when compared to control treatment (low dose dopexamine 6.3% vs. control 12.3%; OR 0.50 [0.28-0.88]; p=0.016).\textsuperscript{33} Duration of post-operative stay was also significantly reduced in the low dose dopexamine group (median 13 vs. 15 days; HR 0.75 [0.64–0.88]; p=0.0005) but was unaffected in the high dose dopexamine group. These meta-analyses highlight the uncertainty surrounding the possible benefits of peri-operative GDHT and the need for a large multi-centre clinical trial to resolve this. The aim of this large multi-centre trial is to evaluate the effects of peri-operative haemodynamic therapy guided by cardiac output on the number of patients who develop complications following major gastrointestinal surgery.
Objective

To establish whether the use of minimally invasive cardiac output monitoring to guide protocolised administration of intra-venous fluid, combined with low dose dopexamine infusion will reduce the number of patients who experience complications within 30 days following major surgery involving the gastro-intestinal tract.

Trial Design

An open, multi-centre, randomised controlled trial.

Primary outcome measure

- Difference in the number of patients developing post-operative complications or dying within 30 days following randomisation between treatment arms (see: Appendix 1 for definitions of post-operative complications).

Secondary outcome measures

- Difference in 30-day post-operative mortality between treatment arms
- Difference in morbidity identified with the Post-Operative Morbidity Survey (POMS) for patients still in hospital on day 7 following randomisation
- Difference in the number of patients developing infectious complications within 30 days following randomisation
- Difference in duration of post-operative hospital stay
- Difference in 30-day critical care free days (i.e. alive and not in critical care)
- Difference in 180-day post-operative mortality
- Difference in cost-effectiveness
- Difference in healthcare costs
**Inclusion Criteria**

Adult patients undergoing major abdominal surgery involving the gastrointestinal tract that is expected to take longer than 90 minutes will be eligible for recruitment provided they satisfy one of the following criteria:

Age 65 years and over

Or...

Age 50-64 plus, one or more of:

- non-elective surgery (see Appendix 2);
- acute or chronic renal impairment (serum creatinine $>130 \, \mu\text{mol/l}$);
- diabetes mellitus;
- presence of a risk factor for cardiac or respiratory disease (see Appendix 3).

**Exclusion criteria**

The exclusion criteria are:

- refusal of consent;
- patients receiving palliative treatment only (likely to die within 30 days);
- acute myocardial ischaemia (within 30 days prior to randomisation);
- acute pulmonary oedema (within 7 days prior to randomisation);
- septic shock;
- thrombocytopenia (platelet count $<50 \times 10^9/l$);
- patients receiving Monoamine Oxidase Inhibitors (MAOIs);
- phaeochromocytoma;
- severe left ventricular outlet obstruction e.g. due to hypertrophic obstructive cardiomyopathy or aortic stenosis;
- known hypersensitivity to dopexamine hydrochloride or disodium edetate;
- participating in another randomised trial;
- pregnancy at time of enrolment;
failure to meet the inclusion criteria.

Recruitment and screening

Potential participants will be screened by research staff at Site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff.

Informed consent

It is the responsibility of the Principal Investigator (PI) at each site, or persons delegated by the PI to obtain written informed consent from each subject prior to participation in this trial. This process will include provision of a patient information sheet accompanied by the relevant consent form, and an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. Wherever possible, the patient will be approached at least 24 hours prior to surgery to allow time for any questions. However, by the nature of the inclusion criteria for this trial, many patients will undergo emergency surgery or arrive in hospital on the morning of surgery. Provided that all reasonable effort has been made to identify a potential participant 24 hours in advance of surgery, they will still be eligible for recruitment within a shorter time frame if this has not proved possible. The most frequent reason will be that the patient is undergoing surgery on an urgent or emergency basis.

The PI or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and consent form will be reviewed and updated if necessary. However, given the short duration of the intervention period, it is most unlikely that new safety information would come to light for an individual patient. Patients who lack capacity to give or withhold informed consent will not be recruited.

Patients who are not entered into this trial should be recorded (including reason not entered) on the patient screening log in the Optimise Investigator Site File.
Randomisation

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 centre, surgical procedure and emergency status. Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability.

To enter a patient into the Optimise trial, research staff at Site will log on to a secure web-based randomisation system via a link on the ICNARC website https://optimise.icnarc.org/ and complete the patient’s details to obtain a unique 4 digit patient number and allocation to a treatment group.

Trial interventions

The trial intervention period will commence at the start of general anaesthesia and continue for six hours after surgery is completed (maximum total duration: 24 hours).

Peri-operative management for all patients

Care for all patients has been loosely defined to avoid extremes of clinical practice but also practice misalignment. All patients will receive standard measures to maintain oxygenation (SpO₂ ≥ 94%), haemoglobin (>8 g/dl), core temperature (37 °C) and heart rate (<100 bpm). 5% dextrose will be administered at 1 ml/kg/hr to satisfy maintenance fluid requirements. An alternative maintenance fluid may be administered (using the same rate of 1ml/kg/hr) at the discretion of the treating clinician. Additional fluid will be administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess.

Mean arterial pressure will be maintained between 60 and 100 mmHg using an alpha adrenoceptor agonist or vasodilator as required. The trial interventions will commence with induction of anaesthesia and continue until six hours after the end of surgery. Post-operative analgesia will be provided by epidural infusion (bupivacaine and fentanyl) or intra-venous infusion (morphine or fentanyl). If required, post-
operative sedation will be provided with propofol or midazolam. Regular monitoring of plasma potassium and glucose levels is recommended. The intervention period will last a maximum of 24 hours (although in most cases much less than this).

**Additional peri-operative management for the intervention group**

This will commence from the induction of general anaesthesia and continue for six hours following surgery. Cardiac output and stroke volume will be measured by arterial waveform analysis (LiDCOrapid system). No more than 500ml of intra-venous fluid will be administered prior to commencing cardiac output monitoring. The manufacturer of the LiDCOrapid system (LiDCO Ltd, UK) will provide this technology on loan to trial sites. In addition to the maintenance fluid and blood products described previously, patients will receive 250ml fluid challenges with a colloid solution as required in order to achieve a maximal value of stroke volume. The absence of fluid responsiveness will be defined as the absence of a sustained rise in stroke volume of at least 10% for 20 minutes or more (refer to the Optimise specific SOP in your Investigator Site File for further guidance).

Patients in the intervention group will also receive dopexamine at a fixed rate of 0.5 µg/kg/min which will be commenced after fluid replacement has been initiated. The dose of dopexamine will be reduced to 0.25 µg/kg/min if the heart rate increases to greater than 120% of the baseline value or 100bpm (whichever is the greater) for more than 30 minutes despite adequate anaesthesia and analgesia. If, despite dose reduction, the heart rate does not decrease below this level, the dopexamine infusion will be discontinued. All other management decisions will be taken by clinical staff.

**Additional peri-operative management for the control group**

Patients in the control group will be managed by clinical staff according to usual practice. As described in the guidance for the management of all patients, this will include 250ml fluid challenges with a colloid solution administered at the discretion of the clinician guided by pulse rate, arterial pressure, urine output, core-peripheral temperature gradient, serum lactate and base excess. If a specific haemodynamic end-point for fluid challenges is to be used, the most appropriate would usually be a sustained rise in central venous pressure of at least 2 mmHg for 20 minutes or more.
Cardiac output monitoring will not be routinely used in the control group unless specifically requested by clinical staff.

**Procedures to minimise bias**

Optimise is a pragmatic effectiveness trial of a treatment algorithm. It is not possible to conceal treatment allocation from all staff in trials of this type. However, procedures will be put in place to minimise the possibility of bias arising because research staff become aware of trial group allocation. Patients will be followed up for complications by a member of research staff who is unaware of trial group allocation. Complications will then be verified by the PI or designee at each site who will also be unaware of trial group allocation. The principal investigator may nominate a senior clinician to assist with this task if he/she becomes aware of the trial group allocation of any individual patient. Research staff will be asked to confirm whether these procedures have been complied with. The decision to admit a trial participant to a critical care unit will be made by clinical staff and this decision must not be affected by trial group allocation.

**Data set collection**

**Randomisation data**

- Full Name
- Date of Birth
- Gender
- Surgical procedure category
- Urgency of surgery / Elective or non-elective surgery
- Planned location following surgery
- Checklist to ensure patient meets eligibility criteria
- Pregnancy

**Baseline data**

- NHS Number/Hospital Number
- Weight
• Residential Postcode
• Baseline Risk Factors
• ASA grade
• Quality of life according to EQ5D health status measure (see Appendix 5)

Measurements taken at 0, 6 hours and at end of trial period

• Surgery
  o Start and end times of anaesthesia
  o Surgical procedure performed
  o Open or laparoscopic procedure
  o ASA grade
  o Anaesthetic technique
  o Extubated at end of surgery (Y/N)
  o Cardiac output monitor use
  o Hours spent in recovery room
  o Actual location following surgery

• Fluids
  o Volume of intra-venous colloid solution during surgery
  o Volume of intra-venous colloid solution during six hours after surgery
  o Volume of intra-venous crystalloid solution during surgery
  o Volume of intra-venous crystalloid solution during six hours after surgery
  o Volume of blood products during surgery
• **Drugs**
  - Use of dopexamine (including start date/time and end date/time) during intervention if applicable
  - Dopexamine batch number
  - Dopexamine rate, infusion concentration, total dose, infusion site
  - Other drugs
  - Post-operative epidural analgesia (Y/N)

• **Research Staff**
  - Additional staff present to deliver intervention during surgery (Y/N)
  - Additional staff present to deliver intervention during six hours after surgery (Y/N)

**Clinical outcomes**

• 30 day post-operative complications (see Appendix 3)
• 30 day and 180 day post-operative mortality
• Post-Operative Morbidity Survey (POMS) for hospital in-patients on day 7 after surgery (see Appendix 4)
• 30 day post-operative infectious complications
• Duration of hospital stay
• 30 day post-operative critical care free days (alive and outside critical care)
• Quality of life according to EQ5D health status measure (30 and 180 days) (see Appendix 5)
Trial Drug

The trial drug or Investigational Medicinal Product (IMP) is presented as dopexamine hydrochloride in a 1% solution (w/v). Each 5 ml ampoule contains 50 mg of dopexamine hydrochloride.

Sourcing, manufacture and supply of IMP

Dopexamine hydrochloride has been commercially available for many years. Cephalon Inc. is the current sole supplier of this agent which is manufactured in the European Economic Area according to principles of Good Manufacturing Practice (GMP). Cephalon Inc. are not the sponsors of this trial and the Optimise trial team will not be responsible for auditing production or adherence to the principles of GMP.

Packaging, receipt, storage, dispensing and return of IMP

The IMP will be supplied individually to each site at a reduced price by Cephalon UK Ltd, 1 Albany Place, Hyde Way, Welwyn Garden City, Hertfordshire, AL7 3BT, UK. As this is an open trial which does not involve the use of placebo or dummy infusions, no special measures are needed in terms of packaging or supply beyond those routinely required.

The receipt, storage and dispensing of the IMP will be the responsibility of the pharmacy department in each individual trial site. This will be performed in accordance with accredited standards for routine pharmacy practice.

Any unused and unopened IMP ampoules will be returned to the pharmacy within each individual site. Any IMP which remains unused having been dispensed and diluted for administration will be disposed of in the clinical area according to the policies of the individual trial sites. Where IMP is stored in clinical areas it will be clearly labelled as such and stored in a separate locked area. Storage will comply with local requirements and Good Clinical Practice (GCP) (i.e. temperature monitoring etc).
**Prescription and labelling of IMP**

The IMP will be prescribed and labelled as shown in Figure 1. The label will refer to the information sheet for clinical staff which will be placed in the patient case notes to provide basic information on the trial and contact details for the PI at the site.

![Label for IMP storage box, prescription chart and syringe](image)

**Figure 1. Label for IMP storage box, prescription chart and syringe**

![Additional patient specific label for patient prescription chart and syringe](image)

**Figure 2. Additional patient specific label for patient prescription chart and syringe**
Administration of IMP

As the dopexamine is reconstituted in dextrose for administration to the patient an additional label (Figure 2) should be affixed to the prescription chart and syringe.

Dopexamine will be administered intravenously by infusion through a catheter in a central or large peripheral vein at an initial rate of 0.5 µg/kg/min using a device which provides accurate control of the rate of flow.

Contact with metal parts in infusion apparatus will be minimised. The drug will be diluted in 5% dextrose solution at a concentration not exceeding 4 mg/ml when administered via a central venous catheter or 1 mg/ml when administered via a cannula in a large peripheral vein.

General precautions for use of dopexamine within the Optimise trial

There are a number of special warnings and precautions for use of dopexamine (see Summary of Product Characteristics, SmPC for more details). Extensive experience from clinical practice and clinical trials suggest that many of the potential adverse effects of dopexamine are unlikely in this population at the dose intended for use. Because of the vasodilator effects of dopexamine, correction of hypovolaemia (if present) should be initiated at least 30 minutes prior to commencement of the infusion.

Arterial pressure endpoints have been set for the use of vasopressors in patients who are hypotensive. As with all high-risk surgical patients, care should also be taken to avoid excessive sodium and fluid administration. All β2-adrenergic agonists may depress plasma potassium and raise plasma glucose levels. These effects are minor and reversible but it is advisable to monitor the potassium and glucose. Dopexamine inhibits the uptake-1 mechanism and may potentiate the effects of exogenous catecholamines such as noradrenaline. Dopexamine may induce a small reversible decrease in circulating platelet numbers although no adverse effects attributable to alterations in platelet count have been seen in clinical studies.

Dopexamine should be administered with caution to patients with a clinical history of ischaemic heart disease especially following acute myocardial infarction or recent episodes of angina pectoris. Benign arrhythmias and more rarely, serious
Arrhythmias have been reported. If excessive tachycardia occurs during dopexamine administration, then a reduction or temporary discontinuation of the infusion should be considered. The risk of thrombophlebitis and local necrosis may be increased if the concentration of dopexamine administered via a peripheral vein exceeds 1 mg/ml.

**IMP data collection in the Case Record Form**

The Case Record Form (CRF) will ask for the following data on the IMP:

- batch number
- total dose received
- date/time infusion commenced
- date/time infusion discontinued
- primary safety endpoints
- rate of dopexamine administered
- infusion concentration

**Prior and concomitant therapies**

Data will be collected describing the recent or concomitant use of:

- intra-venous adrenergic agonists
- adrenergic antagonists
- monoamine oxidase inhibitors

**Subject compliance monitoring**

Administration of the IMP will only take place under the direct supervision of an appropriately trained clinician or nurse in an operating theatre, post-anaesthetic recovery unit or critical care unit. Alterations to the administered dose will be recorded along with the reason for this change.
Predefined protocol deviations and violations

- Failure to administer dopexamine to an intervention group patient
- Administration of incorrect dose of dopexamine to an intervention group patient
- Administration of dopexamine to a control group patient
- Use of cardiac output monitoring in a control group patient

Withdrawal of participants

The infusion will be discontinued or dose of dopexamine reduced if a patient develops symptoms, signs or monitoring criteria suggestive of myocardial ischaemia or tachycardia. In addition to adverse event reporting (see Safety and Adverse Events section) where necessary, data collection and follow-up for participants for such patients will be performed as normal. All randomised patients will be included in the final analysis on an intention to treat basis.

Primary safety endpoints

Primary safety endpoints will be tachycardia, myocardial ischaemia and in patients who receive the drug via a peripheral cannula, thrombophlebitis. Dopexamine has been used for many years in critical care for similar indications to that of the current trial. The drug has a good safety profile when used at a low dose (0.5 μg/kg/min) in the patients eligible for participation in this trial (see inclusion and exclusion criteria). This is particularly the case when administered with continuous monitoring in a critical care area (as in this trial). Published data suggest that when used at this dose and for this indication, dopexamine is not associated with any increase in myocardial injury.34

Sample size calculation

The primary outcome for the trial is the number of patients developing post-operative complications within 30 days following randomisation. In our previous interventional trial, 68% of control group patients and 44% of GDHT patients developed complications following surgery (relative risk 0.63 [0.46-0.87]; p=0.003). Assuming a type I error rate of 5%, 345 patients per group (690 total) would be required to detect
with 90% power a more conservative reduction in 30-day post-operative complications from 50% in the control group to 37.5% in the intervention group (absolute risk reduction 12.5%; relative risk reduction 25%). Allowing for a 3% one way cross-over rate, this increases to 367 per group (734 total). Our experience from previous trials indicates that loss to follow-up will be small. Sample size calculations were performed using Stata 10.1 (StataCorp, College Station, TX).

Data from a recent national study of the high-risk surgical population suggests each site will admit approximately 300 eligible patients each year. For this trial, thirty patients per Site per year over two years will need to be recruited to meet the recruitment target. In recent single-centre trials, as many as 100 patients have been recruited in one year with less than 20% of patients refusing to participate.

**Statistical analysis**

Baseline demographic and clinical data for the two groups will be summarised but not subjected to statistical testing. The primary effect estimate will be the relative risk of 30-day post-operative complications. 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. Logistic regression (for binary outcomes) and linear regression (for continuous outcomes) will be used to perform analyses adjusted for baseline data. All analyses will be performed on an intention to treat basis. Significance will be set at p<0.05.

**Planned sub-group analyses**

Outcome data will be analysed by urgency (elective vs non-elective) and surgical procedure category. Sub-group analyses will be performed by testing for an interaction between the sub-group categories and the treatment group in adjusted (linear or logistic) regression models.

**Interim analysis**

A single interim analysis will be performed following the recruitment and follow-up to 30 days of 350 patients, and reviewed by the Data Monitoring and Ethics Committee (DMEC). The interim analysis will be conducted using a Peto-Haybittle stopping rule (P<0.001) to guide recommendations for early termination due to harm. The DMEC
would be advised not to recommend stopping the trial at this stage due to effectiveness, as any result in this number of patients would be unlikely to be considered sufficiently definitive to change routine practice. Additional interim analyses will be conducted only if required by the DMEC due to specific safety concerns.

**Safety and adverse events**

**Adverse Event (AE)**

An 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 IMP, whether or not considered related to the IMP.

**Adverse Reaction (AR)**

An AR is any untoward and unintended response in a subject to an 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 adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

**Serious Adverse Event (SAE)**

Any untoward medical occurrence that results in:

- death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity or
- is a congenital anomaly/birth defect (note pregnancy is a specific exclusion).
**Suspected Serious Adverse Reaction (SSAR)**

An adverse reaction that is classed as serious and is consistent with the information about dopexamine set out in the Summary of Product Characteristics (SmPC).

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A suspected adverse reaction related to dopexamine that is both unexpected and serious and is not consistent with the information set out in the Summary of Product Characteristics (SmPC).

**Expected adverse and serious adverse events**

The incidence of post-operative complications in the trial population is widely reported as very high, ranging from 45-70%. The majority of such complications can be clearly regarded as expected complications of surgery. Such expected adverse and serious adverse events will be recorded both locally and on the Optimise web portal. Expected complications of surgery will be reported on an individual basis if:

1. they are deemed to be life-threatening, to have caused a congenital anomaly/birth defect or
2. have resulted in death.

**Expected complications of surgery:**

Acute kidney injury

Acute respiratory distress syndrome

Anastamotic breakdown

Gastro-intestinal bleed

Laboratory confirmed bloodstream infection

Nosocomial pneumonia

Post-operative haemorrhage

Pulmonary embolism

Pleural effusions

Paralytic ileus
Surgical site infection
Sepsis, severe sepsis and septic shock
Stroke
Transient ischaemic attack
Urinary tract infection

The following are not expected complications of surgery and will require reporting if they meet SAE criteria as defined on page 27 (N.B. Please note, this list is not exhaustive):

Acute psychosis
Anaphylaxis
Arrhythmia
Bowel infarction
Cardiogenic pulmonary oedema
Cardiac or respiratory arrest
Limb or digital ischaemia
Multi-organ dysfunction syndrome
Myocardial ischaemia or infarction

Recording and documenting of Adverse Events (AEs)

The research team at Sites will be responsible for recording AEs observed during the 30-day trial period. These will be verified by the PI at each site prior to entry onto the CRF. The Adverse Event report page in the CRF will be completed as applicable. AEs must be recorded as defined in the CRF, regardless of relationship to trial drug as determined by the PI. The PI should attempt, if possible, to establish a diagnosis based on the subject’s signs and symptoms. When a diagnosis for the reported signs or symptoms is known, the PI should report the diagnosis as the adverse event, rather than reporting the individual symptoms. The PI must assess causality for any AEs. The PI should follow all AEs observed during the trial until they are resolved or stabilised, or the events are otherwise explained. AEs are recorded at each trial time
point and tabulated for inclusion in an annual report to the Sponsor, Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC). SUSARs will be recorded and reported in line with UK statutory requirements for clinical trials involving IMP.

Pharmacovigilance reporting (SAE and SUSAR)

Where the reporting of an SAE (or SAR or SUSAR) is required, the PI at each site should e-mail the SAE reporting form to the Chief Investigator at Barts and The London School of Medicine and Dentistry at the following address:

rupert.pearse@bartsandthelondon.nhs.uk

If it is not possible to e-mail the SAE to the Chief Investigator, this may be sent by fax with: “SAE for review, for the urgent attention of Dr Rupert Pearse, Optimise Chief Investigator” to the following number:

Fax: 020 7377 7299 (Intensive Care Research Office, Royal London Hospital)

The Chief Investigator (CI) will check that all fields have been completed and that the form has been signed by the PI at that site. The CI will not downgrade SAEs or SUSARs from the treating PI at the site. However the CI can upgrade an AE to a SAE or a SAE to a SUSAR. The CI will then fax the completed SAE form within 24hrs of becoming aware of the event, to the R&D office at Barts and The London School of Medicine and Dentistry who will maintain records in accordance with the responsibilities of the Sponsor and will also be responsible for expedited reporting to the MHRA. Annual Safety Reports will be provided by ICNARC CTU to the MHRA, REC and R&D office at Barts and The London School of Medicine and Dentistry for every year that the trial is running.

Pharmacovigilance Standard Operating Procedures (SOPs) will indicate the required process for reporting of SAE and SUSARs. In brief, these will be logged via the electronic CRF and copies e-mailed to ICNARC CTU, the R&D office at Barts and The London School of Medicine and Dentistry and the local R&D office for the trial site. The PI at each site will nominate a designee to sign the SAE and SUSAR reports in their absence.
Economic analysis

Retrospective economic analyses suggest that the intervention may reduce healthcare costs. A prospective economic analysis will encourage rapid implementation of the findings of this trial. Cost-effectiveness of peri-operative cardiovascular management will be evaluated in two phases.

Phase I: A within-trial economic analysis using prospectively collected clinical and resource use data. Cost estimation will be performed from an NHS perspective using individual patient-level data. Information on resource use will include duration of hospital stay, critical care resource use, concomitant medications, interventions, infusions and investigations for initial hospitalisation, associated complications and re-hospitalisations. Representative national unit costs will be estimated from routine and published literature (e.g. NHS reference costs, etc). The additional cost of the intervention will be assessed using information on the additional resources required to administer the intervention in a critical care unit or post-anaesthetic recovery unit, in addition to the use of fluid, drugs and disposables. The main outcome for this analysis will be the Quality Adjusted Life Year (QALY), which will be assessed using the EuroQoL-5D (EQ-5D) questionnaire.

Phase II: This part of the trial will address the need to extrapolate beyond the trial period and assess the cost effectiveness of the treatment strategies being investigated within the broader perspective of the NHS. An economic model will be developed to predict long term outcomes and costs. Overall cost-effectiveness will be expressed in terms of additional cost per QALY gained. Uncertainty in cost-effectiveness will be presented in terms of the probability that alternative forms of management are most cost-effective given a range of maximum values the NHS might be willing to pay for an additional QALY. Trial data will provide estimates of costs and effects that initially follow clinical outcome data.

To account for long-term costs and benefits of the alternative treatments it will be necessary to extrapolate beyond the trial period. Data from this trial will be combined with that of other relevant trials to facilitate a comparison of alternative approaches to peri-operative cardiovascular management.
To inform future research priorities in the NHS, Bayesian value of information analysis will be used to determine the expected costs of decision uncertainty and the value that can be placed on additional research aimed at reducing this uncertainty.\textsuperscript{51}

**Sub-studies**

**Biological sub-study**

In selected participating sites which have agreed to do so, blood and urine samples will be taken before surgery and then at 24 and 72 hours after the start of the intervention period. Blood samples will be centrifuged within 30 minutes of collection to extract plasma which will be divided and placed in three storage tubes for each patient, clearly labelled and stored in a -80°C freezer. The selected participating sites will be assessed prior to the start of the study to ensure they have the necessary facilities to collect and store the blood and urine samples. Urine samples will be divided and placed in two storage tubes for each patient, clearly labelled and stored in a -80°C freezer. The PI will ensure that all the research staff required to collect and store samples have been adequately trained to do so.

It is anticipated, every six months (depending on recruitment rate), samples will be transferred (by Dr. Rupert Pearse and his research team at Barts and The London School of Medicine & Dentistry) on dry ice to a central laboratory at Barts and The London School of Medicine & Dentistry for storage in a -80°C freezer until analyses are performed. Material Transfer Agreements between sites will be put in place where required to ensure compliance with the Human Tissue Act. Sample analysis will include markers of myocardial injury (B-type natriuretic peptide and troponin I), acute kidney injury (N-GAL and creatinine) and inflammatory markers (II-1, II-6, II-10, TNF\textalpha, C-reactive protein). In addition, plasma and urine will be stored for a maximum of 10 years from the end of the trial to allow further analyses of direct relevance to this field of research. Additional ethics approval will be sought for such analyses.

Laboratory sample analysis contact: Dr Rupert Pearse,
Markers of pre-load responsiveness sub-study

In selected participating sites which have agreed to do so, additional data will be collected regarding the predictive accuracy of a range of ‘dynamic’ markers of preload responsiveness. These variables define the proportional change in global haemodynamics which occurs during the respiratory cycle. The LiDCOrapid monitor automatically calculates the following variables: pulse pressure variation (%), stroke volume variation (%) and systolic pressure variation (%). Implementation of the findings of the Optimise trial may be improved by a better understanding of the predictive accuracy of these variables.

For patients who are monitored using the LiDCOrapid monitor, sites participating in this sub-study will collect the following additional data during the sixty seconds before and after each of three 250ml colloid fluid challenges during surgery and each of three 250ml colloid fluid challenges after surgery:

- Pulse rate
- Mean arterial pressure
- Cardiac index (nominal value)
- Stroke volume (nominal value)
- Central venous pressure (if available)
- Pulse pressure variation (%)
- Stroke volume variation (%)
- Systolic pressure variation (%)

This sub-study is observational and will not result in any change in clinical management.
End of trial and stopping rules

The end of the trial will be defined as the end of the 30-day period of follow-up for the final participant in the trial. Interim analyses will be performed at pre-defined stages by the DMEC. Early termination of trial in response to safety issues will be addressed via the DMEC. They will report any issues pertaining to safety to the CI, who will be responsible for informing the Sponsor and will take appropriate action to halt the trial if concerns exist about participant safety. In keeping with GCP guidelines as Sponsor, the relevant institutions will be responsible for source data verification.

The Main Research Ethics Committee will be notified in writing if the trial has been concluded or terminated early.

Data storage

Data will be transcribed on to the CRF prior to entry on to the secure Optimise data entry web portal. Submitted data will be reviewed for completeness and consistency. Data will be stored securely against unauthorised manipulation and accidental loss as only authorised users at site or at ICNARC CTU will have access. Desktop security is maintained through user names and frequently updated passwords and back up procedures are in place. Storage and handling of confidential trial data and documents will be in accordance with the Data Protection Act 1998.

Confidentiality

The patient's full name, date of birth, hospital number and NHS number will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential.
The PI must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The PI must ensure the patient's confidentiality is maintained at all times.

ICNARC CTU together with Queen Mary's University of London will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial team will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

For central (180 day) follow-up of patients the NHS Medical Information Research Service (MRIS) will be used to trace patients (this will be completed by the Optimise trial team).

**Archiving**

All trial documentation and data will be archived centrally at Queen Mary's University of London and ICNARC CTU in a purpose designed archive facility for twenty years in conformance with the applicable regulatory requirements. Access to these archives will be restricted to authorised personnel. Electronic data sets will be stored indefinitely.

**Trial monitoring, audit and inspection**

The Sponsor will have oversight of the trial conduct at each site. The trial team will take day to day responsibility for ensuring compliance with the requirements of GCP in terms of quality control and quality assurance of the data collected as well as IMP management and pharmacovigilance.
The Optimise Trial Management Group will communicate closely with individual sites and the Sponsor’s representatives to ensure these processes are effective.

A Data Monitoring and Ethics Committee (DMEC) is in place. The committee is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The DMEC agree conduct and remit, which will include the early termination process. The DMEC review the trial data at regular intervals and request interim analyses of efficacy as it sees fit. The DMEC functions primarily as a check for safety by reviewing adverse events (Details of the DMEC can be found on page 40-41).

**Monitoring safety and well being of trial participants**

The Research and Development departments at each trial site perform regular audits of research practice. Systems are in place to ensure that all PIs and designees are able to demonstrate that they are qualified by education, training or experience to fulfil their roles and that procedures are in place which can assure the quality of every aspect of the trial. Because the entire protocol will last less than twelve hours in most cases, it is extremely unlikely that new safety information will arise during the intervention period. Nonetheless should this situation arise, then trial participants will be informed and asked if they wish to continue in the trial. If the subjects wish to continue in the trial they will be formally asked to sign a revised approved patient information sheet and consent form.

Early termination of trial in response to safety issues will be addressed via the DMEC. Day to day management will be undertaken via a Trial Management Group composed of the Chief Investigator and supporting staff. They will meet on a regular basis to discuss trial issues. Site monitoring will be directed by the Optimise Trial Management Group based at ICNARC CTU.
Monitoring safety of Investigators

Each site has health and safety policies for employees. All personnel should also ensure they adhere to any health and safety regulations relating to their area of work. The PI will ensure that all personnel have been trained appropriately to undertake their specific tasks. The trial team will complete GCP and consent training prior to start up.

Ethical considerations

The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Edinburgh (2000) as described at the following internet site: http://www.wma.net/e/policy/b3.htm. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997).

At sites, all accompanying material given to a potential participant will have undergone an independent Ethics Committee review in the UK. Full approval by the Ethics Committee has been obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site.

Trial sponsorship and indemnity

Queen Mary University of London will act as Sponsor and provide no fault insurance for this trial.

Trial Management

The trial management will be conducted by the Optimise Trial Management Group and the ICNARC CTU.

Trial Steering Committee (TSC)
A Trial Steering Committee, consisting of several independent clinicians and trialists lay representation, co-investigators and an independent Chair, will oversee the trial. Face to face meetings will be held at regular intervals determined by need but not less than once a year.

The TSC will take responsibility for:

- approving the final trial protocol;
- major decisions such as a need to change the protocol for any reason;
- monitoring and supervising the progress of the trial;
- reviewing relevant information from other sources;
- considering recommendations from the DMEC and
- informing and advising on all aspects of the trial.

The membership of the TSC is:

**Independent chair:**
Prof Tim Coats, Professor of Emergency Medicine, University of Leicester

**Independent members:**
Dr Geoff Bellinghan, Director of Critical Care, University College London
Mr Dileep Lobo, Senior Lecturer in Surgery, Nottingham University
Ms Lisa Hinton, Lay Member, DIPEX Health Experiences Research Group Department of Primary Health Care, University of Oxford

**Non-independent members:**
Prof David Bennett, Prof Charles Hinds, Dr Rupert Pearse, Prof Kathy Rowan, Aoife Ahern, Dr David Harrison, Dr Rachael Scott, observer from Queen Marys University of London and a representative of the National Institute for Health Research.
Data Monitoring and Ethics Committee (DMEC)

The Data Monitoring and Ethics Committee will consist of independent experts with relevant clinical research and statistical experience. During the period of recruitment into the trial, interim analyses of the accumulating data will be supplied, in strict confidence, to the DMEC, along with any other analyses that the committee may request. The frequency of these analyses will be determined by the committee.

The membership of the DMEC is:

**Independent chair:**

Dr Simon Gates, Principal Research Fellow, University of Warwick.

Prof Danny McAuley, Senior Lecturer and Consultant in Intensive Care Medicine, The Queen's University of Belfast.

Prof Tom Treasure, Professor of Cardiothoracic Surgery, University College London.

Funding

This trial is jointly funded by a National Institute for Health Research Clinician Scientist Award held by Dr Rupert Pearse and ICNARC CTU.

LiDCO will be providing machines on loan including consumables (for trial participants only) free of charge to each site for the duration of the trial.

The IMP will be supplied individually to each site at a reduced price by Cephalon UK Ltd.

(N.B. LiDCO and Cephalon had no input in the production of this protocol).

Publication

Data arising from the research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the Optimise Trial Management Group. The TSC will agree the membership of a writing committee which will take
primary responsibility for final data analysis and authorship of the scientific report. All authors will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission.
References


Appendix 1: Definition of post-operative complications

Myocardial ischaemia or infarction
Acute ECG changes with appropriate clinical findings and changes in cardiac troponins.

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, intravenous fluid, etc).

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

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

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

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:

a) \( \text{PaO}_2: \text{FiO}_2 < 40 \text{kPa} = \textbf{Acute Lung Injury} \)
\( \text{PaO}_2: \text{FiO}_2 < 27 \text{kPa} = \textbf{Acute Respiratory Distress Syndrome.} \)

**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.

**Acute kidney injury**

A two-fold increase in serum creatinine or sustained oliguria of \(< 0.5 \text{ ml kg}^{-1} \text{ hour}^{-1}\) for twelve hours (consensus definition).

**Infection, source uncertain**

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

i) core temperature \(< 36^\circ \text{C} \) or \(>38^\circ \text{C} \)

ii) white cell count \(>12 \times 10^9 \text{ l}^{-1}\) or \(<4 \times 10^9 \text{ l}^{-1}\)

iii) respiratory rate \(>20 \text{ breaths per minute}\) or \(\text{PaCO}_2 < 4.5 \text{kPa}\)

iv) pulse rate \(>90 \text{ bpm}\)
**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.

**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 (>38 °C), 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 °C), urgency, frequency, dysuria, or suprapubic 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 $>10^2$ colonies/mL in nonvoided specimens;

e. $>10^5$ 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 ($>38{}^\circ\text{C}$), localized pain, or localized tenderness at the involved site and at least one of the following:

a. purulent drainage from affected site;

b. organisms cultured from blood that are compatible with suspected site of infection;

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

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

e. 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:
   a. purulent drainage from the deep incision but not from the organ/space component of the surgical site;
   b. 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 (>38°C) or localized pain or tenderness, unless incision is culture-negative;
   c. an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
d. 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 subdiaphragmatic abscess, which would be reported as an organ/space SSI at the intraabdominal specific site. An organ/space 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 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:

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

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

c. 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;

d. 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 at least one of the following signs or symptoms:
fever (>38°C), 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.

**Nosocomial pneumonia**

Ventilator-associated pneumonia (i.e. pneumonia in persons who had a device to assist or control respiration continuously through a tracheostomy or by endotracheal intubation within the 48-hour period before the onset of infection) will be classified separately. **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:

i) Two or more serial chest radiographs with at least one of the following:
   a. new or progressive and persistent infiltrate;
   b. consolidation;
   c. cavitation.

And at least one of the following:
   a. fever (>38°C) with no other recognized cause;
   b. leucopaenia (<4,000 WBC mm\(^{-3}\)) or leucocytosis (>12,000 WBC mm\(^{-3}\))
   c. for adults >70 years old, altered mental status with no other recognized cause.

And at least two of the following:
   a. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
   b. new onset or worsening cough, or dyspnoea, or tachypnoea;
   c. rales or bronchial breath sounds;
   d. worsening gas exchange

Post-operative haemorrhage

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

Stroke

Clinical diagnosis with confirmation by CT scan.
Appendix 2: Classification of urgency of surgery

Elective: At a time to suit both patient and surgeon or within 3 weeks if more urgent.

Non-elective: Within 24 hours of the decision that surgery is required.
Appendix 3: Risk factors for cardiac or respiratory disease

Examples include:

- Exercise tolerance equivalent to six metabolic equivalents (METs) or less as defined by ACC/AHA guidelines;\(^{37}\)
- Past medical history of ischaemic heart disease (angina, myocardial infarction or acute coronary syndrome);
- Angiographically proven ischaemic heart disease;
- Ejection fraction less than 30% (echocardiography);
- Moderate or severe valvular heart disease;
- Clear history or clinical signs of heart failure (requiring treatment, oedema, etc);
- Clinical history indicative of Chronic Obstructive Pulmonary Disease (COPD) ie chronic productive cough for at least three months of two consecutive years;
- Poor lung function demonstrated by spirometry (FEV1 or FVC <75% predicted);
- Radiographically confirmed chronic lung disease (fibrosis, COPD, etc);
- Anaerobic threshold ≤14 ml min\(^{-1}\) kg\(^{-1}\) on sub-maximal exercise testing;
- Heavy smoker.
## Appendix 4: Post-operative morbidity survey (POMS)

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<thead>
<tr>
<th>Morbidity</th>
<th>Criteria</th>
<th>Data source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Diagnostic tests or therapy within the last 24 hr for any of the following: new myocardial infarction or ischemia, hypotension (requiring fluid therapy &gt;200 ml/hr or pharmacological therapy), atrial or ventricular arrhythmias, cardiogenic pulmonary oedema, thrombotic event (requiring anticoagulation).</td>
<td>Treatment chart, Note review</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Has the patient developed a new requirement for oxygen or respiratory support.</td>
<td>Patient observation, Treatment chart</td>
</tr>
<tr>
<td>Infectious</td>
<td>Currently on antibiotics and/or has had a temperature of &gt;38°C in the last 24 hr</td>
<td>Treatment chart, Observation chart</td>
</tr>
<tr>
<td>Renal</td>
<td>Presence of oliguria &lt;500 ml/24 hr; increased serum creatinine (&gt;30% from preoperative level); urinary catheter in situ.</td>
<td>Fluid balance chart, Biochemistry result, Patient observation</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Unable to tolerate an enteral diet for any reason including nausea, vomiting, and abdominal distension (use of anti-emetic).</td>
<td>Patient questioning, Fluid balance chart, Treatment chart</td>
</tr>
<tr>
<td>Neurological</td>
<td>New focal neurological deficit, confusion, delirium, or coma.</td>
<td>Note review, Patient questioning</td>
</tr>
<tr>
<td>Haematological</td>
<td>Requirement for any of the following within the last 24 hr: packed erythrocytes, platelets, fresh-frozen plasma, or cryoprecipitate.</td>
<td>Treatment chart, Fluid balance chart</td>
</tr>
<tr>
<td>Wound</td>
<td>Wound dehiscence requiring surgical exploration or drainage of pus from the operation wound with or without isolation of organisms.</td>
<td>Note review, Pathology result</td>
</tr>
<tr>
<td>Pain</td>
<td>New postoperative pain significant enough to require parenteral opioids or regional analgesia.</td>
<td>Treatment chart, Patient questioning</td>
</tr>
</tbody>
</table>
1: Pulmonary

Has the patient developed a new requirement for oxygen or respiratory support? ☐ ☐

2: Infectious

Is patient currently on antibiotics and/or has the patient had a temperature of ≥ 38°C the last 24 hours? ☐ ☐

3, 4 & 5: Renal

Does the patient have any of the following?

Oliguria (<500ml/d) ☐ ☐
Creatinine (>30% from pre-op level) ☐ ☐
Urinary catheter in-situ ☐ ☐

6 & 7: Gastrointestinal

Unable to tolerate enteral diet (oral or tube feed)? ☐ ☐

Is the patient experiencing nausea, vomiting or abdominal distention? ☐ ☐

8, 9, 10 & 11: Cardiovascular

Has the patient undergone diagnostic tests or therapy within the last 24 hours for any of the following?

New MI ☐ ☐

Ischaemia or hypotension (requiring drug therapy or fluid therapy >200ml/h) ☐ ☐
Atrial or ventricular arrhythmias ☐ ☐
Cardiogenic pulmonary oedema / new anticoagulation

12: Neurological
Does the patient have new confusion, delerium, focal deficit or coma? 

13: Wound complications
Has the patient experienced wound dehiscence requiring surgical exploration or drainage of pus from the operative wound with or without isolation of organisms? 

14 & 15: Haematological
Has the patient received transfusion of any of the following within the last 24 hours?
Red blood cells
Platelets / FFP / Cryoprecipitate

16: Pain
Has the patient experienced surgical wound pain significant enough to require parenteral opioids or regional analgesia? 

17: Mobility
Wheelchair/ Unaided / Aided / Crutches / Zimmer / Bedbound
Appendix 5: EQ5D questionnaire (EuroQoL)

Is patient able to give answers to EQ5D? YES / NO

IF YES THEN ASK EQ5D QUESTIONS. IF NO THEN FOR EACH GROUP BELOW PLEASE INDICATE WHICH STATEMENTS BEST DESCRIBE THE ABOVE NAMED PERSONS HEALTH STATE TODAY. PLEASE RING ONE ANSWER IN EACH QUESTION

We are trying to find out what you think about your health. I will ask you a few brief and simple questions about your own health state today. I will explain the task fully as I go along but please interrupt me if you do not understand something or if things are not clear to you. Please also remember that there are no right or wrong answers. We are interested here only in your personal view.

First I am going to read out some questions. Each question has a choice of three answers. Please tell me which answer best describes your own health state today. Do not choose more than one answer in each group of questions.

IF RESPONDENT HAS DIFFICULTY IN ANSWERING THEN REPEAT QUESTION VERBATUM. FOR EACH QUESTION, RING APPROPRIATE NUMBER ON ANSWER SHEET.

**Question 1: Mobility**

First I'd like to ask you about mobility.

Would you say you have…

1. No problems in walking about?
2. Some problems in walking about?
3. Are you confined to bed?

**Question 2: Self-Care**

Next I'd like to ask you about self-care.

Would you say you have…

1. No problems with self-care?
2. Some problems washing or dressing yourself?
3. Are you unable to wash or dress yourself?

Question 3. Usual activities

Next I'd like to ask you about usual activities, for example work, study, housework, family or leisure activities.

Would you say you have…

1. No problems with performing your usual activities?
2. Some problems with performing your usual activities?
3. Are you unable to perform your usual activities?

Question 4: Pain/Discomfort

Next I'd like to ask you about pain or discomfort.

Would you say you have…

1. No pain or discomfort?
2. Moderate pain or discomfort?
3. Extreme pain or discomfort?

Question 5: Anxiety/Depression

Finally I'd like to ask you about anxiety or depression.

Would you say you are…

1. Not anxious or depressed?
2. Moderately anxious or depressed?
3. Extremely anxious or depressed?

PLEASE REMEMBER IT IS IMPORTANT TO HAVE ONE AND ONLY ONE RESPONSE TO EACH GROUP OF THREE RESPONSES