

Prevention of Respiratory Insufficiency after Surgical Management (PRISM) Trial:

**A pragmatic randomised controlled trial of continuous
positive airway pressure (CPAP) to prevent respiratory
complications and improve survival following major
abdominal surgery**

Short Title *PRISM trial*

Sponsor *Queen Mary University of London*

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1. GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CPAP	Continuous Positive Airway Pressure
DMC	Data Monitoring Committee
EQ5D	EQ5D is a standardised questionnaire for measuring quality of life and a trademark of the Euro-Qol group
ICF	Informed Consent Form
ICU	Intensive Care Unit
JRMO	Joint Research Management Office
NHS REC	National Health Service Research Ethics Committee
NHS R&D	National Health Service Research & Development
Participant	An individual who takes part in a clinical trial
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee

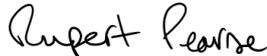
2. SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol (version 1.6, 10/04/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Professor Rupert Pearse

Chief Investigator Affiliation: Queen Mary University of London

Signature and date:  10th April 2017

Statistician Agreement

The clinical study as detailed within this research protocol (version 1.6, 10/04/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP and the current and applicable regulatory requirements.

Statistician name: Dr Claudia Filippini

Signature and date:  10th April 2017

Principal Investigator Agreement

The clinical study as detailed within this research protocol (version 1.6, 10/04/2017), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current and applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Principal Investigator Name:

Principal Investigator Affiliation:

Signature and date:

3. SUMMARY

Short title	PRISM trial
Methodology	International, multi-centre randomised controlled trial with open study group allocation.
Research sites	Hospitals undertaking elective intra-peritoneal surgery in participating countries.
Objectives	To determine whether early postoperative continuous positive airway pressure (CPAP) reduces the incidence of subsequent respiratory complications and improves one-year survival following major intra-peritoneal surgery.
Number of patients	4800 patients
Inclusion criteria	Patients aged 50 years and over undergoing major elective intra-peritoneal surgery.
Statistical analysis	The primary outcome measure is a composite of pneumonia, re-intubation, or death within 30 days of randomisation. The analysis will be conducted according to intention-to-treat principles; all participants with a recorded outcome will be analysed according to the treatment group to which they were randomised. The primary outcome will be analysed using a mixed-effects logistic regression model, which includes centre as a random-intercept, and will be adjusted for the minimisation factors and other pre-specified baseline covariates.
Proposed start date	October 2015
Proposed end date	October 2019
Trial duration	48 months

4. INTRODUCTION

Approximately 310 million surgical procedures are carried out worldwide each year.¹ After surgery more than seven million patients develop complications with one million deaths.² Estimates of postoperative mortality range from 1 to 4% depending on the population sampled and the type of surgical procedure.³ However, it is clear that mortality and morbidity following surgery is greater in high-risk cohorts, where patients have pre-existing medical conditions, are elderly or undergoing a major abdominal procedure, for example surgery to the gastrointestinal tract.⁴ The lasting impact of postoperative morbidity should not be underestimated, since complications following surgery are associated with reduced long-term survival.^{5, 6} Some of the most common postoperative complications affect the respiratory tract.⁷ The published incidence of postoperative pulmonary complications ranges from 9 to 40%, depending on the definition used.^{8, 9}

Major abdominal surgery is associated with adverse changes in respiratory function. Anaesthesia can cause reduced vital capacity, hypoxaemia and impaired central respiratory drive, while surgical manipulation can restrict ventilation, damage the respiratory muscles and cause atelectasis.¹⁰ These factors interact with pre-existing respiratory disease and postoperative pain to create a significant risk of pneumonia and respiratory failure, which may result in death. Evidence from one study suggests that the risk of mortality within 30 days of surgery is increased from 1% to 27% in patients with respiratory failure.⁸ Usual treatments including supplemental oxygen or respiratory physiotherapy may not always prevent deterioration in respiratory function. Subsequent respiratory failure can lead to endotracheal intubation and mechanical ventilation, which is in turn associated with a range of serious morbidities.

Continuous positive airway pressure (CPAP) is a non-invasive method of supporting respiratory function. The patient breathes through a pressurized circuit against a threshold resistor that maintains a pre-set positive airway pressure during both inspiration and expiration.⁹ It is delivered via a facemask, helmet or nasal device by experienced nurses with minimal physician supervision.¹¹ CPAP is often provided in specialist areas of a hospital such as the critical care unit due to the benefit of increased staff numbers. However, this intervention could also be provided on a surgical ward, provided suitably trained nursing staff are available.⁹ The findings of several trials have demonstrated the efficacy of CPAP as a preventative treatment for

high-risk patients following abdominal surgery by reducing the incidence postoperative pulmonary complications. This is supported by evidence from systematic reviews, which call for further research in this area (figure 1).^{9, 12, 13} However, the current evidence base for postoperative CPAP has a number of limitations. Firstly, all of the previous randomised trials have been relatively small (n<250) and therefore lacking in statistical power for patient centered outcomes. Whilst the results of these trials suggest that postoperative CPAP is efficacious, there has yet to be a large multi-centre trial to evaluate the clinical effectiveness of this treatment. Secondly, whilst the several trials of CPAP in the abdominal surgery population have shown encouraging results, there has been limited translation to clinical practice.¹¹ A robust evidence base is needed to justify the changes needed in the perioperative care pathway, and as a result the preventive use of CPAP after major abdominal surgery has not been introduced into routine practice in most healthcare systems. There is a clear need for a major randomised trial to provide definitive evidence to address this uncertainty.

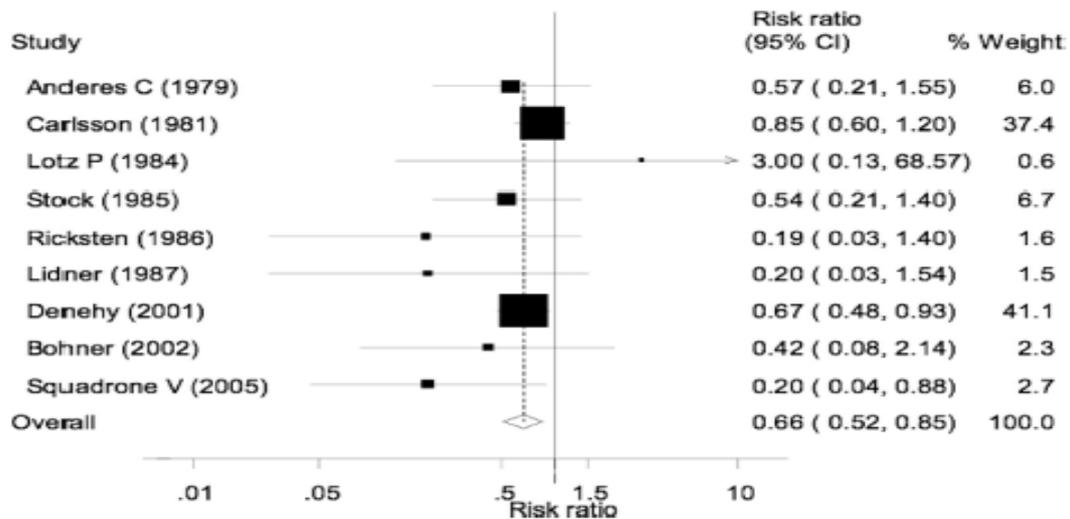


Figure 1. Efficacy of CPAP on a composite endpoint of postoperative pulmonary complications compared to standard treatment.¹²

Current evidence suggests that the routine use of postoperative CPAP is an efficacious preventative treatment that can reduce postoperative respiratory complications. However, evidence of clinical effectiveness is lacking. In particular postoperative CPAP needs to be studied in the context of routine clinical care with reference to patient-centred outcomes. We propose a large, pragmatic, international multi-centre trial to confirm the clinical effectiveness of CPAP administered as routine for four hours immediately following major abdominal surgery, compared to usual clinical care.

5. TRIAL OBJECTIVES

5.1 Primary objective

To determine whether postoperative continuous positive airway pressure (CPAP) reduces the incidence of pneumonia, re-intubation or death following major elective intra-peritoneal surgery compared to usual care in patients aged 50 years and over.

5.2 Primary outcome measure

Composite endpoint of pneumonia, endotracheal re-intubation or death within 30 days of randomisation (Appendix).

5.3 Secondary objectives

To determine whether routine postoperative CPAP reduces other forms of postoperative morbidity, mortality, or improves quality of life.

5.4 Secondary outcome measures

- Pneumonia within 30 days of randomisation
- Endotracheal re-intubation within 30 days of randomisation
- Death within 30 days of randomisation
- Postoperative infection within 30 days of randomisation
- Mechanical ventilation (invasive or non-invasive) within 30 days of randomisation
- All-cause mortality at one year after randomisation
- Quality adjusted life years (QALY) at one year after randomisation

In addition, we will use the following process measures (i.e. non-patient centred outcome measures), to facilitate comparison with other research:

- 30-day re-admission
- Days in critical care
- Duration of hospital stay

5.5 Safety objectives

To determine the safety and tolerability of routine postoperative CPAP.

5.6 Safety outcome measures

Safety outcomes will quantify harm associated with CPAP (appendix). The following pre-defined adverse events will be measured within 24 hours of the end of surgery in patients in the intervention group only:

- Interface intolerance due to excessive air leaks
- Pain
- Cutaneous pressure sore or pressure area
- Claustrophobia
- Oro-nasal dryness
- Hypercapnia
- Haemodynamic instability
- Vomiting
- Aspiration of gastric contents
- Other harm assessed as probably or definitely related to CPAP

A full list of definitions is available in the appendix.

6. METHODOLOGY

6.1 Study design

International, multi-centre randomised controlled trial with open study group allocation.

6.2 Inclusion criteria

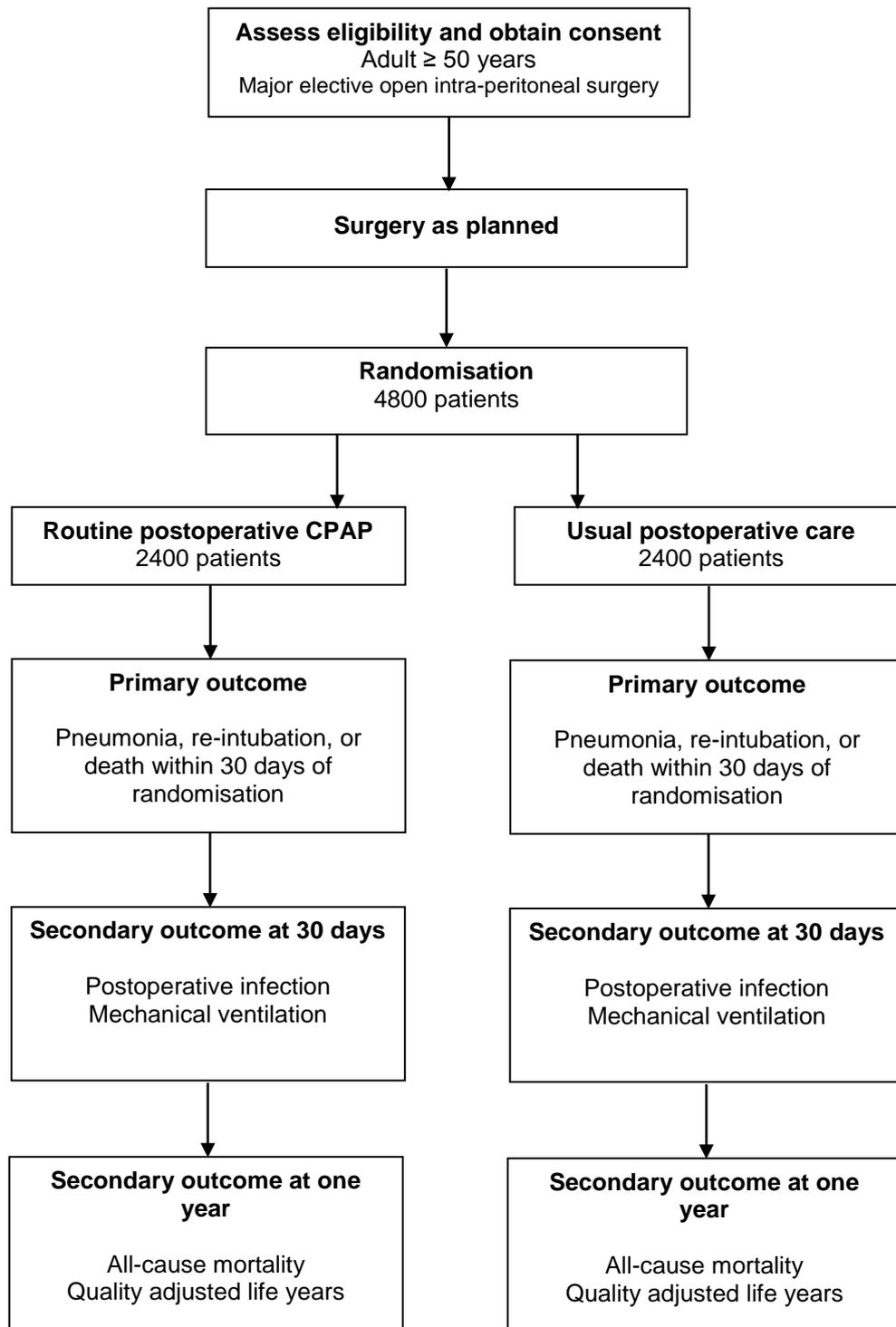
Patients aged 50 years or over undergoing elective major intra-peritoneal surgery using an open surgical technique.

6.3 Exclusion criteria

- Inability or refusal to provide informed consent
- Anticipated requirement for invasive or non-invasive mechanical ventilation for at least four hours after surgery as part of routine care
- Pregnancy or obstetric surgery
- Previous enrollment in PRISM trial
- Current participation in a clinical trial of a treatment with a similar biological mechanism or related primary outcome measure

- Clinician refusal
- Contraindication to continuous positive airway pressure (CPAP)

6.4 Study flow diagram



7. TRIAL PROCEDURES

7.1 Recruitment and screening

This is an international randomised controlled trial. 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. Before surgery, potential participants will be identified and approached by a member of the research team, who are considered part of the direct care team. Wherever possible, the patient will be approached at least 24 hours prior to surgery to allow time for any questions. However, by the nature of the inclusion criteria for this trial, many patients will arrive in hospital on the morning of surgery. Provided that all reasonable efforts have been made to identify a potential participant 24 hours in advance of surgery, they will still be eligible for recruitment within a shorter time frame if this has not proved possible. Written informed consent must be obtained before surgery.

7.2 Informed consent

It is the responsibility of the Principal Investigator (PI) at each site, or persons delegated by the PI to obtain written informed consent from each subject prior to participation in this trial. This process will include provision of a patient information sheet accompanied by the relevant consent form, and an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. The PI or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and consent form will be reviewed and updated if necessary. However, given the short duration of the intervention period, it is most unlikely that new safety information would come to light during the intervention period of an individual patient. Patients who lack capacity to give or withhold informed consent will not be recruited. Patients who are not entered into this trial should be recorded (including reason not entered) on the patient-screening log in the PRISM Investigator Site File.

7.3 Randomisation

Patients will not be randomised before giving written informed consent. Randomisation will be performed immediately after surgery (up to four hours after the

end of the surgical procedure). Participants will be centrally allocated to treatment groups (1:1) by a computer generated dynamic procedure (minimisation) with a random component. Minimisation variables will be country, surgical procedure category and planned use of epidural anaesthesia. The surgical procedure categories are: resection of colon, rectum or small bowel; resection of liver, pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery; vascular procedure; or other intra-peritoneal procedure. Each participant will be allocated with 80% probability to the group that minimises between group differences in these factors among all participants recruited to the trial to date, and to the alternative group with 20% probability. To enter a patient into the PRISM trial, research staff at the site will log on to a secure web-based randomisation and data entry platform and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group. Investigators will declare the intended postoperative care destination before randomisation. This will measure changes in postoperative care that could be attributed to the delivery of the intervention.

7.4 Trial intervention

The trial intervention period will ideally commence immediately after surgery. This will allow widespread implementation of the treatment in post-anaesthetic recovery units, without the need for critical care admission, or other major changes in the perioperative care pathway. After four hours, CPAP will be continued or discontinued at the clinician's discretion.

Intervention group

The trial intervention is defined as CPAP for at least four hours, with minimal interruption, ideally started within four hours after the end of surgery. Where the start of CPAP has been delayed by exceptional circumstances (e.g. equipment failure, critical care admission, etc.), the intervention may be commenced up to twelve hours after the end of surgery. Administration of CPAP will only take place under the direct supervision of appropriately trained staff in an adequately equipped clinical area. Delivery of the trial intervention and monitoring of patients receiving CPAP will be in accordance with local hospital policy or guidelines. Alterations to the administered dose will be recorded along with the reason for this change. Investigators may only use CPAP equipment approved for routine use in their hospital to deliver the

intervention. The starting airway pressure should be 5 cmH₂O and the maximal permissible airway pressure is 10 cmH₂O. The airway pressure may be adjusted within this range at the discretion of the responsible physician. For example, it may be deemed beneficial to increase the airway pressure above 5 cmH₂O for patients with obesity or low chest wall compliance. Since this is a pragmatic clinical effectiveness trial additional training or standardisation of the intervention will not be provided.

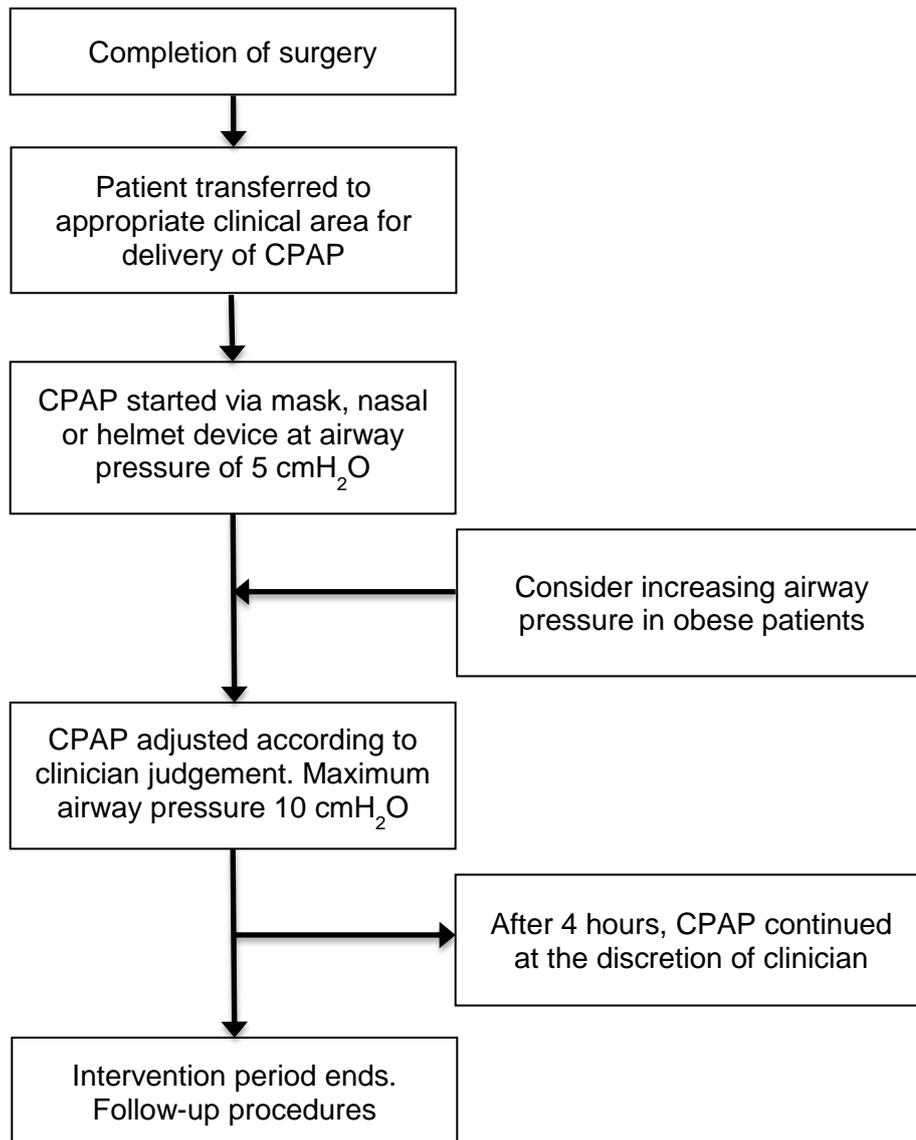
Nasal high flow oxygen is not considered CPAP. It is foreseeable that some patients in the intervention group will not receive CPAP or fail to complete the minimum four hours of CPAP, e.g. due to unplanned invasive or non-invasive ventilation after surgery or because the patient is unable to tolerate the CPAP mask. These situations will be managed as protocol deviations and follow-up data will still be collected. Please see section 7.8 for further details.

Usual care group

Patients in the usual care group will be managed by clinical staff according to local policy and guidelines. The trial findings will therefore reflect the fact that usual care may differ between participating centres, and indeed this is one of the purposes of large clinical effectiveness trials. It is considered good practice for postoperative patients to receive oxygen via a facemask or nasal cannulae. However, this may vary according to local policy. The use of mechanical ventilation, recruitment manoeuvres or high flow nasal oxygen during the intervention period will be recorded on the case report form. It is foreseeable that some patients in the usual care group could receive CPAP as part of usual care. This will be managed as a protocol deviation and follow-up data will still be collected. Please see section 7.8 for further details.

7.5 Intervention algorithm

This algorithm illustrates the steps for delivering postoperative CPAP to patients in the intervention group. Patients in the usual care group will receive postoperative care according to local guidelines. Further details are listed in the CPAP SOP.



7.6 Procedures to minimise bias

It is not possible to conceal treatment allocation from all staff in trials of this type. However, procedures will be put in place to minimise the possibility of bias arising because research staff become aware of trial group allocation. Patients will be followed up for complications by a member of research staff who is unaware of trial group allocation. Complications will then be verified by the local PI or designee who will also be unaware of trial group allocation. The local principal investigator may nominate a senior clinician to assist with this task if he/she becomes aware of the trial group allocation of any individual patient. During the course of follow-up it is possible that a member of the research team may become aware of the treatment group allocation. To quantify the degree of blinding, research staff will make a self-assessment of blinding when collecting follow-up data. The decision to admit a trial participant to a critical care unit will be made by clinical staff and this decision must not be affected by trial group allocation.

7.7 Data collection

The following data will be collected from all sites before and after the trial intervention. Component data will be collected to calculate the ARISCAT score.¹⁴

Randomisation data

- Checklist to ensure the patient meets the eligibility criteria
- Surgical procedure category
- Centre ID
- Planned use of epidural anaesthesia

Baseline data

- Full name
- Gender
- Age/DOB
- ASA grade
- Planned surgical procedure
- Diagnosis of chronic lung disease (COPD, Asthma, Interstitial lung disease, bronchiectasis)

- Respiratory infection within the previous month (including tuberculosis)
- Diagnosis of ischaemic heart disease
- Diagnosis of diabetes
- Diagnosis of stroke
- Diagnosis of heart failure
- Diagnosis of cirrhosis
- Diagnosis of active cancer
- Diagnosis of Human Immunodeficiency Virus (HIV) infection
- Preoperative haemoglobin
- Preoperative creatinine
- Quality of life according to EQ-5D
- Height
- Weight
- NHS number or corresponding patient identifier for database follow-up
- Residential postcode or corresponding patient identifier for database follow-up

Intraoperative period

- Surgical procedure category
- Open technique used
- Anaesthetic technique (general, spinal, regional)
- Mechanical ventilation (Y/N)
 - Duration
 - Maximum PEEP
 - Maximum Vt
 - Maximum FiO₂ (excluding pre-oxygenation during induction of anaesthesia)
 - Total IV fluid input (sum of crystalloid and colloid)
 - Total blood product input (sum of all blood products)
- Extubated at the end of surgery (Y/N)
- Intraoperative recruitment manoeuvre (Y/N)

24 hours postoperative

- Patient received CPAP within twelve hours after the end of surgery? (Y/N)
 - Total duration of CPAP within 12 hours of surgery

- Delivery method (mask, nasal, helmet)
- Maximum airway pressure
- Additional research staff present to help deliver CPAP (Y/N)
- Were tools used to monitor CPAP and inspiratory oxygen fraction? (Y/N)
- Did the patient have a nasogastric tube *in situ* during CPAP? (Y/N)
- Did the patient receive high flow nasal oxygen? (Y/N)
- Adverse events during CPAP (tertiary outcomes)
 - Interface intolerance due to excessive air leaks (Y/N)
 - Pain (Y/N)
 - Cutaneous pressure sore or pressure area (Y/N)
 - Claustrophobia (Y/N)
 - Oro-nasal dryness (Y/N)
 - Hypercapnia (Y/N and peak PaCO₂)
 - Haemodynamic instability (Y/N)
 - Vomiting (Y/N)
 - Aspiration of gastric contents (Y/N)

Clinical outcomes within 30 days of randomisation

- Pneumonia (Y/N)
- Re-intubation (Y/N)
- Death (date)
- Mechanical ventilation (Y/N)
- Quality of life according to EQ5D

Health economic outcomes

- Duration of primary hospital stay
- Days in critical care during the first 30 days after index surgical procedure

Clinical outcomes within one year of randomisation

- Death (date)
- Quality of life according to EQ5D

7.8 Predefined protocol deviations

- Failure to administer CPAP to patients in the intervention group. This includes patients that unexpectedly remain intubated after surgery, or where CPAP is started more than twelve hours after the end of surgery
- Starting CPAP at a dose other than 5 cmH₂O.
- Administration of CPAP to a patient in usual care group. If this occurs within 12 hours of the end of surgery, investigators should consider this a protocol deviation.
- Administration of CPAP for less than 4 hours duration for a patient in the intervention group.
- Administration of CPAP with significant interruption for a patient in the intervention group. Brief interruptions to CPAP to adjust mask, for oral care or routine nursing care are considered part of the intervention. However, if the interruption is prolonged this should be considered a protocol deviation. Investigators will make a judgement about whether the interruption is prolonged and encouraged to record the duration of any interruption on a protocol deviation form. As a guide, a continuous interruption of more than 15 minutes would usually be considered relevant.

7.9 Follow-up procedures

To minimise bias, follow-up data will be collected by an investigator who is unaware of the study group allocation. Investigators will review a participant's medical record (paper or electronic) and contact participants on the telephone to conduct brief interviews at 30 days and one year after surgery. The health economic analysis will be restricted to data derived from UK centres. To facilitate this, we will request hospital episode statistics and mortality data from NHS Digital or equivalent for UK participants. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.

7.10 Withdrawal of participants

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

7.11 Self-assessment of blinding by research staff

The primary outcome will be assessed by an investigator that is blinded to the study group allocation. However, during the course of the primary outcome assessment, the investigator may become un-blinded, for example if the patient reveals information suggesting they received CPAP. To quantify the degree of un-blinding, the investigator will complete a self-assessment of blinding with respect to the treatment group allocation, at the time of assessing the primary outcome. This will allow a measure of the effectiveness of blinding procedures to be reported. Investigators will grade themselves as one of the following:

- Suitably blinded
- May have known study group allocation
- Definitely knew study group allocation

7.12 End of study definition

The end of the study is defined as the point when the last patient has completed one-year telephone follow-up. An interim analysis will be performed at a pre-defined point by the DMEC. Early termination of the study on safety grounds will be addressed via the DMEC. They will report any concerns to the Chief Investigator, who will inform the Sponsor and take appropriate action, which may include stopping the trial, to address concerns about participant safety. The Research Ethics Committee will be informed in writing if the trial is suspended or terminated early.

7.13 Schedule of assessment

Event/Visit	Screening	Pre-op	24 hrs post-op	Hospital discharge	Post-op day 30	Post-op one year
Inclusion/exclusion criteria	x					
Informed consent	x					
Demographic information		x				
Medical history		x				
Height and weight		x				
EQ5D questionnaire (UK only)		x			x	x
Randomisation		x				
Intraoperative information			x			
CPAP			x			
Review of medical notes				x		
Days of ICU and hospital				x		
Telephone contact					x	x
AE/SAE			x	x	x	x
End of trial form						x

8. STATISTICAL CONSIDERATIONS

8.1 Sample size calculation

The primary outcome is a composite endpoint of pneumonia, re-intubation, or death within 30 days following randomisation. The incidence of postoperative pneumonia in previous trials was 8.0% in the usual care group and 4.3% (relative risk reduction of 46%) in the intervention arm. However, the total number of patients included in these five trials was less than 600 patients. The incidence of postoperative pneumonia, admission to intensive care (a surrogate marker of re-intubation) and death in a large international cohort (n ~9000) was 11.7% for patients aged over 45 years.¹⁵ In order to detect a reduction from 11.7% to 8.8% in the primary outcome measure (relative risk reduction of 25%), with a power of 90%, an overall type I error rate of 5%, and a loss to follow up rate of 4%, we would require a total sample size of **4800 patients** (2400 per group). This sample size will allow us to detect a 26% relative risk reduction (7.7% vs. 5.7%) in the secondary outcome measure of mortality at one year after randomisation, with a power of 80% and an overall type I error rate of 5%. Sample size calculations were performed using STATA 14.0 (StataCorp, College Station, TX).

8.2 Statistical analysis

All analyses will be conducted according to intention-to-treat principles, meaning that all patients with a recorded outcome will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. Baseline patient characteristics will be presented, stratified according to treatment allocation. The primary outcome (pneumonia, endotracheal re-intubation, or death within 30 days of randomisation) will be analysed using a mixed-effect logistic regression model. Centre will be included as a random-intercept, and the model will be adjusted for the minimisation variables (country, planned use of epidural anaesthesia and planned surgical procedure category (resection of colon, rectum or small bowel; resection of liver, pancreas or gall bladder; resection of stomach (non-obesity surgery); obesity surgery; vascular procedure; or other intra-peritoneal procedure) and planned use of epidural anaesthesia), as well as the following pre-specified baseline covariates: age, gender, co-morbid disease (chronic respiratory disease, ischaemic heart disease, diabetes mellitus, heart failure, liver cirrhosis, active cancer, and previous stroke or transient ischaemic attack), smoking status and ASA score. The significance level will be set at 0.05. A full statistical analysis plan will be

developed prior to analysis. Clinical outcomes are defined in appendix.

8.3 Health economic analysis

The health economics analysis will be restricted to data derived from UK centres, due to the different payment models operated in participating countries. The analysis will assess whether routine postoperative CPAP is likely to be cost-effective on average. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up period. The cost-effectiveness analysis will therefore take the form of a decision model with one-year mortality as an input in terms of treatment effectiveness. Other stages in the model will relate to subsequent non-fatal events. Effectiveness of the intervention will be defined by any differences in mortality and will be used as a parameter input into the model. Unit costs will be estimated from published literature, NHS and government sources, including NHS Reference costs and Personal Social Services Research Unit Costs of Health and Social Care, to generate a total cost per trial participant for the relevant resource use. Quality adjusted life years (QALYs) over the patients' lifetime will be used as the primary outcome measure of the cost-effectiveness analysis. Trial mortality data will be quality-adjusted on the basis of EQ-5D data and allowing for non-fatal clinical events experienced in the two trial arms. A long-term extrapolation will be undertaken to estimate QALYs over a patient's expected lifetime. This will involve the use of parametric survival modelling together with relevant clinical and epidemiological data on patients' long-term life expectancy given their age, recovery from high-risk an abdominal surgery and whether or not they have experienced non-fatal clinical events following surgery.

8.4 Secondary studies

The use of PRISM trial data for further secondary studies is encouraged. Secondary studies of UK data are detailed in the appendix.

9. RESEARCH ETHICS

The PI will ensure that this trial is conducted in accordance with the Principles of the Declaration of Helsinki as amended in Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996), Edinburgh (2000), Washington DC (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013) as described at the following internet site:

<http://www.wma.net/en/30publications/10policies/b3/index.html>. The trial will fully adhere to the principles outlined in the Guidelines for Good Clinical Practice ICH Tripartite Guideline (January 1997). The study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable and applicable legal and regulatory requirements. Research ethics and regulatory approvals will be sought before starting the trial at each site, in accordance with national research legislation/guidelines for that country. This will usually require the translation of the trial protocol and patient facing documents. Where a document is translated it will be back translated into English to check for consistency with the original. Other trial documents will be translated at the discretion of the national lead investigator. At sites, all accompanying material given to a potential participant will have undergone an independent Research Ethics Committee review within that country. Full approval by the Research Ethics Committee will be obtained prior to starting the trial and fully documented by letter to the Chief Investigator naming the trial site, local PI (who may also be the Chief Investigator) and the date on which the ethics committee deemed the trial as permissible at that site. All members of the trial steering committee will declare conflicts of interest before joining the study group. These will be listed on any publications arising from the trial.

10. DATA HANDLING AND RECORD KEEPING

10.1 Confidentiality

Information related to participants will be kept confidential and managed in accordance with the Data Protection Act (UK), NHS Caldecott Principles (UK), The Research Governance Framework for Health and Social Care (UK), and the conditions of Research Ethics Committee Approval, or corresponding legislation or approvals for a particular participating country or site. The patient's full name, date of birth, hospital number and NHS number (UK) will be collected at randomisation to allow tracing through national records. The personal data recorded on all documents will be regarded as confidential. The PI must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The PI must ensure the patient's confidentiality is maintained at all times. The Sponsor will ensure that all participating partner organisations will maintain the confidentiality of all subject data and will not reproduce or disclose any information by

which subjects could be identified, other than reporting of serious adverse events. Representatives of the trial management team will require access to patient notes for quality assurance purposes and source data verification, but patients should be reassured that their confidentiality will be respected at all times. In the case of special problems and/or competent authority queries, it is also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

10.2 Data storage

Data will be transcribed on to the paper CRF prior to entry on to the secure PRISM 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 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).

10.3 Archiving

All central trial documentation and data will be archived centrally by the Sponsor in a purpose designed archive facility for twenty years in accordance with regulatory requirements. Access to these archives will be restricted to authorised personnel. Electronic data sets will be stored indefinitely.

10.4 Patient identifiable data

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 for other countries.

11. PRODUCTS, DEVICES AND TECHNIQUES

11.1 CPAP delivery

CPAP machines are routinely used in secondary care. Investigators may only use CPAP equipment approved for routine use in their hospital to deliver the intervention. Please see the CPAP SOP for specific details of the intervention.

12. SAFETY REPORTING

12.1 Adverse Events (AE)

An AE is an untoward medical occurrence in a PRISM trial participant. This may be any unfavourable and unintended sign, symptom or disease. It is expected that patients undergoing major abdominal surgery may often suffer medical complications, up to and including death. It follows that a large number of PRISM trial participants will experience complications of surgery, which are completely unrelated to the trial intervention. In the PRISM trial, only AEs clearly related to the use of CPAP will be reported. It is anticipated that almost all of these will fall under one of the following predefined categories:

- Interface intolerance due to excessive air leaks
- Pain
- Cutaneous pressure sore or pressure area
- Claustrophobia
- Oro-nasal dryness
- Hypercapnia
- Haemodynamic instability
- Vomiting
- Aspiration of gastric contents

The Principal Investigator (or suitably qualified nominee) is responsible for confirming the relatedness of any AE to the trial intervention. If an AE occurs the clinician responsible for the patient should decide whether it is safe to continue CPAP, with or without modification, or whether CPAP should be discontinued.

12.2 Notification and reporting Adverse Events or reactions

Individual sites will record all adverse events in the CRF (supplementary form) and submit this information via the online database. Paper copies should be kept locally.

12.3 Serious Adverse Event (SAE)

Whilst unlikely, it is recognised that an AE related to CPAP may become a SAE. Prompt reporting of SAEs is required to ensure any factors which affect the safety of other trial participants can be identified and acted upon. The Principal Investigator (or suitably qualified nominee) must assess the SAE as probably or definitely related to CPAP and meet one of the following criteria:

- (a) Results in death;
- (b) Is life threatening;
- (c) Clearly prolongs the hospital stay;
- (d) Causes significant disability or incapacity.

12.4 Reporting a Serious Adverse Event

Potential SAEs should be reported to the PRISM trial co-ordinating centre within 24 hours. For details of how to report a potential SAE please see the adverse event reporting SOP.

12.5 Notification and reporting of Serious Adverse Events

The chief investigator will determine whether an adverse event meets the criteria for an SAE and consider what further action should be taken, if any, to protect current and future trial participants. This may involve discussion within the Principal Investigator, and if necessary, the independent chairs of the TSC and DMEC. Confirmed SAEs will be reported by the trial management group to the sponsor and/or ethics committee as required by national research regulations for the country in question.

12.6 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of trial participants from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the REC prior to implementing these safety measures is not required. However, it is the responsibility

of the CI to inform the sponsor and Research Ethics Committee of this event within three days. The sponsor must be sent a copy of the correspondence with regards to this matter.

12.7 Annual safety reporting

The CI will send the annual progress report to the REC and to the sponsor.

12.8 Overview of the safety reporting responsibilities

The CI/PI has the overall oversight responsibility. The CI/PI will ensure that safety monitoring and reporting is conducted in accordance with the sponsor's requirements.

13. MONITORING & AUDITING

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 PRISM Trial Management Group will communicate closely with individual sites and the Sponsor's representatives to ensure these processes are effective. A Data Monitoring and Ethics Committee (DMEC) will be appointed (details of the DMEC can be found on page 28).

13.1 Training of investigators

All investigators will complete training consistent with their national regulations for clinical research, as well as those in the country of the trial sponsor (UK). A representative of the national coordinating centre for that country will conduct a site initiation visit at each site before patient recruitment commences. This visit will include an induction to the trial protocol and procedures, the standardised assessment of outcome measures, and the trial database. Where new investigators join the research team at a particular site during the course of the trial, the responsibility for induction training will fall to the local principal investigator.

13.2 Monitoring the safety and wellbeing of trial participants

The Research and Development departments at each trial site should perform

regular audits of research practice. Systems are in place to ensure that all PIs and designees are able to demonstrate that they are qualified by education, training or experience to fulfill their roles and that procedures are in place that assures the quality of every aspect of the trial. The intervention will last only four hours in most cases, therefore 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. Early termination of trial in response to safety issues will be addressed via the DMEC. Day to day management and monitoring of individual sites will be undertaken via the Trial Management Group composed of the Chief Investigator and supporting staff. They will meet on a regular basis to discuss trial issues. A formal schedule of data monitoring can be found in the data monitoring SOP.

13.3 Monitoring the safety of investigators

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

14. TRIAL MANAGEMENT & COMMITTEES

14.1 Trial management group

Day-to-day trial management will be co-ordinated by a trial management group consisting of the Chief Investigator and his/her support staff.

14.2 Trial steering committee

The Trial Steering Committee will oversee the trial and will consist of:

- several independent clinicians and trialists
- lay/patient representation
- co-investigators (including a representative of each participating nation)
- an independent Chair

Meetings will be held at regular intervals determined by need but not less than once a year. The TSC will take responsibility for:

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

14.3 Data monitoring and ethics committee

The Data Monitoring and Ethics Committee (DMEC) is independent of the trial team and comprises of two clinicians with experience in undertaking clinical trials and a statistician. The committee will agree conduct and remit, which will include the early termination process. The principle responsibility of the DMEC will be to safeguard the interests of trial participants, including assessing the safety of the intervention, reviewing relevant new external evidence, and monitoring the overall conduct of the trial. The DMEC will provide recommendations about stopping, modifying or continuing the trial to the Trial Steering Committee. The DMEC may also make recommendations regarding selection, recruitment, or retention of participants, their management, protocol adherence and retention of participants, and procedures for data management and quality control. The Trial Steering Committee will be responsible for promptly reviewing the DMEC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required. The DMEC will review trial data relating to patient safety and the quality of trial conduct. The DMEC will perform a single interim analysis during the recruitment period. In the light of this analysis, the DMEC will advise the chief investigator if, in their view, the randomised comparisons have provided both (i) 'proof beyond reasonable doubt' that for all, or some specific types of patient, one particular treatment is clearly contra-indicated in terms of a net difference in adverse events or serious morbidity, and (ii) evidence that might reasonably be expected to materially influence future patient management. 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.

15. FINANCE AND FUNDING

This is an investigator led trial. This trial is supported by unrestricted grants from the Association of Anaesthetists of Great Britain and Ireland, the National Institute for Health Research (UK) and Intersurgical Ltd who will also provide CPAP consumables.

16. SPONSORSHIP & INDEMNITY

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

17. PUBLICATION

Data arising from the research will be made available to the scientific community in a timely and responsible manner. A detailed scientific report will be submitted to a widely accessible scientific journal on behalf of the PRISM Trial Steering Committee. The TSC will agree the membership of a writing committee, which will take primary responsibility for final data analysis and authorship of the scientific report. All authors will comply with internationally agreed requirements for authorship and will approve the final manuscript prior to submission. Please see PRISM trial publication charter for further details.

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Appendix: definitions

Clinical outcome measures

Primary outcome measure

Composite of pneumonia, re-intubation, or death within 30 days of randomisation.

Pneumonia

Care will be taken to distinguish between tracheal colonisation, upper respiratory tract infections and early onset pneumonia. Pneumonia must meet the following criteria:

Two or more serial chest radiographs with at least one of the following features (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

- a) new or progressive and persistent infiltrate
- b) consolidation
- c) cavitation

AND at least one of the following:

- a) fever ($>38^{\circ}\text{C}$) with no other recognised cause
- b) leucopaenia ($< 4 \times 10^9/\text{L}$) or leucocytosis ($>12 \times 10^9/\text{L}$)
- c) for adults >70 years old altered mental status with no other cause

AND at least two of the following:

- a) new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements
- b) new onset or worsening cough or dyspnoea, or tachypnoea
- c) rales or bronchial breath sounds
- d) worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

Endotracheal re-intubation

Re-insertion of an endotracheal tube after the patient has been extubated following the completion of the index surgical procedure. Endotracheal extubation is defined as an intentional clinical decision to remove an endotracheal tube. Extubation does not include accidental or inadvertent removal of an endotracheal tube. Re-intubation does not include intubation and anaesthesia for subsequent surgical procedures within the follow-up period, unless the patient is not extubated at the end of the later surgical procedure.

Secondary outcome measures (listed alphabetically)

Acute Kidney Injury

According to the KIDGO consensus definition of moderate or severe acute kidney injury (2012):

- a) a two-fold increase in serum creatinine compared the preoperative baseline measurement
- b) or an increase in serum creatinine $\geq 354 \mu\text{mol/L}$ ($\geq 4.0 \text{ mg/dL}$) with an acute rise of $> 44 \mu\text{mol/L}$ (0.5 mg/dL)
- c) or oliguria of $< 0.5 \text{ ml/kg/hour}$ for twelve consecutive hours
- d) or the initiation of new renal replacement therapy

Note: Cannot be diagnosed in patients with existing end stage renal failure.

Acute psychosis or delirium

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

Acute respiratory distress syndrome

According to the Berlin consensus criteria (2012):

- a) Within one week of a known clinical insult or new worsening respiratory symptoms
- b) AND bilateral opacities on chest imaging, not fully explained by effusions, lobar/lung collapse, or nodules
- c) AND respiratory failure not explained by cardiac failure or fluid overload (requires objective assessment e.g. echocardiogram to exclude hydrostatic oedema if no risk factors are present)
- d) AND supplemental oxygenation (requires correcting if altitude >1000m):
 - Mild: $\text{PaO}_2:\text{FiO}_2$ 26.7-40.0 kPa with PEEP or CPAP $\geq 5\text{cmH}_2\text{O}$
 - Moderate: $\text{PaO}_2:\text{FiO}_2$ 13.3-26.6 kPa with PEEP $\geq 5\text{cmH}_2\text{O}$
 - Severe: $\text{PaO}_2:\text{FiO}_2 \leq 13.3$ kPa with PEEP $\geq 5\text{cmH}_2\text{O}$

Anastamotic leak

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

Aspiration pneumonitis

Acute lung injury after the inhalation of gastric contents.

Bowel infarction

Demonstrated at laparotomy.

Bronchospasm

Newly detected expiratory wheeze treated with bronchodilators.

Cardiac events

Myocardial infarction

Increase in serum cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and at least one of the following criteria:

- a) symptoms of new ischaemia
- b) new or presumed new significant ST segment or T wave ECG changes or new left bundle branch block
- c) development of pathological Q waves on ECG
- d) radiological or echocardiographic evidence of new loss of viable myocardium or new regional wall motion abnormality
- e) identification of intracoronary thrombus at angiography or autopsy

Arrhythmia

ECG evidence of cardiac rhythm disturbance.

Cardiac arrest with successful resuscitation

Cardiac arrest according to UK Resuscitation Council definition. Successful resuscitation is defined as return of spontaneous circulation for at least one hour.

Cardiogenic pulmonary oedema

Appropriate clinical history and examination with consistent chest radiograph.

Infective complications

Infection, source uncertain

Strong clinical suspicion of infection but the course has not been confirmed. Requires two or more of the following criteria:

- a) core temperature $<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$
- b) white cell count $>12 \times 10^9/\text{L}$ or $<4 \times 10^9/\text{L}$
- c) respiratory rate >20 breaths per minute or $\text{PaCO}_2 < 4.5 \text{ kPa}$
- d) pulse rate >90 beats per minute

Urinary tract infection

This is a simplified version of the CDC criteria taken from the ESA-ESICM consensus on perioperative outcome measures (Jammer et al. 2014).

Urinary tract infection is defined as a positive urine culture of $\geq 10^5$ colony forming units per ml with no more than two species of micro-organisms AND with at least one of the following signs or symptoms:

- a) fever ($>38^{\circ}\text{C}$)
- b) urgency
- c) frequency
- d) dysuria
- e) suprapubic tenderness
- f) costo-vertebral angle pain or tenderness with no other recognised cause

Surgical site infection (superficial)

A superficial surgical site infection must meet the following criteria:

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

- a) purulent drainage from the superficial incision;
- b) organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision;
- c) at least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat, and superficial incision is deliberately opened by surgeon, unless incision is culture-negative;
- d) diagnosis of superficial incisional surgical site infection by the surgeon or attending physician.

Surgical site infection (deep)

A deep incisional surgical site infection must meet the following criteria:

Infection occurs within 30 days after the operative procedure AND involves deep soft tissues (e.g., fascial and muscle layers) of the incision AND patient has at least one of the following:

- a) purulent drainage from the deep incision but not from the organ/space component of the surgical site
- b) a deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever ($>38^{\circ}\text{C}$) or localised pain or tenderness, unless incision is culture-negative
- c) an abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathological or radiologic examination

- d) diagnosis of a deep incisional surgical site infection by a surgeon or attending physician

An infection that involves both superficial and deep incision sites should be classified as a deep incisional surgical site infection.

Surgical site infection (organ/space)

An organ/space surgical site infection involves any part of the body, excluding the skin incision, fascia, or muscle layers that is opened or manipulated during the operative procedure. An organ/space surgical site infection must meet the following criteria:

Infection occurs within 30 days after the operative procedure AND appears related to the previous surgery AND the infection involves any part of the body, excluding the skin incision, fascia, or muscle layers opened or manipulated during the operative procedure AND patient has at least one of the following:

- a) purulent drainage from a drain that is placed through a stab wound into the organ/space;
- b) organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/ space;
- c) an abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination;
- d) diagnosis of an organ/space surgical site infection by a surgeon or attending physician.

Laboratory-confirmed bloodstream infection

Requires at least one of the following criteria:

- a) Patient has a recognised pathogen cultured from one or more blood cultures and the organism cultured from blood is not related to an infection at another site.
- b) Patient has a fever ($>38^{\circ}\text{C}$), chills, or hypotension and at least one of the following:
 - a. Common skin contaminant is cultured from two or more blood cultures drawn on separate occasions;
 - b. Common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy;
 - c. Positive antigen blood test.

Perforated viscus

Demonstrated at laparotomy or by contrast enhanced radiograph or CT scan. For example perforated bowel, gall bladder etc.

Pleural effusion

Radiological evidence of significant fluid accumulation in the pleural cavity. Most commonly this will be detected using a chest radiograph or an ultrasound scan.

Pneumothorax

Air in the pleural cavity with no visceral bed surrounding the visceral pleura. Usually results from damage to the pleural membranes or lung tissue.

Postoperative haemorrhage*Gastro-intestinal bleed*

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

Other postoperative haemorrhage

Overt blood loss, not from the gastro-intestinal tract, requiring transfusion of two or more units of blood in two hours.

Pulmonary embolism

A new blood clot or thrombus within the pulmonary arterial system identified by computed tomography pulmonary angiogram (CTPA) with an appropriate clinical history.

Stroke

Clinical diagnosis with confirmation by computed tomography (CT) scan.

Definitions of pre-defined adverse events related to CPAP

Interface intolerance due to excessive air leak

Air leaks associated with delivery device sufficient to prevent effective CPAP. Subjective assessment by clinician.

Pain

Pain associated with contact of delivery device against the skin, sufficient to prevent effective CPAP. Subjective assessment of severity by the investigator.

Cutaneous pressure sore or pressure area

Pressure sore or pressure area associated with contact of the delivery device against the skin. Assessment of severity to be completed by investigator and reported on page two of the supplementary adverse event form according to Waterlow grading¹⁶:

- a) Grade 1: discolouration of intact skin, not affected by light pressure
- b) Grade 2: partial thickness skin loss/damage involving the dermis or epidermis
- c) Grade 3: Full thickness skin loss/damage involving the subcutaneous tissue but not the underlying fascia.
- d) Grade 4: Full thickness skin loss/damage with extensive destruction and necrosis of the underlying tissue.

Claustrophobia

Claustrophobia associated with the delivery device sufficient to prevent effective CPAP. Subjective assessment of severity by investigator.

Oronasal dryness

Oronasal dryness associated with delivery device sufficient to prevent effective CPAP. Subjective assessment of severity by the investigator.

Hypercapnia

Hypercapnia *directly resulting* from CPAP and sufficient to prevent effective CPAP. This should not include hypercapnia not directly caused by CPAP. Subjective assessment by investigator and to record peak PaCO₂ on page two of the supplementary adverse event form.

Haemodynamic instability

Systolic blood pressure of less than 70 mmHg *or* need for inotropic drugs to maintain systolic blood pressure higher than 85 mmHg for two hours or more, *or* electrocardiogram evidence of ischemia or significant ventricular arrhythmias.

Vomiting

Vomiting, which is sufficient to prevent effective CPAP. Subjective assessment of severity by investigator.

Aspiration of gastric contents

Inhalation of regurgitated gastric contents directly related to CPAP.

Other definitions

Active cancer

A current diagnosis of cancer excluding non-melanoma skin cancers. A previous diagnosis of cancer where the patient underwent curative treatment with remission is not considered active cancer. A surgical procedure where the indication is a presumed diagnosis of cancer, but which has not yet been confirmed with histology, should be considered active cancer.

Cancer surgery

Intended to be a curative treatment

The surgical procedure is intended to cure the cancer.

Intended to be palliative treatment

The surgical procedure is not intended to cure the cancer. For example surgical debulking in metastatic disease, partial removal of a tumour or for the purpose of pain or other symptom control.

End of surgery

Completion of surgery. Usually marked by suturing of the wound and application of dressing(s).

Intraoperative recruitment manoeuvre

A technique used by the anaesthetist to transiently increase the transpulmonary pressure. This is usually by increasing tidal volume or inspiratory pressure for at least one breath.

Levels of care after surgery

Level 3 care: Critical care unit

A clinical area capable of providing invasive mechanical ventilation or support to at least two organ systems.

Level 2 care: Critical care unit or step-down unit

A clinical area capable of providing support to a single organ system, but not including invasive mechanical ventilation, which is considered level 3 care.

Post-anaesthesia care unit (PACU)

Short-stay clinical area dedicated to caring for patients that are recovering from anaesthesia. If the PACU is providing level 2 care then level 2 care should be recorded on the CRF.

Surgical ward

Hospital ward environment not offering single-organ support or dedicated to patients recovering from anaesthesia.

Critical care unit admission

Either level two or level three care, as defined above.

Open surgical technique

Open abdominal surgery is usually distinguished from laparoscopic by the fact that for laparoscopic surgery the incision is only large enough to remove the resected specimen. Some procedures may involve the use of a laparoscope as well as an open incision, where the incision is larger than required to remove the specimen – this is considered open surgery.

Preoperative oxygen saturation (SpO₂)

Pulse-oximetry on room air before surgery.

Primary hospital admission

The hospital admission for elective surgery during which the participant was randomised as part of the PRISM trial. The duration of the primary hospital stay

should be calculated from the date of randomisation.

Respiratory support

Invasive mechanical ventilation

Positive pressure ventilation via an endotracheal tube or supraglottic airway device.

Non-invasive mechanical ventilation

Positive pressure mechanical ventilation via a face-mask, hood or helmet, or nasal device. However, Continuous Positive Airway Pressure (CPAP) is not considered non-invasive mechanical ventilation.

High flow nasal oxygen

Humidified oxygen therapy delivered via large-bore nasal prongs at flow rates greater than 50 litres per minute.

Maximum positive end expiratory pressure (PEEP) during surgery

The maximum pressure, above atmospheric pressure, that exists at the end of expiration and provided by mechanical ventilation.

Maximum set tidal volume (V_t) during surgery

The maximum volume of air displaced between inspiration and expiration during mechanical ventilation as set on the ventilator.

Start of surgery

Time of the induction of anaesthesia before the surgical procedure.

Appendix: National registry linkage (UK only)

1. Background

More than 1.5 million patients undergo major surgery in the UK each year with reported hospital mortality between 1 and 4%.¹⁻³ Complications following major surgery are a leading cause of morbidity and mortality; respiratory complications, including pneumonia, are some of the most frequent and severe.⁴⁻⁹ The PRISM trial aims to determine whether continuous positive airway pressure (CPAP), given immediately after surgery, can reduce the incidence of respiratory complications and improve long-term survival after major abdominal surgery.

In the United Kingdom (UK), individual patient consent will be sought to allow linkage of PRISM data to national registries for hospital episodes and mortality. This expands the scope of the trial, whilst putting no additional burden on individual participants.

2. Data source

In the UK mortality registry data is collated at a national level by the Office for National Statistics (ONS). Hospital Episode Statistics (HES) are collated at a national level by separate organisations for England, Scotland, Wales and Northern Ireland. These data include details of hospital admissions, hospital procedures, demographic information and hospital length of stay.

3. Methods

These analyses will utilise both ONS mortality statistics and hospital episode statistics. Individual patient consent will be obtained from UK participants for data linkage to national databases/registries. Individual applications for access to HES and mortality data will be made through national organisations in each of the devolved nations, e.g. NHS Digital for England. Patient identifiable data will be transferred to NHS Digital (or equivalent organisation) to facilitate data linkage. A dataset including linked data will be returned, either using patient identifiers or pseudo-identifiers, depending on data access rules. Alternatively, the full PRISM (UK) dataset with patient identifiers could be transferred to NHS Digital and a completely anonymised dataset returned after data linkage, i.e. with patient identifiable data removed.

4. Specific sub-studies

4.1. One-year mortality

The majority of previous studies of postoperative CPAP have focused on short-term or in-hospital clinical outcomes. Therefore, the impact of CPAP on postoperative complications after hospital discharge is unclear. This sub-study aims to describe the impact of postoperative CPAP on mortality up to one year after surgery in a UK cohort.

4.2. Long-term mortality

Data from the USA suggests that there is a relationship between the presence of any postoperative complication and reduced long-term survival.¹⁰ However, this relationship has not been confirmed in a UK surgical cohort. This sub-study aims to describe the incidence risk of mortality up to five years after surgery, to identify association between the presence of complications in the immediate postoperative period (up to 30 days after surgery) and survival up to five years after surgery, and the impact of postoperative CPAP on five-year postoperative mortality in a UK surgical cohort.

4.3. Health Economic analysis

Cost effectiveness is a key determinant of successful implementation of a new intervention. This sub-study aims to assess whether routine postoperative CPAP is likely to be cost-effective on average. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up period. The cost-effectiveness analysis will therefore take the form of a decision model with one-year and/or five-year mortality as an input in terms of treatment effectiveness. Quality adjusted life years (QALYs) over the patients' lifetime will be used as the primary outcome measure of the cost-effectiveness analysis. Trial mortality data will be quality-adjusted on the basis of EQ-5D data and allowing for non-fatal clinical events experienced in the two trial arms.