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)
PROBESE

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
- [ ] Scotland
- [ ] 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 review bodies are you applying to?

- [ ] HRA Approval
- [x] NHS/HSC Research and Development offices
- [ ] Social Care Research Ethics Committee
- [x] Research Ethics Committee
- [ ] Confidentiality Advisory Group (CAG)
- [ ] National Offender Management Service (NOMS) (Prisons & Probation)

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

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

(•) Yes ( ) No

5a. Are all the research costs and infrastructure costs for this study provided by an NIHR Biomedical Research Centre, NIHR Biomedical Research Unit, NIHR Collaboration for Leadership in Health Research and Care (CLAHRC) or NIHR Research Centre for Patient Safety & Service Quality in all study sites?

( ) Yes (•) No

If yes and you have selected HRA Approval in question 4 above, your study will be processed through HRA Approval.

If yes, and you have not selected HRA Approval in question 4 above, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

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 (CRN) Portfolio? Please see information button for further details.

(•) Yes ( ) No

If yes, you must complete a NIHR Clinical Research Network (CRN) Portfolio Application Form immediately after completing this project filter and before submitting other applications. If you have selected HRA Approval in question 4 above your study will be processed through HRA Approval. If not, NHS permission for your study will be processed through the NIHR Coordinated System for gaining NHS Permission (NIHR CSP).

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

NHS/HSC R&D Form (project information)

Please refer to the Submission and Checklist tabs for instructions on submitting R&D applications.

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)
PROBESE

PART A: Core study information

1. ADMINISTRATIVE DETAILS

A1. Full title of the research:

PRotective Ventilation with Higher versus Lower PEEP during General Anesthesia for Surgery in OBESE Patients – The PROBESE Randomized Controlled Trial

A3-1. Chief Investigator:

	Title	Forename/Initials	Surname
	Professor	Gary H	Mills
Post	Consultant in Anaesthesia and Intensive Care Medicine		
Qualifications	BMedSci, MBChB, PhD, UKDICM, FFICM, FRCA		
Employer	Sheffield Teaching Hospital NHS Foundation Trust		
Work Address	General Intensive Care Unit, Northern General Hospital, Herries Road, Sheffield		
Post Code	S5 7AU		
Work E-mail	g.h.mills@sheffield.ac.uk		
* Personal E-mail	gary.mills@sth.nhs.uk		
Work Telephone	01142712381		
* Personal Telephone/Mobile	07788643925		
Fax			

** 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
	Dr	Erica	Wallis
Address	Sheffield Clinical Research Office		
	Royal Hallamshire Hospital, D floor		
	Glossop Rd, Sheffield		
Post Code	S10 2JF		
E-mail	erica.wallis@sth.nhs.uk		
Telephone	01142265931		
Fax	01142265937		

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):	STH18510
Sponsor's/protocol number:	
Protocol Version:	3
Protocol Date:	30/05/2015
Funder's reference number:	WKR020110082
Project website:	http://www.peg-dresden.de/probese/doku.php?id=PROBESE

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): NCT02148692

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.*

Introduction
Deterioration of breathing to the point that patients need artificial help with breathing after surgery is a major problem

and can lead to the death of surgical patients. Anaesthetists inconsistently use positive end–expiratory pressure (PEEP), which is a way of preventing small airways in the lungs from closing up during operations. Some may use recruitment manoeuvres, whereby the lungs are inflated with some large artificial breaths to reopen closed airways, in the hope that this may improve oxygenation and protect against lung problems after the operation. These lung problems are normally referred to as postoperative pulmonary complications (PPCs) and often are worse in obese patients. It is uncertain whether using higher levels of PEEP with recruitment manoeuvres truly prevents PPCs. The balance between the helpful effect on the lung versus any unhelpful effects on blood pressure is unknown in obese patients. Therefore it is important to find out if PEEP and recruitment manoeuvres are helpful overall.
Objectives
To compare ventilation using higher levels of PEEP with recruitment manoeuvres against using lower levels of PEEP without recruitment manoeuvres in obese patients at an intermediate–to–high risk for PPCs.
Hypotheses
Higher levels of PEEP and recruitment manoeuvres during surgery, as compared to ventilation with lower levels of PEEP without recruitment manoeuvres, prevents PPCs in obese patients at an intermediate–to–high risk for PPC.
Study design
International multicentre randomized controlled trial.
Study population
Obese patients with BMI ≥ 35 kg/m2 at intermediate–to–high risk for PPCs scheduled for surgery under general anaesthesia.
Main study parameters/endpoints
The primary endpoint is the proportion of patients with PPCs. Secondary endpoints include intra–operative complications, need for postoperative ventilatory support (invasive and/or non–invasive ventilation), need for unexpected ICU admission or ICU readmission, the number of hospital–free days and 90-day survival/mortality.

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, R&D office 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.

This study is part of a Europewide study. European grant funding has been awarded by the European Society of Anaesthesiology
The study compares two established ways of setting the ventilator that is normally used during the anaesthesia for surgery, to see which produces the best results. It therefore does not represent a major departure from usual practice, no matter which arm of the study the patient is randomised to.
All the patients recruited will receive a high standard of care. The ethical issues relate to random allocation to treatment groups, access and recording of patient data. Plus storage of patient data, and the minimal inconvenience of study involvement.
When patients are anaesthetised for surgery inside the abdomen some operations can be performed through a type of telescope called a laparoscope, but most major operations need the abdomen to be open. Abdominal surgery, especially if it involves opening the abdominal wall, affects the upper abdomen leading to collapse of the small air passages within the lung. This in turn means that respiratory failure may happen or recovery may be delayed. This sometimes leads to pneumonia and even death, so finding out the best way to keep the air passages open is an important area of research.
The advantage of this study is that mechanical ventilation is already essential for the types of surgery under study. What we need to know is whether one particular way of setting the ventilator is better than another.
Potential patients will be informed of the possible study by letter when they are asked to come for preop assessment. Far less commonly
They will then be consented and have the opportunity to ask questions when they come to the hospital for preoperative assessment or for surgery.
The choice of ventilation technique is between a conventional approach or a technique that has been widely used on intensive care for prolonged ventilation. Therefore adverse events directly related to the ventilation strategy are unlikely. The risks are therefore small and as all patients will be attended throughout the surgery by an anaesthetist any difficulties will potentially be spotted as soon as they occur.
Data will be gathered from preoperative notes, intraoperative routine recordings and postoperative recordings of routinely collected data. This data will be entered onto a secure web-link. All hard data will be kept in locked filing cabinets on Trust secure premises. These databases will be registered and will comply with the Data Protection Act.
In the unexpected event that the randomisation code has to be broken, the fact that one person has received one type of ventilation rather than another would not normally be regarded as personally sensitive information.

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 determine which method of lung–protective mechanical ventilation strategy results in reduced postoperative complications and better patient outcomes in the obese patient.
That is to say, does the addition of extra PEEP, which is background raised airway pressure whilst patients are breathing out and recruitment manoeuvres, which are occasional large breaths help reduce complications after surgery associated with the lungs.
The number and type of postoperative pulmonary complications will be examined.

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

We will look at complications during the operation in relation to:
1) Oxygen saturation, which is the level of oxygen in the blood. In particular how many times did the saturation fall below 92% for more than one minute.
2) Falls in blood pressure during recruitment manoeuvres, defined by systolic arterial pressure less than 90 mmHg for more than 2min.
3) The frequency of the need for postoperative mechanical ventilatory support, whether invasive ventilation, which is via a tube passed into the lungs or noninvasive ventilation, which is via a mask or special helmet. Both ways are standard approaches to helping someone who cannot breath adequately.
Unexpected need for ICU admission (i.e., before
surgery the patient is not scheduled
for ICU admission, but is admitted eventually) or ICU readmission within 30 days
Need for hospital readmission within 30 days.

As a broader assessment we will also look at the number of:

Hospital free days at day 90
Mortality at day 90
None lung complications after surgery
Postoperative wound healing

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

Mechanical ventilation is a life–saving strategy in patients with respiratory failure. Not only that, but its use is absolutely vital to allow most major abdominal surgery.
However mechanical ventilation does not expand lungs in the same distribution as

normal spontaneous breathing. As a result strategies have evolved to try to keep the small airways open, because those in dependent areas of the chest tend to close up. These techniques have been adopted on the intensive care unit, but their usefulness for mechanical ventilation during surgery is undefined in this group of obese patients.
Some studies have suggested benefit by ventilating with small breaths and positive end–expiratory pressure (PEEP) during the surgical period in patients without previous lung injury.
However, recently, an experimental study suggested that such a strategy might even lead to increased inflammation and what is called "ventilator associated lung injury" in normal lungs. On the other hand, large breaths with low PEEP may overdistend non–injured lungs, in particular non–dependent lung tissue. In addition, too low levels of PEEP may promote collapse/closure of very small air sacs in the lung called alveoli, resulting in repetitive collapse/reopening of dependent lung tissue. Both phenomena may stress the non–injured lung, triggering local inflammation and local coagulation.
Use of recruitment manoeuvers (RMs) to open the lungs has been found to improve the effectiveness of PEEP with regard to gas exchange ie passage of oxygen and carbon dioxide across the membrane between the blood and the air sacks during general anesthesia.
As a result the evidence remains conflicting and the evidence in obese patients is limited, so the use of PEEP and recruitment manoeuvres during surgery is controversial and needs to be examined in this group of patients.

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.*

This will be a randomised controlled trial.
Screening:
Potential participants will be identified from information provided by the waiting list manager for the relevant surgical specialties to the clinical anaesthesia team or the preop assessment team at the local Trust.

A letter of introduction will be sent to the patients, briefly introducing the project so they can have some feeling as to whether they wish to be approached about the study, when they come to the preop assessment clinic.
They will then be approached at the preop assessment clinic by a member of the research team. If they are willing to discuss the project, the patients will be able to ask any questions they wish about the study.
Once the participant has had time to consider the information a member of the research team will again review the inclusion and exclusion criteria and obtain written informed consent.
Preoperative variables will be collected to allow the patients obesity and physical status and comorbidities to be defined, including evidence of sleep apnoea, COPD, smoking or recent respiratory infection.
Randomisation:
Patients consented are then randomised to one of two arms:
1) “Conventional strategy” mechanical
ventilation with positive end–expiratory pressure (PEEP) at 4 cmH2O pressure
(the “conventional strategy”) without RMs
2) “Protective strategy” mechanical
ventilation with PEEP at 12 cmH2O. This group will also include the use of recruitment manoeuvres (RMs)

In the event of oxygen saturations falling a rescue regime involving changes to inspired oxygen concentration, PEEP and recruitment manoeuvres has been designed for each arm of the study.

In all participating centers at least 2 investigators will be involved with the study. One researcher is involved with randomization and mechanical ventilation practice in the operation room, the other investigator, blinded for randomization arm, will score the primary and secondary post–operative endpoints.
Data collection and follow up:
Preoperative data collected according to the protocol
Intraoperative data is collected after induction of anesthesia, and relates to the function of the lungs, cardiovascular system and features of the anaesthetic and surgery.
manoeuvre.
Patients are followed up to day 5 after surgery (data collected on days 1, 3, 4 & 5) and also on the day of hospital discharge (or at day 90 if still in hospital at this time). Patients who have gone home will have the number of hospital free days since discharge calculated at day 90.
As mentioned above, an investigator, blinded for the randomized intervention will assess post–operative variables.
Clinical data and the presence of pulmonary and extra–pulmonary postoperative
complications are scored according to strict criteria.

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?

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

Give details of involvement, or if none please justify the absence of involvement.
Study was designed by a European group of academics and clinicians.

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
- [x] Respiratory
- [ ] Skin
- [ ] Stroke

Gender:	Male and female participants
Lower age limit: 18	Years
Upper age limit:	No upper age limit

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

Patient scheduled for surgery under general anesthesia
Intermediate to high risk for PPCs following surgery, according to the ARISCAT risk score (≥26) (see APPENDIX i)
BMI ≥ 35kg/m2
Expected duration of surgery ≥ 2hours

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

Age < 18 years
Previous lung surgery (any)
Persistent hemodynamic instability, intractable shock (considered hemodynamically unsuitable for the study by the patient's managing physician)
History of previous severe chronic obstructive pulmonary disease (COPD) (non invasive ventilation and/or oxygen therapy at home, repeated systemic corticosteroid therapy for acute exacerbations of COPD)
Recent immunosuppressive medication(patients receiving chemotherapy or radiation therapy up to two months prior to surgery)
Severe cardiac disease (New York Heart Association class III or IV, acute coronary syndrome or persistent ventricular tachyarrhythmias)
Invasive mechanical ventilation longer than 30 minutes (e.g., general anesthesia for surgery) within last 30 days
Pregnancy
Prevalent acute respiratory distress syndrome expected to require prolonged postoperative mechanical ventilation
Severe pulmonary arterial hypertension, defined as systolic pulmonary artery pressure > 40 mmHg
Intracranial injury or tumor
Neuromuscular disease (any)
Need for intraoperative prone or lateral decubitus position Need for one-lung ventilation Cardiac surgery Neurosurgery
Planned reintubation following surgery Enrolled in other interventional study or refusal of informed consent

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
Invitation to take part in research (invitation letter sent to participant)	1	0	5 mins	Posted with clinical info/waiting list coordinators info
First patient contact - discussing study with potential participants	1	0	10 mins	Research doctor or nurse
Taking informed written consent for participation in research project	1	0	15 mins	Research doctor or nurse
Randomisation	1	0	10 mins	Research doctor or nurse, performed using a dedicated website
Collection of demographic data and medical history before surgery (baseline) Virtually all available from normal preop assessment	1	1	15 mins	Research doctor or nurse

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
Mechanical ventilation with PEEP at 4 cmH2O without RMs OR mechanical ventilation with PEEP at 12 cmH2O and recruitment manouevres (RM). All patients with tidal volume 7ml/kg ideal body weight	1	0	5 mins	Anaesthetist will perform this in operating theatre once patient anaesthetised.
Blood sampling	4	4	10 mins	Results from blood samples collected as part of routine clinical care will be recorded in CRF
Collection of medical images	2	2	10 mins	If X-ray performed by clinical staff as part of routine clinical care, the research team will record results of these images
Physical examination including pulse rate, blood pressure, heart rate, temperature. Recorded in CRF. May well have been done clinically.	5	0	10 mins	Research doctor or nurse
SpO2 (Saturation of Peripheral Oxygen) in room air	5	5	2 mins	Research doctor or nurse
Collection of respiratory and haemodynamic variables during surgery and temperature	8	0	10 mins	Data collected every hr during surgery by anaesthetist, study doctor or nurse
Postoperative data. Mostly routinely collected. Includes record of need for ICU, CPAP, NIV extra mechanical ventilation. Mobility assessment, record of wound healing or infection, need for transfusion	7	0	20 mins	Research doctor or nurse
Record of hospital free days and mortality at 30 and 90 days	2	0	10 mins	Research doctor or nurse

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?

Up to their day of discharge from hospital, or 90 days post surgery (whichever is sooner).

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.

Patient burden and risks are considered to be low: data collection is non-invasive (self-reported by the patient or collected from medical records). The patient will not experience any discomfort because he/she is under general

anesthesia during the trial.
The intervention alternatives consist of techniques routinely used in theatre. WE would expect patients to receive something the same of very close to either of the two alternative ventilator settings as part of normal care. This study will help determine which settings could provide advantages for the future, or if there is any difference at all.

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?

There is no benefit for the research particpants themselves but this work may impact on care of patients in the future.

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.*

Not applicable - the intervention (mechanical ventilation) will only be provided during surgery.

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

None

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).*

Potential participants will be identified by a member of their clinical
care team - usually the anaesthetist in the preop assessment clinic and their consultant/specialist nurse colleagues or the anaesthetist involved with the potential surgery or the surgeon involved with the case- from the list of patients due to attend the preoperative clinics prior to abdominal surgery. This list will usually be provided by the waiting list manager or by the surgical team secretary, although this process may vary from hospital to hospital. This list can be discussed anonymously for suitability with the research project lead or their deputy.
Some patients who are in hospital already may be identified by the clinical team and may therefore be included as potential recruits, providing there is sufficient time to allow them to make an informed decision as to whether they wish to take part.
An invitation letter and a patient information sheet will be posted to patients who are outside the hospital, or given to patients when they come to the surgical or preop assessment clinic if has not proved possible to send them information in advance. If they agree to discuss the project further once they have looked at the letter of invitation and the patient information sheet, a delegated member of the research team will then discuss the study in detail, answer any questions and discuss consent. Patients will be given as much time as they need to decide if they wish to take part.

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:
Yes, but these will be initially screened by a member of the clinical care team or waiting list manager.

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.*

Screening and the initial approach will be done by a member of the patient's existing clinical care team (usually the anaesthetist in the preop assessment clinic and their consultant/specialist nurse colleagues or the anaesthetist involved with the potential surgery) or the waiting list manager. This will allow initial information to be sent to the potential patient, so that they can decide if they wish to be approached further.

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

○ Yes ◉ No

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 initial approach will be by a member of the healthcare team or by initial information posted to them. If the patient is interested in further information, the study will be discussed with them in depth by the doctor or research nurse working on the study.
Patients will be posted a letter of invitation and patient information sheet when it is decided they are going to have surgery. The preoperative assessment staff or one of the clinicians looking after the patient will ask whether they are prepared to see one of the research team. If so the project can then be discussed further at the preoperative assessment clinic or outpatients by one of the research team if the patient is interested in participating and discussing things further.
If there has not been time for the patient to receive and consider this letter of invitation they can be provided a copy in the outpatients or preoperative assessment clinic, and again if they wish to discuss this further a member of the research team will talk to them.
A small number of patients may be in hospital and then proceed to surgery. If they are deemed suitable by the clinical team they can be given a letter of invitation and a patient information sheet and if then they are happy to be seen by one of the research team they can then be seen on the ward with a view to discussing the project further and potentially giving consent. In all cases patients will be given as much time as they need to come to a decision as to whether to take part or not.

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.

The initial approach and consent will not be made to any vulnerable groups.
Initial information will be provided with a letter of invitation and patient information sheet.
In the event that patients lose competence during the follow up we will obtain consultee consent

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

Not applicable

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?

As long as is needed. This would normally be more than 24 hrs between introducing the study to participants (via invitation letter and information sheets) and taking consent.

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 would include participants enrolled in observational studies, however participants are excluded in they are currently enrolled in another interventional study. This is listed in the exclusion criteria in the protocol.

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)*

The Patient Information Sheet is written in English and fees for translation are not available, therefore potential participants must have a good understanding of both written and verbal English in order to participate.

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?

Any new information relevant to the conduct of the trial received during the course of the study will be disseminated to all Principal Investigators by the Chief Investigator.

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:

We will ask patients if they lose capacity during the study if they would wish to continue to be included.
We will create consultee information and consent forms to allow consultees to advise on what they feel their relative or friend would wish in this situation.

Please complete Part B, Section 6, giving further information about arrangements for including adults unable to consent for themselves.

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
- [ ] Electronic transfer by magnetic or optical media, email or computer networks
- [x] 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
- [x] Storage of personal data on any of the following:
  - [x] Manual files including X−rays
  - [x] NHS computers
  - [ ] Home or other personal computers
  - [x] University computers
  - [ ] Private company computers
  - [ ] Laptop computers

Further details:
Data storage will be stored in accordance with the Data Protection Act. Data will be stored on password protected NHS or University computers and paper files will be stored on NHS secure premises.
Data will be passed onto the European collaborators for analysis. This will be anonymised before it passes onto the European investigators.

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

Manual files will be stored within locked rooms in a secure hospital Unit. At the end of the study all files will be archived securely.

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.*

Confidentiality will be maintained as a priority. Only that information which is required for the study will be recorded.

Each participant will be assigned a unique ID at the start of their visit. The unique ID will be used in the analyses of the gathered data to ensure data is fully anonymised before transfer to other study personnel for analysis, and no personal identifiable data (PID) will be used in publication or dissemination of findings.

The participants' PID will be accessible only to the named investigators working on the study.

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 direct care team and the study team will have access to participant's personal data. The transfer of anonymised data to other study personal outside of the UK is disclosed in the ethically approved participant information sheet and participants consent to this data transfer (which is for the purposes of analysis).

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?

The data will be analysed by the research team based at University Hospital Dresden in Germany led by Professor Marcelo Gama de Abreu.

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

	Title	Forename/Initials	Surname
	Professor	Marcelo	Gama de Abreu
Post	Professor of Anaesthesia		
Qualifications	MSc MD PhD DESA		
Work Address	Department of Anesthesiology and Intensive Care Medicine Fetscherstr. 74 01307 Dresden, Germany		
Post Code	01307		
Work Email	mgabreu@uniklinikum-dresden.de		
Work Telephone			
Fax			

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:
All enrolled patients will receive a random patient identification code. The codebook will be stored digitally, encrypted with a double password, and as a hard copy under lock and key. All data will be stored for the length of the study and afterwards as required by local law or for further publication. All handling of personal data will comply with local law. Identifiable data on screening / enrollment logs will be stored om site until the end of the study. At the end of the study the data will be archived along with any other data collected.
We aim to store the data for a length of 20 years. This is according to German law, because the Dresden University is the originator of the overall European study. Therefore all centres are being asked to comply to this request.
In the event the situation changes and the lead for the study asks us to destroy data earlier we will comply with the relevant instructions provided this does not conflict with UK legal requirements.

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

Years: 20
Months: 0

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.*

It is the responsibility of the local PI to store the data files in a secure place. The Dresden team will store the centralised data securely and safely. The data will only be accessible by the research teams involved. The data will be stored in password protected computers in a looked room. Any paper data will be stored in a locked filing cabinet in a

locked room, until it is archived.

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.
The study is listed on the ClinicalTrials.gov
Identifier:
NCT02148692

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:*

- [x] Peer reviewed scientific journals
- [ ] Internal report
- [x] Conference presentation
- [x] 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?

Published data will not be identifiable. It will take the form of summary data and statistical analysis.

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.
Participants are informed in the ethically approved participant information sheet that if they would like to know the results of the study they can request these from their study doctor.

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
- [ ] 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:
1) External peer review by the funding body as part of the grant application review process.
2) Review by the multi-centre multi-country research group

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

☑ Review by a statistician within the Chief Investigator's institution

☐ 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
	Prof	Jochen	Schmitt
Department	Department of Outcome Research of the University Hospital Carl Gustav Carus		
Institution	Dresden University of Technology		
Work Address	Fetscherstr 74, 01307, Dresden, Germany		
Post Code			
Telephone			
Fax			
Mobile			
E-mail			

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

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

The primary endpoint is a collapsed composite of postoperative pulmonary complications occurring in the first five days after surgery. These complications include aspiration pneumonitis, bronchospasm, mild respiratory failure, moderate respiratory failure, severe respiratory failure, development of acute respiratory distress syndrome, pulmonary infection, atelectasis, pulmonary edema caused by cardiac failure, pleural effusion, pneumothorax and new pulmonary infiltrates (for definition, see Appendix iii). Patients who develop a least one of the above mentioned complications are considered as meeting the primary endpoint.
For the primary efficacy analysis rates of postoperative pulmonary complications will be compared between the two intervention groups and the odds ratio relative risks with corresponding 95% confidence levels interval will be calculated using logistic regression analysis.

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

The primary endpoints are those relating to respiratory complications.
Secondary outcome measures relate to other complications such as cardiovascular complications, systemic inflammatory response syndrome, infection, neurological, haematological, renal and hepatic complications, critical care admission or readmission, hospital readmission and death.

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:	30
Total international sample size (including UK):	748
Total in European Economic Area:	700

Further details:
Sample size calculation was based on our primary hypothesis and primary study outcome, and was informed by data collected during a multicenter Spanish trial (ARISCAT) (1) and a single-center, relatively small study reporting the effects of intraoperative higher PEEP and recruitment maneuvers on the incidence of postoperative desaturation, chest

infection and bronchospasm in obese patients who underwent laparoscopic bariatric surgery (2).
1) Appendix 1 of protocol
2) Talab HF, Zabani IA, Abdelrahman HS, Bukhari WL, Mamoun I, Ashour MA, Sadeq BB, El Sayed SI: Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. Anesth Analg 2009; 109: 1511-6

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.*

These calculations indicate that 356 patients are required per group, assuming a two–sided significance level of 0.05 and a power of 80%, to detect the expected difference in postoperative pulmonary complications between the higher PEEP group of 30% and the lower PEEP group of 40% (risk ratio of 0.75). Assuming a dropout rate of 5%, a total of 748 patients (n=374 per group) are to be included into the study.

A61. Will participants be allocated to groups at random?

(●) Yes ( ) No

If yes, please give details of the intended method of randomisation:
Randomisation is performed by a secure website.
Computer generated random allocation.

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.

For the primary efficacy analysis rates of postoperative pulmonary complications will be compared between the two intervention groups and the odds ratio relative risks with corresponding 95% confidence levels interval will be calculated using logistic regression analysis.

Normally distributed variables will be expressed by their mean and standard deviation; non-normally distributed variables will be expressed by their medians and interquartile ranges. Categorical variables will be expressed as n (%). Student's t-test will be used to test groups of continuous normally distributed variables. Conversely, if continuous data is non-normally distributed, the Mann-Whitney-U test will be used. Categorical variables will be compared with the Chi–square test, Fisher's exact tests or, where appropriate, as relative risks. Time dependent data will be analyzed using a proportional hazard model adjusted for possible imbalances of patients' baseline characteristics.

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
	Professor	Marcelo	Gama de Abreu
Post	Professor of Anaesthesia		
Qualifications	MSc MD PhD DESA		
Employer	University Hospital Dresden		
Work Address	Department of Anesthesiology and Intensive Care Medicine		
	Fetscherstr. 74		
	01307 Dresden, Germany		
Post Code	01307		
Telephone			
Fax			
Mobile			
Work Email	mgabreu@uniklinikum-dresden.de		

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	University Hospital Dresden
Given name	Marcelo
Family name	Gama de Abreu
Address	Department of Anesthesiology and Intensive Care Medicine
Town/city	Fetscherstr. 74
Post code	01307
Country	GERMANY
Telephone	004935145818007
Fax	00493514584336
E-mail	mgabreu@uniklinikum-dresden.de

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.

Legal representative of the sponsor

Contact person

Name of organisation	Sheffield Teaching Hospitals NHS Foundation Trust
Given name	Professor Simon
Family name	Heller
Address	Research Department, 1st Floor, 11 Broomfield Road
Town/city	Sheffield
Post code	S10 2SE
Country	UNITED KINGDOM
Telephone	01142265938
Fax	01142265937
E-mail	s.heller@sheffield.ac.uk

A65. Has external funding for the research been secured?

- [x] 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	European Society of Anaesthesiology Research Committee
Address	Professor Andreas Hoft 24 Rue des Comédiens BE-1000 Brussels, Belgium
Post Code	VAT BE 0447 289 368
Telephone	003227433290
Fax	003227433298
Mobile	
Email	research@esahq.org

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

Amount: 30000 euros

Duration
Years: 3
Months: 0

If applicable, please specify the programme/ funding stream:

What is the funding stream/ programme for this research project?
European Society of Anaesthesiology

Organisation	NIAA Grants Committee and Anaesthesia/AAGBI
Address	Association of Anaesthetists of Great Britain and Ireland 21 Portland Place, London
Post Code	W1B 1PY
Telephone	02076311650
Fax	
Mobile	

Email secretariat@aagbi.org

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

Amount: £10054

Duration
Years: 2
Months: 0

If applicable, please specify the programme/ funding stream:

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

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	Erica	Wallis
Organisation	Sheffield Teaching Hospitals NHS Foundation Trust		
Address	Research Department, 1st Floor, 11 Broomfield Road		
	Sheffield		
Post Code	S10 2SE		
Work Email	erica.wallis@sth.nhs.uk		
Telephone	01142265931		
Fax	01142265937		
Mobile			

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

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

Planned start date: 01/04/2015
Planned end date: 01/09/2016
Total duration:
Years: 1 Months: 5 Days: 1

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 17

Number of sites anticipated in the Community

Does this trial involve countries outside the EU?

◉ Yes ○ No

- ☑ USA
- ☑ Other international (please specify)

Canada

A72. What host organisations (NHS or other) in the UK will be responsible for the research sites? *Please indicate the type of organisation by ticking the box and give approximate numbers of planned research sites:*

☑ NHS organisations in England	17
☐ NHS organisations in Wales	
☐ NHS organisations in Scotland	
☐ HSC organisations in Northern Ireland	
☐ GP practices in England	
☐ GP practices in Wales	
☐ GP practices in Scotland	
☐ GP practices in Northern Ireland	
☐ Social care organisations	
☐ Phase 1 trial units	
☐ Prison establishments	
☐ Probation areas	
☐ Independent hospitals	
☐ Educational establishments	
☐ Independent research units	
☐ Other (give details)	
Total UK sites in study:	17

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?

A Data Safety Monitoring Board (DSMB) has been convened. The DSMB is composed of 4 individuals, one of which will be the chairman.

The DSMB will first meet approximately 9 months after the first patient is enrolled. The first meeting will be scheduled after the first 100 patients. Subsequent to this meeting the DSMB will meet every 6 months. One meeting per year will be by phone and the other in person.

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?

All adverse events reported will be sent to the DSMB for review. The DSMB will review the overall status of the program: number of patients enrolled overall and in each center, adherence to the protocol overall and by each centre.

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 main concern is not to withhold positive effects of the treatment to the control group (lower pressures group), therefore if analyses reveal a statistically significant difference in outcomes between the two group the study will be stopped.

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.

- [x] NHS indemnity scheme will apply (NHS sponsors only)
- [ ] Other insurance or indemnity arrangements will apply (give details below)

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.

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

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.

- [x] 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

B. All research other than CTIMPs

In this sub-section, an adult means a person aged 16 or over.

B1. What impairing condition(s) will the participants have?

The study must be connected to this condition or its treatment.

The study participants will all be able to give consent initially. However because they are undergoing surgery it is possible, just as in any medical studies, that during the follow up period that they may develop postoperative complications that mean they would for example need to be transferred to or back to critical care for mechanical ventilation. Alternatively, they may develop an illness totally unrelated to the surgery. This illness could mean that they are no longer competent or any related sedation could render them incompetent. Under the Mental Capacity Act they would then need to have the continuation of data gathering considered by a Consultee Process.

B2. Justify the inclusion of adults unable to consent for themselves. It should be clear why the research could not be carried out as effectively if confined to adults capable of giving consent.

We would not initially include adults who cannot consent for themselves. However under the scenario described in B1 above we would need to obtain a Consultee Consent so that we could continue gathering data, otherwise we would risk biasing our data by being forced to exclude patients who had developed complications relating to the surgery or who had become severely unwell for unrelated reasons

B3. Who in the research team will decide whether or not the participants have the capacity to give consent? What training/experience will they have to enable them to reach this decision?

We will decide if they have lost capacity by either assessing the patient directly ourselves as part of the research team or in the first instance by asking the clinician looking after them.
The medical members of the research team have experience of assessing patients who have lost capacity during their work on Intensive Care.

B4. Does the research have the potential to benefit participants who are unable to consent for themselves?

○ Yes ◉ No

B5. Will the research contribute to knowledge of the causes or the treatment or care of persons with the same impairing condition (or a similar condition)?

◉ Yes ○ No

If Yes, please explain how the research will achieve this:

It is common for patients undergoing major surgery to lose capacity in the postoperative period if they develop complications of surgery. The conclusions from this study would benefit them and would also benefit patients who do not lose capacity.

B6. Will the research involve any foreseeable risk or burden for these participants, or interfere in any way with their freedom of action or privacy?

○ Yes ◉ No

Questions B7 and B8 apply to any participants recruited in England and Wales.

B7. What arrangements will be made to identify and consult persons able to advise on the presumed wishes and feelings of participants unable to consent for themselves and on their inclusion in the research?

We will seek to contact the next of kin, a close relative or friend. If none exists we will consult with an independent mental capacity representative (doctor responsible for the care of the patient).

Please enclose a copy of the written information to be provided to consultees. This should describe their role under section 32 of the Mental Capacity Act and provide information about the research similar to that which might be given to participants able to consent for themselves.

B8. Is it possible that a participant requiring urgent treatment might need to be recruited into research before it is possible to identify and consult a person under B7?

○ Yes ◉ No

If Yes, say whether arrangements will be made instead to seek agreement from a registered medical practitioner and outline these arrangements. Or, if this is also not feasible, outline how decisions will be made on the inclusion of participants and what arrangements will be made to seek consent from the participant (if capacity has been recovered) or advice from a consultee as soon as practicable thereafter.

If a participant regains capacity during his stay in the recruiting hospital we will advise him that he lost capacity and will ask him to agree or not to his continued participation in the remainder of the study follow up

B9. What arrangements will be made to continue to consult such persons during the course of the research where necessary?

We will attempt to identify a contact number and name for such a person during the initial consenting process of the patient. Other contact details will also be available via the patients records in most situations.

B10. What steps will you take, if appropriate, to provide participants who are unable to consent for themselves with information about the research, and to consider their wishes and feelings?

This will already have been done when they were able to consent in the first instance.

B11. Is it possible that the capacity of participants could fluctuate during the research? How would this be handled?

If it appears clear from the opinion of the clinicians looking after the patient that they have lost mental capacity and that this is likely to be the case for more than 7 days or if this occurs when they have gone home and is likely to last for more than 7 days during a follow up phase a Consultee will be approached.

B12-1. What will be the criteria for withdrawal of participants?

If the Patient or Consultee requests the patients withdrawal. If a Consultee requests withdrawal and if subsequently the patient regains capacity and is wishes to continue they will be retained in the study.

B13. Describe what steps will be taken to ensure that nothing is done to which participants appear to object (unless it is to protect them from harm or minimise pain or discomfort).

The intervention occurs right at the start of the study, so this situation will not apply in this study.

B14. Describe what steps will be taken to ensure that nothing is done which is contrary to any advance decision or statement by the participant?

We will ask the patient about any advance decisions in place during consent with respect to the study

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		Forename	Gary
			Middle name	Hylton
			Family name	Mills
	Country: England		Email	g.h.mills@sheffield.ac.uk
			Qualification (MD...)	BMedSci, MBChB, PhD, UKDICM, FFICM, FRCA
			Country	UNITED KINGDOM
	Organisation name	SHEFFIELD TEACHING HOSPITALS NHS FOUNDATION TRUST		
	Address	NORTHERN GENERAL HOSPITAL HERRIES ROAD SHEFFIELD SOUTH YORKSHIRE		
	Post Code	S5 7AU		
IN2 ☐	◉ NHS site ○ Non-NHS site		Forename	Packianathaswamy
			Middle name	
			Family name	Balaji
	Country: England		Email	indbalaji@gmail.com
			Qualification (MD...)	
			Country	UNITED KINGDOM
	Organisation name	HULL AND EAST YORKSHIRE HOSPITALS NHS TRUST		
	Address	HULL ROYAL INFIRMARY ANLABY ROAD HULL EAST YORKSHIRE		
	Post Code	HU3 2JZ		
IN3 ☐	◉ NHS site ○ Non-NHS site		Forename	Nahla
			Middle name	
			Family name	Awad
	Country: England		Email	Nahla.Awad@ULH.nhs.uk

Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	UNITED LINCOLNSHIRE HOSPITALS NHS TRUST
Address	LINCOLN COUNTY HOSPITAL GREETWELL ROAD LINCOLN LINCOLNSHIRE
Post Code	LN2 4AX

IN4 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	Sara
Middle name	
Family name	Bowman
Email	sarabowman@hotmail.com
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	HOMERTON UNIVERSITY HOSPITAL NHS FOUNDATION TRUST
Address	HOMERTON ROW LONDON GREATER LONDON
Post Code	E9 6SR

IN5 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	James
Middle name	
Family name	Ryan
Email	James.ryan@stees.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	SOUTH TEES HOSPITALS NHS FOUNDATION TRUST
Address	JAMES COOK UNIVERSITY HOSPITAL MARTON ROAD MIDDLESBROUGH CLEVELAND
Post Code	TS4 3BW

IN6 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	Wright
Middle name	
Family name	Stephen
Email	Stephen.Wright@nuth.nhs.uk

Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	THE NEWCASTLE UPON TYNE HOSPITALS NHS FOUNDATION TRUST
Address	FREEMAN HOSPITAL FREEMAN ROAD HIGH HEATON NEWCASTLE-UPON-TYNE TYNE AND WEAR
Post Code	NE7 7DN

IN7 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	
Middle name	
Family name	
Email	Pramod.Nalwaya@uhns.nhs.uk
Qualification (MD...)	
Country	

Organisation name	UNIVERSITY HOSPITAL OF NORTH STAFFORDSHIRE NHS TRUST
Address	NORTH STAFFORDSHIRE ROYAL INFIRMARY PRINCES ROAD STOKE-ON-TRENT STAFFORDSHIRE
Post Code	ST4 7LN

IN8 ☐

◉ NHS site
○ Non-NHS site

Country: England

Forename	Amir
Middle name	
Family name	Rafi
Email	amir.rafi@cddft.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

Organisation name	COUNTY DURHAM AND DARLINGTON NHS FOUNDATION TRUST
Address	DARLINGTON MEMORIAL HOSPITAL HOLLYHURST ROAD DARLINGTON COUNTY DURHAM
Post Code	DL3 6HX

IN9 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	TAUNTON AND SOMERSET NHS FOUNDATION TRUST
Address	MUSGROVE PARK HOSPITAL TAUNTON SOMERSET
Post Code	TA1 5DA

Forename	Leanne
Middle name	
Family name	Foote
Email	Leanne.Foote@tst.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

IN10 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	ROYAL CORNWALL HOSPITALS NHS TRUST
Address	ROYAL CORNWALL HOSPITAL TRELISKE TRURO CORNWALL
Post Code	TR1 3LJ

Forename	Jonathan
Middle name	
Family name	Paddle
Email	jonathan.paddle@rcht.Cornwall.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

IN11 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	YORK TEACHING HOSPITAL NHS FOUNDATION TRUST
Address	YORK HOSPITAL WIGGINTON ROAD YORK NORTH YORKSHIRE
Post Code	YO31 8HE

Forename	Simon
Middle name	
Family name	Davies
Email	drsimondavies@googlemail.com
Qualification (MD...)	
Country	UNITED KINGDOM

IN12 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	WESTERN SUSSEX HOSPITALS NHS TRUST
Address	WORTHING HOSPITAL LYNDHURST ROAD WORTHING WEST SUSSEX
Post Code	BN11 2DH

Forename	Mike
Middle name	
Family name	Margarson
Email	m.margarson@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

IN13 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	UNIVERSITY HOSPITALS OF LEICESTER NHS TRUST
Address	GWENDOLEN HOUSE GWENDOLEN ROAD LEICESTER LEICESTERSHIRE
Post Code	LE5 4QF

Forename	Christopher
Middle name	
Family name	Bouch
Email	chrisbouch@live.com
Qualification (MD...)	
Country	UNITED KINGDOM

IN14 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	ASHFORD AND ST PETER'S HOSPITALS NHS FOUNDATION TRUST
Address	ST PETERS HOSPITAL GUILDFORD ROAD CHERTSEY SURREY
Post Code	KT16 0PZ

Forename	Mark
Middle name	
Family name	Magregor
Email	Mark.Macgregor@asph.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

IN15 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	ROYAL UNITED HOSPITAL BATH NHS TRUST
Address	COMBE PARK BATH AVON
Post Code	BA1 3NG

Forename	Tim
Middle name	
Family name	Cook
Email	timcook@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

IN16 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	NORTH TEES AND HARTLEPOOL NHS FOUNDATION TRUST
Address	UNIVERSITY HOSPITAL OF HARTLEPOOL HOLDFORTH ROAD HARTLEPOOL CLEVELAND
Post Code	TS24 9AH

Forename	Asokhan
Middle name	
Family name	Krishnaier
Email	francisco.sandiego@nth.nhs.uk
Qualification (MD...)	
Country	UNITED KINGDOM

IN17 ☐

◉ NHS site
○ Non-NHS site

Country: England

Organisation name	LEEDS TEACHING HOSPITALS NHS TRUST
Address	ST. JAMES'S UNIVERSITY HOSPITAL BECKETT STREET LEEDS WEST YORKSHIRE
Post Code	LS9 7TF

Forename	Andrew
Middle name	
Family name	Lumb
Email	andrew.lumb@nhs.net
Qualification (MD...)	
Country	UNITED KINGDOM

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 Professor Gary Mills on 30/09/2015 11:07.

Job Title/Post:	Consultant in anaesthesia and ICM
Organisation:	Sheffield Teaching Hospitals NHS Foundation Trust
Email:	g.h.mills@sheffield.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 Dipak Patel on 30/09/2015 12:01.

Job Title/Post:	Research Manager
Organisation:	Sheffield Teaching Hospitals NHS Foundation Trust
Email:	dipak.patel@sth.nhs.uk