Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

Please enter a short title for this project (maximum 70 characters)
OPTIMISE II

1. Is your project research?

(●) Yes ( ) No

2. Select one category from the list below:

( ) Clinical trial of an investigational medicinal product

( ) Clinical investigation or other study of a medical device

( ) Combined trial of an investigational medicinal product and an investigational medical device

(●) Other clinical trial to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

( ) Basic science study involving procedures with human participants

( ) Study administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

( ) Study involving qualitative methods only

( ) Study limited to working with human tissue samples (or other human biological samples) and data (specific project only)

( ) Study limited to working with data (specific project only)

( ) Research tissue bank

( ) Research database

If your work does not fit any of these categories, select the option below:

( ) Other study

2a. Will the study involve the use of any medical device without a CE Mark, or a CE marked device which has been modified or will be used outside its intended purposes?

( ) Yes (●) No

2b. Please answer the following question(s):

a) Does the study involve the use of any ionising radiation? ( ) Yes (●) No

b) Will you be taking new human tissue samples (or other human biological samples)? ( ) Yes (●) No

c) Will you be using existing human tissue samples (or other human biological samples)? ( ) Yes (●) No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- [x] England
- [x] Scotland
- [x] Wales
- [ ] Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- (•) England
- ( ) Scotland
- ( ) Wales
- ( ) Northern Ireland
- ( ) This study does not involve the NHS

4. Which applications do you require?

IMPORTANT: If your project is taking place in the NHS and is led from England select 'IRAS Form'. If your project is led from Northern Ireland, Scotland or Wales select 'NHS/HSC Research and Development Offices' and/or relevant Research Ethics Committee applications, as appropriate.

- [x] IRAS Form
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

For NHS/HSC R&D Offices in Northern Ireland, Scotland and Wales the CI must create NHS/HSC Site Specific Information forms, for each site, in addition to the study wide forms, and transfer them to the PIs or local collaborators.

For participating NHS organisations in England different arrangements apply for the provision of site specific information. Refer to IRAS Help for more information.

5. Will any research sites in this study be NHS organisations?

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs (funding for the support and facilities needed to carry out research e.g. NHS Support costs) for this study provided by a NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC), NIHR Patient Safety Translational Research Centre or a Diagnostic Evidence Co-operative in all study sites?

Please see information button for further details.

( ) Yes (•) No

Please see information button for further details.

5b. Do you wish to make an application for the study to be considered for NIHR Clinical Research Network (CRN) Support and inclusion in the NIHR Clinical Research Network Portfolio?

Please see information button for further details.

(•) Yes ( ) No

The NIHR Clinical Research Network provides researchers with the practical support they need to make clinical studies happen in the NHS e.g. by providing access to the people and facilities needed to carry out research "on the ground".

If you select yes to this question, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form (PAF) immediately after completing this project filter question and before submitting other applications. Failing to complete the PAF ahead of other applications e.g. HRA Approval, may mean that you will be unable to access NIHR CRN Support for your study.

6. Do you plan to include any participants who are children?

○ Yes ◉ No

7. Do you plan at any stage of the project to undertake intrusive research involving adults lacking capacity to consent for themselves?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the Confidentiality Advisory Group to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

8. Do you plan to include any participants who are prisoners or young offenders in the custody of HM Prison Service or who are offenders supervised by the probation service in England or Wales?

○ Yes ◉ No

9. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

10. Will this research be financially supported by the United States Department of Health and Human Services or any of its divisions, agencies or programs?

○ Yes ◉ No

11. Will identifiable patient data be accessed outside the care team without prior consent at any stage of the project (including identification of potential participants)?

○ Yes ◉ No

Integrated Research Application System
Application Form for Other clinical trial or investigation

IRAS Form (project information)

Please refer to the E-Submission and Checklist tabs for instructions on submitting this application.

The Chief Investigator should complete this form. Guidance on the questions is available wherever you see this symbol displayed. We recommend reading the guidance first. The complete guidance and a glossary are available by selecting Help.

Please define any terms or acronyms that might not be familar to lay reviewers of the application.

Short title and version number: (maximum 70 characters - this will be inserted as header on all forms)
OPTIMISE II

Please complete these details after you have booked the REC application for review.

REC Name:
London: Brent

REC Reference Number:
16/LO/2067

Submission date:
07/11/2016

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

Optimisation of Peri-operative Cardiovascular Management to Improve Surgical Outcome II (OPTIMISE II) Trial: Open, multi-centre, randomised controlled trial of cardiac output-guided fluid therapy with low dose inotrope infusion compared to usual care in patients undergoing major elective gastrointestinal surgery.

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Rupert	Pearse
Post	Professor of Intensive Care Medicine		
Qualifications	BSc(Hons) MBBS MD FRCA FFICM		
Employer	Queen Mary University of London		
Work Address	Adult Critical Care Unit, Royal London Hospital London		
Post Code	E1 1BB		
Work E-mail	r.pearse@qmul.ac.uk		
* Personal E-mail			
Work Telephone	+442035940346		

* Personal Telephone/Mobile	
Fax	+442035943140

** This information is optional. It will not be placed in the public domain or disclosed to any other third party without prior consent.*
A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application.

A4. Who is the contact on behalf of the sponsor for all correspondence relating to applications for this project?
This contact will receive copies of all correspondence from REC and HRA/R&D reviewers that is sent to the CI.

	Title	Forename/Initials	Surname
	Miss	Ann	Thomson
Address	Yvonne Carter Building		
	58 Turner Street		
	London		
Post Code	E1 2AB		
E-mail	ann.thomson@qmul.ac.uk		
Telephone	02078822556		
Fax			

A5-1. Research reference numbers. *Please give any relevant references for your study:*

Applicant's/organisation's own reference number, e.g. R & D (if available):

Sponsor's/protocol number:

Protocol Version:

Protocol Date:

Funder's reference number:

Project website:

Registry reference number(s):
The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

International Standard Randomised Controlled Trial Number (ISRCTN):

ClinicalTrials.gov Identifier (NCT number):

Additional reference number(s):

Ref.Number Description	Reference Number

A5-2. Is this application linked to a previous study or another current application?

○ Yes ◉ No

Please give brief details and reference numbers.

2. OVERVIEW OF THE RESEARCH

To provide all the information required by review bodies and research information systems, we ask a number of specific questions. This section invites you to give an overview using language comprehensible to lay reviewers and members of the public. Please read the guidance notes for advice on this section.

A6-1. Summary of the study. *Please provide a brief summary of the research (maximum 300 words) using language easily understood by lay reviewers and members of the public. Where the research is reviewed by a REC within the UK Health Departments' Research Ethics Service, this summary will be published on the Health Research Authority (HRA) website following the ethical review. Please refer to the question specific guidance for this question.*

We aim to resolve a long standing controversy in the care of patients undergoing major surgery by evaluating the safety and effectiveness of a technology called cardiac output monitoring in guiding the dose and timing of intra-venous fluid and powerful drugs which increase heart function.

Around 40,000 NHS patients aged 65 years and over undergo major planned gut surgery each year. After surgery, more than 12,000 patients develop hospital acquired infection, and 3,600 die within 180 days. Patients who survive complications to leave hospital commonly suffer a loss of mobility, independence and reduced long-term survival. Hospital acquired infections in this patient group cost the NHS more than £80 million each year. We know that complications after surgery are more likely if patients receive too much or too little intra-venous fluid (administered into a vein). The use of small doses of drugs that increase heart function (inotropic drugs) is also important. Currently, the type and dose of these drug treatments is decided by a doctor based on subjective assessment of the patient. Advanced cardiac monitoring technologies may provide a more reliable guide to the use of these treatments. However, only one third of eligible patients currently receive this treatment because many doctors are concerned this approach is more aggressive and may therefore harm some patients by causing small heart attacks. Only a large clinical trial can resolve this uncertainty, allowing us to provide this treatment to all eligible patients if beneficial, or withdraw it from use if ineffective or harmful.

We aim to confirm the effect of cardiac output guided therapy on the number of patients who develop hospital acquired infection within 30 days after major planned gastrointestinal surgery. We propose an international multi-centre clinical trial in 2502 patients aged 65 and over recruited over a three year period.

A6-2. Summary of main issues. *Please summarise the main ethical, legal, or management issues arising from your study and say how you have addressed them.*

Not all studies raise significant issues. Some studies may have straightforward ethical or other issues that can be identified and managed routinely. Others may present significant issues requiring further consideration by a REC, HRA, or other review body (as appropriate to the issue). Studies that present a minimal risk to participants may raise complex organisational or legal issues. You should try to consider all the types of issues that the different reviewers may need to consider.

There are few significant issues with the proposed trial.

Consent
We will only recruit patients with capacity to consent. Patients will be approached before surgery, and in the great majority of cases this will be in the pre-operative assessment clinic several days before surgery. This is preferable both for the patient and the investigators. However, some patients will arrive in hospital on the morning of surgery having not attended a pre-operative assessment clinic. Provided that all reasonable efforts have been made to identify a potential participant at least 24 hours in advance of surgery, they will still be eligible for recruitment within a shorter time frame if this has not proved possible.

Risks, burdens and benefits
Cardiac output-guided haemodynamic therapy has been used routinely in NHS hospitals for many years. It is likely that many patients enrolled in this trial will benefit. The treatment has a good safety record, and all eligible hospitals already employ trained staff to administer this intervention to this patients group according to well established protocols.

3. PURPOSE AND DESIGN OF THE RESEARCH

A7. Select the appropriate methodology description for this research. *Please tick all that apply*:

☐ Case series/ case note review

- ☐ Case control
- ☐ Cohort observation
- ☐ Controlled trial without randomisation
- ☐ Cross-sectional study
- ☐ Database analysis
- ☐ Epidemiology
- ☐ Feasibility/ pilot study
- ☐ Laboratory study
- ☐ Metanalysis
- ☐ Qualitative research
- ☐ Questionnaire, interview or observation study
- ☑ Randomised controlled trial
- ☐ Other (please specify)

A10. What is the principal research question/objective? *Please put this in language comprehensible to a lay person.*

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

A11. What are the secondary research questions/objectives if applicable? *Please put this in language comprehensible to a lay person.*

To determine whether cardiac output-guided haemodynamic therapy reduces other types of complications after surgery. These include kidney failure, heart attacks and death within 180 days of surgery. We will also determine the healthcare costs and cost-effectiveness of this intervention.

A12. What is the scientific justification for the research? *Please put this in language comprehensible to a lay person.*

Approximately 310 million surgical procedures are carried out worldwide each year. After surgery more than seven million patients develop complications with one million deaths. Estimates of postoperative mortality range from 1 to 4% depending on the population sampled and the type of surgical procedure. However, it is clear that mortality and morbidity following surgery is greater in high-risk populations, where patients have pre-existing medical conditions, are elderly or undergoing a major abdominal procedure. Hospital acquired infections are the most common complication after major gastrointestinal surgery, affecting 30% of this group. These infections have a major impact on hospital length of stay, short and long term mortality and healthcare costs.

We know that complications after surgery are more likely if patients receive too much or too little intravenous fluid (administered into a vein). The use of small doses of drugs that improve heart function (inotropic drugs) may also be important. Currently, the type and dose of these drug treatments is decided by a doctor based on subjective assessment of the patient. Advanced cardiac monitoring technologies now allow routine measurement of the amount of blood pumped around the body by the heart each minute. These measurements may provide a more reliable guide for dosing of intra-venous fluid and inotropic drugs and hence improve patient outcomes. However, only one third of eligible patients currently receive this treatment even though it has been recommended by the National Institute for Health and Care Excellence (NICE). This situation reflects genuine uncertainty amongst doctors regarding the potential benefit and harms of this treatment. A recent evidence based review of 38 (mostly small) clinical trials suggests the benefits of this treatment are less certain than previously thought. This uncertainty has been reinforced by a recent multi-centre trial (OPTIMISE), the findings of which suggest, but do not confirm, that cardiac output guided therapy is associated with reduced hospital acquired infection after surgery. However, the results also suggest the treatment may increase the number of patients who develop minor heart attacks. These findings could mean the treatment does not work but it may also be that the previous clinical trials are simply too small. This uncertainty must be resolved so we can either provide this treatment to all eligible patients (if beneficial) or withdraw it from routine use (if ineffective or harmful).

OPTIMISE II is a large international clinical trial to compare cardiac output guided intra-venous fluid and inotropic therapy with routine (usual) treatment for patients aged 65 years and over undergoing major gut surgery. We will recruit

2502 patients over three years in ten NHS hospitals and 40 other hospitals worldwide. In addition to hospital acquired infection, we will look at how many patients die within six months of surgery, the number of harmful cardiac events (possible side effect), kidney damage and patients' quality of life. We will incorporate a health economics analysis to determine the cost effectiveness of this treatment in the NHS.

A13. Please summarise your design and methodology. *It should be clear exactly what will happen to the research participant, how many times and in what order. Please complete this section in language comprehensible to the lay person. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

Study design
Randomised controlled trial with open study group allocation

Patients
We will recruit patients aged 65 and over with co-morbidities (American Society of Anesthesiologists score 2 or higher) scheduled for major elective surgery on the gastrointestinal tract expected to take longer than 90 minutes.

Randomisation
Randomisation will occur after the participant has provided informed consent but before the surgical procedure is due to start. It will occur on the day of surgery when surgery is confirmed. 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 by country and surgical procedure category. The surgical procedure categories are: resection of colon, rectum or small bowel; resection of pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery.

Trial intervention
The trial intervention period will commence at the start of general anaesthesia and continue for four hours after surgery is completed (maximum total duration: 24 hours). In the very unlikely event that surgery is prolonged we would disconnect the treatment after 24 hours (please note this is very unlikely to happen). Patients in the intervention group will receive intravenous fluid therapy according to a protocol based on readings from a cardiac output monitor, with a low dose infusion of a drug to improve heart function (inotrope). Edward Lifesciences will be providing the same cardiac output monitoring equipment to all participating sites. The device comprises of an EV1000 (monitor), ClearSight (non-invasive sensor) and FloTrac (invasive sensor)and sites will be using all three components. Patients in the usual care group will be managed by clinical staff according to local policy and guidelines.

Data collection
Patients will be assessed at screening, where the trial inclusion/exclusion criteria will be checked. Pre-operatively, demographic information, medical history, height/weight and quality of life will be assessed and the patient will be randomised. 24 hours post-operatively, intraoperative information, use of cardiac output guided haemodynamic therapy and adverse events will be assessed. On hospital discharge, there will be a review of the medical notes, days of ICU and hospital will be checked and adverse events will be assessed. 30 days and 180 days after randomisation, investigators will review the patient's medical record to assess specific postoperative complications and treatments for postoperative complications and contact the patient by telephone to conduct a brief interview and assess quality of life. To facilitate the health economic analysis, in terms of hospital episode data, and in cases where the participant is un-contactable during the follow-up period, we will request hospital episode statistics and mortality data from the NHS Digital for UK participants or equivalent national database for other participating countries. Prospective consent for ONS/HES data linkage will be sought before enrollment into the trial.

A14-1. In which aspects of the research process have you actively involved, or will you involve, patients, service users, and/or their carers, or members of the public?

- [x] Design of the research
- [x] Management of the research
- [x] Undertaking the research
- [x] Analysis of results
- [x] Dissemination of findings
- [ ] None of the above

Give details of involvement, or if none please justify the absence of involvement.
The OPTIMISE II proposal has been reviewed in detail by the Royal College of Anaesthetists Patient Carer and Public Involvement and Engagement (PCPIE) in Research Group which was formed to provide high quality guidance on

research proposals in the field of perioperative medicine. Detailed feedback from this group has informed both the design and conduct of the proposed trial.

The group agreed that the findings of the previous smaller trial (OPTIMISE) were not conclusive and require confirmation. Importantly, the recently completed James Lind Alliance Priority Setting Partnership for Anaesthesia and Perioperative Care has ranked this topic amongst the ten most important research questions in our field. This confirms the importance of this research question to both patients and clinicians.

The RCoA PCPIE group nominated Lauren Osborne to join the OPTIMISE II project group as a lay applicant. Lauren has been involved throughout the preparation of this application, providing detailed input and representing the views of the PCPIE group with respect to issues of safety and the experience of participating patients.

4. RISKS AND ETHICAL ISSUES

RESEARCH PARTICIPANTS

A15. What is the sample group or cohort to be studied in this research?

Select all that apply:

- [ ] Blood
- [ ] Cancer
- [ ] Cardiovascular
- [ ] Congenital Disorders
- [ ] Dementias and Neurodegenerative Diseases
- [ ] Diabetes
- [ ] Ear
- [ ] Eye
- [x] Generic Health Relevance
- [ ] Infection
- [ ] Inflammatory and Immune System
- [ ] Injuries and Accidents
- [ ] Mental Health
- [ ] Metabolic and Endocrine
- [ ] Musculoskeletal
- [ ] Neurological
- [ ] Oral and Gastrointestinal
- [ ] Paediatrics
- [ ] Renal and Urogenital
- [ ] Reproductive Health and Childbirth
- [ ] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 65	Years
Upper age limit:	Years

A17-1. Please list the principal inclusion criteria (list the most important, max 5000 characters).

1. Aged 65 years or over
2. Undergoing major elective surgery on the gastrointestinal tract that is expected to take longer than 90 minutes.

A17-2. Please list the principal exclusion criteria (list the most important, max 5000 characters).

1. Inability or refusal of patient consent
2. Clinician refusal
3. American Society of Anesthesiologists (ASA) score of I
4. Patients expected to die within 30 days
5. Acute myocardial ischaemia within 30 days prior to randomisation
6. Acute pulmonary oedema within 30 days prior to randomisation
7. Contra-indication to low-dose inotropic medication
8. Pregnancy at time of enrolment
9. Previous enrolment in the OPTIMISE II trial

RESEARCH PROCEDURES, RISKS AND BENEFITS

A18. Give details of all non-clinical intervention(s) or procedure(s) that will be received by participants as part of the research protocol. *These include seeking consent, interviews, non-clinical observations and use of questionnaires.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days)
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Informed consent	1	0	30 minutes	Appropriately trained member of the research team
EQ-5D-3L questionnaire	3	0	15 minutes	Appropriately trained member of the research team
Telephone follow-up	2	0	10 minutes	Appropriately trained member of the research team

A19. Give details of any clinical intervention(s) or procedure(s) to be received by participants as part of the research protocol. *These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material. Include procedures which might be received as routine clinical care outside of the research.*

Please complete the columns for each intervention/procedure as follows:

1. Total number of interventions/procedures to be received by each participant as part of the research protocol.
2. If this intervention/procedure would be routinely given to participants as part of their care outside the research, how many of the total would be routine?
3. Average time taken per intervention/procedure (minutes, hours or days).
4. Details of who will conduct the intervention/procedure, and where it will take place.

Intervention or procedure	1	2	3	4
Cardiac output-guided haemodynamic therapy	1	0	max 24 hours	Appropriately trained member of clinical staff as part of the patient's direct clinical care team

A20. Will you withhold an intervention or procedure, which would normally be considered a part of routine care?

○ Yes ◉ No

A21. How long do you expect each participant to be in the study in total?

After informed consent, the study period will begin. Postoperative follow up will continue until 180 days after the date of randomisation.

A22. What are the potential risks and burdens for research participants and how will you minimise them?

For all studies, describe any potential adverse effects, pain, discomfort, distress, intrusion, inconvenience or changes to lifestyle. Only describe risks or burdens that could occur as a result of participation in the research. Say what steps would be taken to minimise risks and burdens as far as possible.

Previous research suggests that the treatment we are investigating will benefit the majority of patients. The risks of this study to patient health are very small. Cardiac output-guided haemodynamic therapy is used in around a third of patients undergoing major surgery already, and the fluids and inotropic drugs within the protocol are in routine clinical use. In a small number of cases there may be temporary side effects such as an increase in heart rate or irritation of the vein. The trial intervention will only be administered by trained clinical staff according to local hospital policies in an appropriate clinical area.

Adverse events will be assessed by the Data Monitoring and Ethics Committee (DMEC) and the Trial Management Group (TMG) using serious adverse event report assessment. The DMEC is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The DMEC will perform a single interim analysis as it sees fit. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile.

A23. Will interviews/ questionnaires or group discussions include topics that might be sensitive, embarrassing or upsetting, or is it possible that criminal or other disclosures requiring action could occur during the study?

○ Yes ◉ No

A24. What is the potential for benefit to research participants?

The findings of several trials have demonstrated the efficacy of cardiac output-guided haemodynamic therapy as a treatment for high-risk patients during and after gastrointestinal surgery by reducing the incidence of postoperative infections and other complications.

The information learned from this trial is likely to result in safer surgery for future patients.

A25. What arrangements are being made for continued provision of the intervention for participants, if appropriate, once the research has finished? *May apply to any clinical intervention, including a drug, medical device, mental health intervention, complementary therapy, physiotherapy, dietary manipulation, lifestyle change, etc.*

Any further treatment will be decided by the treating clinician.

A26. What are the potential risks for the researchers themselves? *(if any)*

None anticipated.

RECRUITMENT AND INFORMED CONSENT

In this section we ask you to describe the recruitment procedures for the study. Please give separate details for different study groups where appropriate.

A27-1. How will potential participants, records or samples be identified? Who will carry this out and what resources will be used?*For example, identification may involve a disease register, computerised search of GP records, or review of*

medical records. Indicate whether this will be done by the direct healthcare team or by researchers acting under arrangements with the responsible care organisation(s).

Patients will be identified and approached by a member of the research team before surgery. Potential participants will be screened by research staff at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff. Members of the research team are considered part of the patient's direct clinical care team.

A27-2. Will the identification of potential participants involve reviewing or screening the identifiable personal information of patients, service users or any other person?

◉ Yes ○ No

Please give details below:
Members of the research team, who also form part of the patient's direct clinical care team, at the participating sites will have access to patient records as part of their medical care and will use these records to screen for potentially eligible patients. Patients who consent to enter the trial are informed that staff from the research team, the sponsor (and its representatives), relevant regulatory authorities, or from the NHS Trust/Health Board may require access to their full medical records for monitoring and auditing purposes.

A27-3. Describe what measures will be taken to ensure there is no breach of any duty of confidentiality owed to patients, service users or any other person in the process of identifying potential participants.*Indicate what steps have been or will be taken to inform patients and service users of the potential use of their records for this purpose. Describe the arrangements to ensure that the wishes of patients and service users regarding access to their records are respected. Please consult the guidance notes on this topic.*

The paper data collection sheets will be stored securely in a locked cupboard and handled only by members of the research team. They are familiar will handling and storage of personal data and work in accordance with Good clinical Practice Guidance and the Data Protection Act. Computer security is maintained through user names and frequently updated passwords and back up procedures are in place.

A27-4. Will researchers or individuals other than the direct care team have access to identifiable personal information of any potential participants?

◉ Yes ○ No

A27-5. Has prior consent been obtained or will it be obtained for access to identifiable personal information?

◉ Yes ○ No

If Yes, please give details below.

UK participants will be asked to give consent for their Name, NHS Number, Date of Birth and Postcode to be collected and stored in a secure electronic environment. This data will be sent to NHS Digital at the end of the study for linkage with ONS and HES databases in order to obtain study outcomes. Access to this data will be highly restricted, it will be limited to (a) members of the clinical care team who are entering the data and (b) a member of the research team who will extract and send the data to NHS digital. The data that NHS Digital will return to the research team for analysis will be striped of all patient identifiers.

A28. Will any participants be recruited by publicity through posters, leaflets, adverts or websites?

○ Yes ◉ No

A29. How and by whom will potential participants first be approached?

The majority of potential participants will be approached regarding involvement in the trial at a pre-admission clinic appointment or in the admissions unit prior to surgery. Where this is not possible, potential participants may be approached by their own doctor or nurse, followed by a telephone call with one of the research team to discuss

participation in the trial further. Each member of the research team has experience in obtaining informed consent and is Good Clinical Practice trained.

A30-1. Will you obtain informed consent from or on behalf of research participants?

◉ Yes ○ No

If you will be obtaining consent from adult participants, please give details of who will take consent and how it will be done, with details of any steps to provide information (a written information sheet, videos, or interactive material). Arrangements for adults unable to consent for themselves should be described separately in Part B Section 6, and for children in Part B Section 7.

If you plan to seek informed consent from vulnerable groups, say how you will ensure that consent is voluntary and fully informed.

Written informed consent will be obtained by a member of the local research team after the participant has had the opportunity to read a participant information sheet, ask questions and consider their participation. If they wish to participate they will then sign the patient consent form. Each member of the research team has experience in obtaining informed consent and is GCP trained.

If you are not obtaining consent, please explain why not.

Please enclose a copy of the information sheet(s) and consent form(s).

A30-2. Will you record informed consent (or advice from consultees) in writing?

◉ Yes ○ No

A31. How long will you allow potential participants to decide whether or not to take part?

Where possible participants will be approached in advance of their surgical procedure in order to provide them with an information sheet to read days in advance. However, it is inevitable that a small number of eligible patients will arrive in hospital on the day of surgery without having previously attended pre-operative assessment clinic. Where it was not possible to approach the patient before the day of surgery, these patients will still be eligible to participate in the trial provided appropriate efforts had been made to approach them at an earlier stage.

A32. Will you recruit any participants who are involved in current research or have recently been involved in any research prior to recruitment?

◉ Yes

○ No

○ Not Known

If Yes, please give details and justify their inclusion. If Not Known, what steps will you take to find out?

We will recruit patients who are currently enrolled in other trials as long as the trial does not have a similar biological mechanism or related primary outcome measure. However, we will only ask such participants to take part after careful consideration of the total burden of research participation.

A33-1. What arrangements have been made for persons who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?*(e.g. translation, use of interpreters)*

Where necessary a translator will be used to take consent. In each centre there are many healthcare professionals who can assist in this respect.

A33-2. What arrangements will you make to comply with the principles of the Welsh Language Act in the provision of information to participants in Wales?

Effort will be made to enroll all eligible patients into the trial. If local interpreters are not available at the hospital and

fully informed consent is not deemed possible, the patient would not be considered for the study.

Individual sites may translate patient information sheets and consent forms according to local needs but these will also need to be back-translated. Translations and back translations should be submitted for ethics approval prior to being used at site.

A34. What arrangements will you make to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?

The intervention will last for a maximum of 24 hours and usually much less than this. It is extremely unlikely that new safety information will arise during the intervention period. Nonetheless, should this situation arise, participants will be informed and asked if they wish to discontinue the intervention. 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.

A35. What steps would you take if a participant, who has given informed consent, loses capacity to consent during the study? *Tick one option only.*

- ○ The participant and all identifiable data or tissue collected would be withdrawn from the study. Data or tissue which is not identifiable to the research team may be retained.
- ○ The participant would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant.
- ○ The participant would continue to be included in the study.
- ○ Not applicable – informed consent will not be sought from any participants in this research.
- ◉ Not applicable – it is not practicable for the research team to monitor capacity and continued capacity will be assumed.

Further details:
Patients will not have capacity during surgery or in cases where sedation is continued after the end of surgery.

CONFIDENTIALITY

In this section, personal data means any data relating to a participant who could potentially be identified. It includes pseudonymised data capable of being linked to a participant through a unique code number.

Storage and use of personal data during the study

A36. Will you be undertaking any of the following activities at any stage (including in the identification of potential participants)?*(Tick as appropriate)*

- ☑ Access to medical records by those outside the direct healthcare team
- ☐ Access to social care records by those outside the direct social care team
- ☑ Electronic transfer by magnetic or optical media, email or computer networks
- ☑ Sharing of personal data with other organisations
- ☐ Export of personal data outside the EEA
- ☑ Use of personal addresses, postcodes, faxes, emails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☑ Storage of personal data on any of the following:

- [x] Manual files (includes paper or film)
- [x] NHS computers
- [ ] Social Care Service computers
- [ ] Home or other personal computers
- [x] University computers
- [ ] Private company computers
- [ ] Laptop computers

Further details:
The research team will have access to the medical records in order to record the preoperative and postoperative outcome data. Paper (case report forms) CRFs will be stored in a locked NHS office.

Some coded data will be stored on NHS password protected computers.

University computers will not be used to store patient identifiable information under any circumstances.

The database (data entry web portal) will be hosted by the Pragmatic Clinical Trials Unit, which uses a safe haven to store data. The unit has Information Governance Toolkit level 3.

A37. Please describe the physical security arrangements for storage of personal data during the study?

Data will be transcribed on to the paper CRF prior to entry on to the secure OPTIMISE II data entry web portal. Submitted data will be reviewed for completeness and consistency by authorised users within the study group. Submitted data will be stored securely against unauthorised manipulation and accidental loss since only authorised users at site, the Sponsor organisation or at Queen Mary University of London (host of the data entry portal) will have access. Desktop security is maintained through user names and frequently updated passwords. Data 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 (UK).

A38. How will you ensure the confidentiality of personal data?*Please provide a general statement of the policy and procedures for ensuring confidentiality, e.g. anonymisation or pseudonymisation of data.*

All data will be pseudo−anonymised or coded wherever possible. To facilitate linkage to national databases for the collection of follow-up data, patient identifiable data will be collected and entered on to the secure data entry web portal. Data will be stored and handled in accordance with the Data Protection Act 1998 (UK) or equivalent legislation for a particular country or site. In the event that patient identifiable data needs to be transferred between authorised users, this will occur by email from @nhs.net to @nhs.net accounts in the UK or equivalent secure email transfer other countries. The data will be stored and kept for a maximum of 20 years as per trust policy.

A40. Who will have access to participants' personal data during the study? *Where access is by individuals outside the direct care team, please justify and say whether consent will be sought.*

Members of the research team and R&D staff for the purpose of audit and monitoring will have access to the patients' personal data on the data sheets during the study. Consent will be sought for this.

Storage and use of data after the end of the study

A41. Where will the data generated by the study be analysed and by whom?

Trial data will be analysed by a statistician at Queen Mary University of London.

A42. Who will have control of and act as the custodian for the data generated by the study?

	Title	Forename/Initials	Surname
	Professor	Rupert	Pearse
Post	Professor of Intensive Care Medicine		
Qualifications	MBBS BSc FRCA MD FFICM		
Work Address	Adult Critical Care Unit		
	The Royal London Hospital		
	Whitechapel		
Post Code	E1 1BB		
Work Email	r.pearse@qmul.ac.uk		
Work Telephone	02035940352		
Fax	02035940352		

A43. How long will personal data be stored or accessed after the study has ended?

- ○ Less than 3 months
- ○ 3 – 6 months
- ○ 6 – 12 months
- ○ 12 months – 3 years
- ◉ Over 3 years

If longer than 12 months, please justify:
20 years in line with local policy.

A44. For how long will you store research data generated by the study?

Years: 20
Months:

A45. Please give details of the long term arrangements for storage of research data after the study has ended.*Say where data will be stored, who will have access and the arrangements to ensure security.*

The data will be archived for 20 years in accordance with local standards and Queen Mary University London procedures for quality & assurance. Accessed by members of the research study team.

INCENTIVES AND PAYMENTS

A46. Will research participants receive any payments, reimbursement of expenses or any other benefits or incentives for taking part in this research?

○ Yes ◉ No

A47. Will individual researchers receive any personal payment over and above normal salary, or any other benefits or incentives, for taking part in this research?

○ Yes ◉ No

A48. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

◯ Yes ◉ No

NOTIFICATION OF OTHER PROFESSIONALS

A49-1. Will you inform the participants' General Practitioners (and/or any other health or care professional responsible for their care) that they are taking part in the study?

◉ Yes ◯ No

If Yes, please enclose a copy of the information sheet/letter for the GP/health professional with a version number and date.

A49-2. Will you seek permission from the research participants to inform their GP or other health/ care professional?

◉ Yes ◯ No

It should be made clear in the participant's information sheet if the GP/health professional will be informed.

PUBLICATION AND DISSEMINATION

A50. Will the research be registered on a public database?

The Department of Health's Research Governance Framework for Health and Social Care and the research governance frameworks for Wales, Scotland and Northern Ireland set out the requirement for registration of trials. Furthermore: Article 19 of the World Medical Association Declaration of Helsinki adopted in 2008 states that "every clinical trial must be registered on a publicly accessible database before recruitment of the first subject"; and the International Committee of Medical Journal Editors (ICMJE) will consider a clinical trial for publication only if it has been registered in an appropriate registry. Please see guidance for more information.

◉ Yes ◯ No

Please give details, or justify if not registering the research.
ISRCTN registration
Protocol will be published
Statistical analysis plan will be published

Please ensure that you have entered registry reference number(s) in question A5-1.

A51. How do you intend to report and disseminate the results of the study?*Tick as appropriate:*

☑ Peer reviewed scientific journals
☐ Internal report
☑ Conference presentation
☑ Publication on website
☐ Other publication
☐ Submission to regulatory authorities
☑ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
☐ No plans to report or disseminate the results
☐ Other (please specify)

A52. If you will be using identifiable personal data, how will you ensure that anonymity will be maintained when publishing the results?

Only summary/aggregated data will be presented. No individual patient data will be included in any of the study outputs.

A53. Will you inform participants of the results?

(●) Yes ( ) No

Please give details of how you will inform participants or justify if not doing so.
A copy of the scientific report will be available to any participant who requests it.

5. Scientific and Statistical Review

A54. How has the scientific quality of the research been assessed?*Tick as appropriate:*

- [x] Independent external review
- [ ] Review within a company
- [x] Review within a multi−centre research group
- [x] Review within the Chief Investigator's institution or host organisation
- [x] Review within the research team
- [ ] Review by educational supervisor
- [ ] Other

Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:
The proposal has undergone internal and external peer review.

For all studies except non-doctoral student research, please enclose a copy of any available scientific critique reports, together with any related correspondence.

For non-doctoral student research, please enclose a copy of the assessment from your educational supervisor/ institution.

A56. How have the statistical aspects of the research been reviewed?*Tick as appropriate:*

- [ ] Review by independent statistician commissioned by funder or sponsor
- [ ] Other review by independent statistician
- [ ] Review by company statistician
- [x] Review by a statistician within the Chief Investigator's institution
- [x] Review by a statistician within the research team or multi−centre group
- [ ] Review by educational supervisor
- [ ] Other review by individual with relevant statistical expertise
- [ ] No review necessary as only frequencies and associations will be assessed – details of statistical input not required

In all cases please give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title	Forename/Initials	Surname
	Mr	Brennan	Kahan
Department	Pragmatic Clinical Trials Unit		
Institution	Queen Mary University of London		
Work Address	58 Turner St		

	London
Post Code	E1 2AB
Telephone	
Fax	
Mobile	
E-mail	b.kahan@qmul.ac.uk

Please enclose a copy of any available comments or reports from a statistician.

A57. What is the primary outcome measure for the study?

Difference in the number of patients developing post-operative infections within 30 days following randomisation between treatment arms.

A58. What are the secondary outcome measures?*(if any)*

• Difference in 180-day post-operative mortality between treatment arms
• Difference in the number of patients developing acute kidney injury within 30 days following randomisation
• Difference in the number of patients developing acute cardiac event at 24 hours and 30 days following randomisation (safety outcome)
• Difference in Quality-Adjusted Life Years, assessed at 180-days following randomisation (UK arm only)
• Mean cost from the perspective of NHS at 180 days post-randomisation
• Incremental cost-effectiveness ratio

In addition, we will use the following process measures:
• Days in critical care
• Duration of hospital stay

A59. What is the sample size for the research? *How many participants/samples/data records do you plan to study in total? If there is more than one group, please give further details below.*

Total UK sample size:	1251
Total international sample size (including UK):	2502
Total in European Economic Area:	1502

Further details:
Remaining participants (1000) to be recruited in North America

A60. How was the sample size decided upon? *If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

In order to detect a 5% absolute reduction (from 30% to 25%) for the primary outcome of postoperative infection up to 30 days (a risk ratio of 0.83), with 80% power, and an overall type I error rate of 5%, we require 2502 patients (1251 per arm). This sample size would also allow us to detect an absolute reduction in the primary outcome of 6% (from 30% to 24%) with 92% power.

A61. Will participants be allocated to groups at random?

◉ Yes ○ No

If yes, please give details of the intended method of randomisation:
Randomisation will occur after the participant has provided informed consent but before the surgical procedure is due to start. Participants will be centrally allocated to treatment groups in a 1:1 ratio by minimisation with a random component. Minimisation variables will be country, surgical procedure category, and ASA grade. The surgical procedure categories are: resection of colon, rectum or small bowel; resection of pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery. ASA grades are: II, III, IV, and V. Each participant will be allocated with 80% probability to the group that minimises the 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 II trial, research staff at the site will log on to a secure web-based randomisation and data entry platform hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. A patients treatment allocation will only be revealed to the research staff at the site following randomisation.

A62. Please describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.

Statistical analysis

Analyses will be performed according to intention-to-treat; all patients with a recorded outcome will be included in the analysis, and analysed according to the treatment to which they were randomised. Summary statistics by group, treatment effects, 95% confidence intervals, and p-values will be presented for primary and secondary outcomes, and process measures. Baseline and all other follow up data for the two groups will be summarised by treatment arm, but not subjected to statistical testing.

The primary outcome of postoperative infection within 30 days from randomisation will be analysed using a mixed-effects logistic regression model with a random intercept for country. The model will adjust for procedure category, age, gender, ASA grade, baseline haemoglobin, and baseline creatinine. ASA grade will be included as a categorical variable with categories, II, III, and IV and V. Age, baseline haemoglobin, and baseline creatinine will be adjusted for using restricted cubic splines with three knots, and knot locations based on Harell's recommendations. Missing baseline data will be accounted for using mean imputation. A statistical analysis plan will be written prior to any data analysis taking place and any member of the trial team having access to unblinded data.

HEALTH ECONOMIC ANALYSIS INSERT HERE

6. MANAGEMENT OF THE RESEARCH

A63. Other key investigators/collaborators. *Please include all grant co−applicants, protocol co−authors and other key members of the Chief Investigator's team, including non-doctoral student researchers.*

	Title	Forename/Initials	Surname
	Dr	Mark	Edwards
Post	Consultant in Anaesthesia		
Qualifications	BMedSci BMBS MRCP FRCA MD(Res)		
Employer	University Hospital Southampton NHS Foundation Trust		
Work Address	Department of Anaesthesia Southampton General Hospital Tremona Road, Southampton		
Post Code	SO16 6YD		
Telephone	07702 744753		
Fax			
Mobile	07702 744753		
Work Email	mark.edwards2@uhs.nhs.uk		

	Title	Forename/Initials	Surname
	Dr	Andrew	Rhodes
Post	Consultant in Anaesthesia and Intensive Care Medicine		
Qualifications	MBBS MD (Res.) FFICM FRCP FRCA		
Employer	St. Georges Healthcare NHS Trust		
Work Address	Blackshaw Road Tooting		

	London
Post Code	SW17 0QT
Telephone	0208 725 5699
Fax	
Mobile	
Work Email	andrewrhodes@nhs.net

Title	Forename/Initials	Surname
Dr	Tom	Abbott

Post	Clinical Research Fellow in Perioperative Medicine
Qualifications	BA BM BCh MRCP
Employer	Barts Health NHS Trust
Work Address	Adult Critical Care Research Office, Room 14, Central Tower Royal London Hospital Whitechapel
Post Code	E1 1BB
Telephone	0203 59 40352
Fax	
Mobile	
Work Email	tom.abbott@bartshealth.nhs.uk

A64. Details of research sponsor(s)

A64-1. Sponsor

Lead Sponsor

Status:
- ○ NHS or HSC care organisation
- ◉ Academic
- ○ Pharmaceutical industry
- ○ Medical device industry
- ○ Local Authority
- ○ Other social care provider (including voluntary sector or private organisation)
- ○ Other

Commercial status: Non-Commercial

If Other, please specify:

Contact person

Name of organisation	Queen Mary University of London
Given name	Sally
Family name	Burtles
Address	Joint Research Management Office (JRMO), Queen Mary Innovation Centre, LG Floor, 5 Walden St
Town/city	London
Post code	E1 2EF

Country	UNITED KINGDOM
Telephone	020 7882 7250
Fax	020 7882 7276
E-mail	s.burtles@qmul.ac.uk

Is the sponsor based outside the UK?

◯ Yes ◉ No

Under the Research Governance Framework for Health and Social Care, a sponsor outside the UK must appoint a legal representative established in the UK. Please consult the guidance notes.

A65. Has external funding for the research been secured?

☑ Funding secured from one or more funders

☐ External funding application to one or more funders in progress

☐ No application for external funding will be made

What type of research project is this?

◯ Standalone project

◯ Project that is part of a programme grant

◯ Project that is part of a Centre grant

◉ Project that is part of a fellowship/ personal award/ research training award

◯ Other

Other – please state:

Please give details of funding applications.

Organisation	NIHR Trainee's co-ordinating centre
Address	Leeds Innovation Centre 103 Clarendon Road Leeds
Post Code	LS2 9DF
Telephone	0113 346 6260
Fax	
Mobile	
Email	

Funding Application Status: ◉ Secured ◯ In progress

Amount: £1,300,000.00

Duration

Years: 5

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

Organisation	Edwards Lifesciences Corporation
Address	1 Edwards Way
	Irvine
	California
Post Code	CA 92614
Telephone	+1 949-250-2500
Fax	+1 949-250-2525
Mobile	
Email	

Funding Application Status: (•) Secured ( ) In progress

Amount: £1,100,000.00

Duration

Years: 4

Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?

'Edwards Lifesciences open access project grant'

A66. Has responsibility for any specific research activities or procedures been delegated to a subcontractor (other than a co-sponsor listed in A64-1) ? *Please give details of subcontractors if applicable.*

( ) Yes (•) No

A67. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK or another country?

( ) Yes (•) No

Please provide a copy of the unfavourable opinion letter(s). You should explain in your answer to question A6-2 how the reasons for the unfavourable opinion have been addressed in this application.

A68-1. Give details of the lead NHS R&D contact for this research:

Title	Forename/Initials	Surname
Dr	Sally	Burtles

Organisation	Queen Mary University of London
Address	Queen Mary University of London
	Joint R&D Office
	5 Walden Street, London
Post Code	E1 2EF
Work Email	sponsorsrep@bartshealth.nhs.uk
Telephone	020 7882 7250
Fax	020 7882 7276

Mobile

Details can be obtained from the NHS R&D Forum website: http://www.rdforum.nhs.uk

A68-2. Select Local Clinical Research Network for NHS Organisation identified in A68-1:

North Thames

For more information, please refer to the question specific guidance.

A69-1. How long do you expect the study to last in the UK?

Planned start date: 15/12/2016
Planned end date: 14/12/2020
Total duration:
Years: 4 Months: 0 Days: 0

A71-1. Is this study?

- ○ Single centre
- ◉ Multicentre

A71-2. Where will the research take place? *(Tick as appropriate)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland
- ☑ Other countries in European Economic Area

Total UK sites in study 10

Number of sites anticipated in the Community 50

Does this trial involve countries outside the EU?

◉ Yes ○ No

- ☑ USA
- ☑ Other international (please specify)

Canada

A72. Which organisations in the UK will host the research?*Please indicate the type of organisation by ticking the box and give approximate numbers if known:*

☑ NHS organisations in England	8
☑ NHS organisations in Wales	1
☑ NHS organisations in Scotland	1
☐ HSC organisations in Northern Ireland	

☐ GP practices in England
☐ GP practices in Wales
☐ GP practices in Scotland
☐ GP practices in Northern Ireland
☐ Joint health and social care agencies (eg community mental health teams)
☐ Local authorities
☐ Phase 1 trial units
☐ Prison establishments
☐ Probation areas
☐ Independent (private or voluntary sector) organisations
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

Total UK sites in study: 10

A73-1. Will potential participants be identified through any organisations other than the research sites listed above?

○ Yes ◉ No

A74. What arrangements are in place for monitoring and auditing the conduct of the research?

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 safety reporting. The OPTIMISE II Trial Management Group will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective.

A75-1. What arrangements will be made to review interim safety and efficacy data from the trial? Will a formal data monitoring committee or equivalent body be convened?

A Data Monitoring and Ethics Committee (DMEC) will be appointed. 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 will perform a single interim analysis as it sees fit. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.

If a formal DMC is to be convened, please forward details of the membership and standard operating procedures to the Research Ethics Committee when available. The REC should also be notified of DMC recommendations and receive summary reports of interim analyses.

A75-2. What are the criteria for electively stopping the trial or other research prematurely?

The Trial Steering Committee will decide if the trial should be stopped early. They will review any recommendation from the Data Monitoring and Ethics Committee and will make any decisions in continuing or stopping the trial, or modifying the protocol.

A76. Insurance/ indemnity to meet potential legal liabilities

***Note:** in this question to NHS indemnity schemes include equivalent schemes provided by Health and Social Care (HSC) in Northern Ireland*

A76-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research? *Please tick box(es) as applicable.*

Note: Where a NHS organisation has agreed to act as sponsor or co-sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (NHS sponsors only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Queen Mary University of London Indemnity arrangements will apply.

Please enclose a copy of relevant documents.

A76-2. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research? *Please tick box(es) as applicable.*

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), please describe the arrangements and provide evidence.

- ☐ NHS indemnity scheme will apply (protocol authors with NHS contracts only)
- ☑ Other insurance or indemnity arrangements will apply (give details below)

Queen Mary University of London Indemnity arrangements will apply.

Please enclose a copy of relevant documents.

A76-3. What arrangements will be made for insurance and/ or indemnity to meet the potential legal liability of investigators/collaborators arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through the NHS schemes or through professional indemnity. Indicate if this applies to the whole study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, please describe the arrangements which will be made at these sites and provide evidence.

- ☑ NHS indemnity scheme or professional indemnity will apply (participants recruited at NHS sites only)
- ☐ Research includes non-NHS sites (give details of insurance/ indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

A77. Has the sponsor(s) made arrangements for payment of compensation in the event of harm to the research participants where no legal liability arises?

○ Yes ◉ No

Please enclose a copy of relevant documents.

A78. Could the research lead to the development of a new product/process or the generation of intellectual property?

○ Yes ◉ No ○ Not sure

PART C: Overview of research sites

Please enter details of the host organisations (Local Authority, NHS or other) in the UK that will be responsible for the research sites. *For NHS sites, the host organisation is the Trust or Health Board. Where the research site is a primary care site, e.g. GP practice, please insert the host organisation (PCT or Health Board) in the Institution row and insert the research site (e.g. GP practice) in the Department row.*

Investigator identifier	Research site		Investigator Name	
IN1	(●) NHS site ( ) Non-NHS site Country: England	Organisation name Address Post Code	BARTS AND THE LONDON NHS TRUST TRUST OFFICES, WHITECHAPEL THE ROYAL LONDON HOSPITAL WHITECHAPEL LONDON GREATER LONDON E1 1BB	Forename Middle name Family name Email Qualification (MD...) Country	NEIL MACDONALD n.macdonald2@nhs.net MBBS UNITED KINGDOM
IN6	(●) NHS site ( ) Non-NHS site Country: England	Organisation name Address Post Code	SOUTHAMPTON UNIVERSITY HOSPITALS NHS TRUST MAILPOINT 18 SOUTHAMPTON GENERAL HOSPITAL TREMONA ROAD SOUTHAMPTON HAMPSHIRE SO16 6YD	Forename Middle name Family name Email Qualification (MD...) Country	MARK EDWARDS Mark.Edwards2@uhs.nhs.uk BMedSci BMBS MRCP FRCA MD(Res) UNITED KINGDOM
IN2	(●) NHS site ( ) Non-NHS site			Forename Middle name Family name	MORT KELLEHER

Country: Scotland

Email	v1mkell3@exseed.ed.ac.uk
Qualification (MD...)	MBBS
Country	UNITED KINGDOM

Institution name	NHS LOTHIAN
Department name	ROYAL INFIRMARY OF EDINBURGH
Street address	51 LITTLE FRANCE CRESCENT
Town/city	EDINBURGH
Post Code	EH16 4SA

IN3

(●) NHS site
( ) Non-NHS site

Country: England

Forename	THOMAS
Middle name	
Family name	OWEN
Email	Thomas.Owen@lthtr.nhs.uk
Qualification (MD...)	MBBS
Country	UNITED KINGDOM

Organisation name	LANCASHIRE TEACHING HOSPITALS NHS FOUNDATION TRUST
Address	CHIEF EXECUTIVE'S OFFICE ROYAL PRESTON HOSPITAL SHAROE GREEN LANE, FULWOOD PRESTON LANCASHIRE
Post Code	PR2 9HT

IN4

(●) NHS site
( ) Non-NHS site

Country: Wales

Forename	TAMAS
Middle name	
Family name	SZAKMANY
Email	tamas.szakmany@wales.nhs.uk
Qualification (MD...)	MBBS
Country	UNITED KINGDOM

Institution name	ANEURIN BEVAN LOCAL HEALTH BOARD
Department name	ROYAL GWENT HOSPITAL
Street address	CARDIFF ROAD
Town/city	NEWPORT
Post Code	NP20 2UB

IN1

(●) NHS site
( ) Non-NHS site

Country: England

Forename	Mark
Middle name	
Family name	Blunt
Email	mark.blunt@qehkl.nhs.uk
Qualification (MD...)	MBBS

			Country	UNITED KINGDOM
	Organisation name	THE QUEEN ELIZABETH HOSPITAL, KING'S LYNN. NHS FOUNDATION TRUST		
	Address	QUEEN ELIZABETH HOSPITAL GAYTON ROAD KINGS LYNN NORFOLK		
	Post Code	PE30 4ET		

IN2

(●) NHS site
( ) Non-NHS site

Country: England

			Forename	Richard
			Middle name	
			Family name	Innes
			Email	richard.innes@tst.nhs.uk
			Qualification (MD...)	MBBS
			Country	UNITED KINGDOM
	Organisation name	TAUNTON AND SOMERSET NHS FOUNDATION TRUST		
	Address	MUSGROVE PARK HOSPITAL TAUNTON SOMERSET		
	Post Code	TA1 5DA		

IN3

(●) NHS site
( ) Non-NHS site

Country: England

			Forename	Ben
			Middle name	
			Family name	Attwood
			Email	ben.attwood@swft.nhs.uk
			Qualification (MD...)	MBBS
			Country	UNITED KINGDOM
	Organisation name	SOUTH WARWICKSHIRE NHS FOUNDATION TRUST		
	Address	WARWICK HOSPITAL LAKIN ROAD WARWICK WARWICKSHIRE		
	Post Code	CV34 5BW		

PART D: Declarations

D1. Declaration by Chief Investigator

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

3. If the research is approved I undertake to adhere to the study protocol, the terms of the full application as approved and any conditions set out by review bodies in giving approval.

4. I undertake to notify review bodies of substantial amendments to the protocol or the terms of the approved application, and to seek a favourable opinion from the main REC before implementing the amendment.

5. I undertake to submit annual progress reports setting out the progress of the research, as required by review bodies.

6. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer. I understand that I am not permitted to disclose identifiable data to third parties unless the disclosure has the consent of the data subject or, in the case of patient data in England and Wales, the disclosure is covered by the terms of an approval under Section 251 of the NHS Act 2006.

7. I understand that research records/data may be subject to inspection by review bodies for audit purposes if required.

8. I understand that any personal data in this application will be held by review bodies and their operational managers and that this will be managed according to the principles established in the Data Protection Act 1998.

9. I understand that the information contained in this application, any supporting documentation and all correspondence with review bodies or their operational managers relating to the application:

    - Will be held by the REC (where applicable) until at least 3 years after the end of the study; and by NHS R&D offices (where the research requires NHS management permission) in accordance with the NHS Code of Practice on Records Management.
    - May be disclosed to the operational managers of review bodies, or the appointing authority for the REC (where applicable), in order to check that the application has been processed correctly or to investigate any complaint.
    - May be seen by auditors appointed to undertake accreditation of RECs (where applicable).
    - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
    - May be sent by email to REC members.

10. I understand that information relating to this research, including the contact details on this application, may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.

11. I understand that the main REC or its operational managers may share information in this application or supporting documentation with the Medicines and Healthcare products Regulatory Agency (MHRA) where it is relevant to the Agency's statutory responsibilities.

12. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named below. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

Contact point for publication*(Not applicable for R&D Forms)*

NRES would like to include a contact point with the published summary of the study for those wishing to seek further information. We would be grateful if you would indicate one of the contact points below.

- ○ Chief Investigator
- ○ Sponsor
- ◉ Study co-ordinator
- ○ Student
- ○ Other – please give details
- ○ None

Access to application for training purposes *(Not applicable for R&D Forms)*

Optional – please tick as appropriate:

☑ I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

This section was signed electronically by Dr Rupert Pearse on 07/11/2016 10:49.

Job Title/Post:	Professor of Intensive Care Medicine
Organisation:	Queen Mary University of London
Email:	r.pearse@qmul.ac.uk

D2. Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co−sponsors by a representative of the lead sponsor named at A64-1.

I confirm that:

1. This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.

2. An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.

3. Any necessary indemnity or insurance arrangements, as described in question A76, will be in place before this research starts. Insurance or indemnity policies will be renewed for the duration of the study where necessary.

4. Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.

5. Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.

6. The duties of sponsors set out in the Research Governance Framework for Health and Social Care will be undertaken in relation to this research.

   Please note: *The declarations below do not form part of the application for approval above. They will not be considered by the Research Ethics Committee.*

7. Where the research is reviewed by a REC within the UK Health Departments Research Ethics Service, I understand that the summary of this study will be published on the website of the National Research Ethics Service (NRES), together with the contact point for enquiries named in this application. Publication will take place no earlier than 3 months after issue of the ethics committee's final opinion or the withdrawal of the application.

8. Specifically, for submissions to the Research Ethics Committees (RECs) I declare that any and all clinical trials approved by the HRA since 30th September 2013 (as defined on IRAS categories as clinical trials of medicines, devices, combination of medicines and devices or other clinical trials) have been registered on a publically accessible register in compliance with the HRA registration requirements for the UK, or that any deferral granted by the HRA still applies.

This section was signed electronically by Dr Sally Burtles on 07/11/2016 10:58.

Job Title/Post:	Director of Research Services and Business Development
Organisation:	Queen Mary University of London
Email:	sponsorsrep@bartshealth.nhs.uk