Postoperative continuous positive airways pressure (CPAP) to prevent pneumonia, re-intubation and death after major abdominal surgery: An international randomised trial.

Running title: Clinical trial of CPAP to prevent respiratory complications after surgery

Writing committee for the PRISM trial group[§]

[§] Members of the PRISM trial group are listed in the supplementary appendix, pages 2-11.

Trial registration: ISRCTN56012545 [https://doi.org/10.1186/ISRCTN56012545]

Correspondence to:
Rupert Pearse
Queen Mary University of London,
Adult Critical Care Unit,
Royal London Hospital,
London E1 1FR
United Kingdom.
e-mail: r.pearse@qmul.ac.uk
Tel: +44 20 3594 0351

Abstract word count: 282 Manuscript word count: 4500

Keywords: Surgery; Anaesthesia; Pneumonia; Postoperative complications; Mortality

Abstract

Background: We hypothesised that continuous positive airways pressure (CPAP) administered via mask or hood immediately after major abdominal surgery could prevent respiratory complications, which are an important source of postoperative morbidity.

Methods: Pragmatic, international, open-label, randomised trial in 70 hospitals across six countries. Patients aged ≥50 years undergoing elective major open abdominal surgery were randomly assigned to CPAP, started within four hours after the end of surgery and continued for at least four hours, or usual postoperative care. Patients were randomised using a computer-generated minimisation algorithm with inbuilt concealment. The primary outcome was a composite of pneumonia, endotracheal re-intubation or death within 30 days after randomisation. The final analysis was by intention-to-treat and presented as odds ratios (OR) with 95% confidence intervals and crude data as n (%). Trial registration with ISRCTN registry: ISRCTN56012545.

Findings: Between February 2016 and November 2019, 4806 patients were enrolled and 4793 were included in the analysis: 2396 in the CPAP group and 2397 in the control group. The mean (SD) age was 67·8 (9·2) years and 2230/4793 (46·5%) patients were female. The primary outcome occurred in 195/2396 (8·1%) patients in the intervention group compared to 197/2397 (8·2%) patients in the usual care group (OR 1·01 [0·81-1·24]; p=0·95). There were 276 adverse events among 200/2396 (8·3%) patients who received CPAP, including claustrophobia (78/276), oro-nasal dryness (43/276), excessive air leak (36/276), vomiting (26/276) and pain (24/276). There were two serious adverse events.

Interpretation: In this large clinical effectiveness trial, CPAP did not reduce the incidences of pneumonia, endotracheal re-intubation or death after major abdominal surgery.

Funding: Barts Charity, Intersurgical Ltd, Association of Anaesthetists and Sapienza Università di Roma.

Research in Context

Evidence before this study: A systematic review and meta-analysis by the Cochrane Collaboration included 10 small clinical trials of postoperative Continuous Positive Airways Pressure (CPAP), delivered through a mask or hood, with a total of 709 participants. Most trials were single centre, and the risk of bias was high. In five trials (n=563), CPAP reduced the incidence of pneumonia (RR 0·43 [0·21-0·84]; I^2=0%). In two trials (n=411), CPAP reduced the incidence of re-intubation, a marker of severe respiratory failure (RR 0·14 [0·03-0·56]; I^2=0%). In two trials (n=413) there was no clear difference in all-cause mortality between CPAP and control group patients (RR 1·28 [0·35-4·66]; I^2=75%). In six trials that reported pulmonary atelectasis (n=249), CPAP reduced the incidence of atelectasis (RR 0·62 [0·45-0·86]; I^2=61%). The existing evidence to support CPAP is derived from mostly small, single-centre trials. Routine postoperative CPAP has not been adopted as standard clinical practice in any country.

Added value of this study: PRISM was a pragmatic, randomised clinical trial of preventative CPAP after major open abdominal surgery in 70 hospitals in six countries, including 4793 patients. In a widely generalisable, real-world sample of patients, we found that CPAP did not reduce the incidence of pneumonia, re-intubation or death within 30 days after surgery, or mortality within one-year after surgery. This trial substantially increases the quality of the available evidence that anaesthetists, surgeons and critical care physicians can use to inform their clinical practice.

Implications of all the available evidence: The current body of evidence does not support the routine use of CPAP as a preventative intervention to reduce the incidence pneumonia, endotracheal re-intubation or death after major open abdominal surgery.

Introduction

One in six patients undergoing major surgery experience a postoperative complication before hospital discharge, including respiratory complications and infections, which are strongly associated with reduced long-term survival.[1-4] Poor postoperative outcomes are very important for society with more than 310 million patients undergoing major surgery worldwide every year,[5] many of whom are older with significant comorbidities.[6,7] One of the most frequent and serious complications is pneumonia, which can lead to respiratory failure requiring mechanical ventilation and, in some cases, death.[8] The risk of postoperative respiratory complications may be increased by the residual effects of anaesthesia and surgery, including postoperative pain, depression of respiratory drive by narcotic medication, neuromuscular blockade, atelectasis and pulmonary collapse.[9,10] These factors are particularly important after major abdominal surgery, where surgical manipulation within the abdomen and post-operative pain can further impair respiratory function, reducing natural protective mechanisms such as coughing, and worsening pulmonary atelectasis.

Continuous positive airways pressure (CPAP) is a safe and reliable method of non-invasive respiratory support, which is widely available in the majority of hospitals around the world.[11-14] CPAP can be delivered by facemask, nasal mask or hood device, and applies a continuous positive pressure to the upper airways throughout the entire respiratory cycle. Evidence mostly from small single-centre trials suggests that preventative CPAP early after major surgery may prevent subsequent respiratory complications, perhaps by reducing atelectasis and pulmonary collapse.[15-17] CPAP may also improve outcomes in

patients that develop respiratory failure after major surgery.[16,17] However, this treatment approach has not been adopted into routine clinical practice in any country.

We designed the PRISM trial to test the hypothesis that CPAP administered within four hours after major open abdominal surgery would reduce the incidence of pneumonia, endotracheal re-intubation and death within 30 days after randomisation, compared to usual postoperative care.

Methods

Trial design and setting

This was an investigator-initiated, pragmatic, international randomised trial that compared the application of CPAP to usual care in patients who had undergone major open abdominal surgery. We conducted the trial in Italy, Norway, South Africa, Spain, Sweden, and the United Kingdom. Centres were hospitals undertaking major open abdominal surgery.

Trial oversight

The trial was overseen by a Trial Steering Committee (TSC) with an independent chair and two additional independent members (appendix). Safety monitoring was conducted by an independent Data Monitoring and Ethics Committee (DMEC), which reported to the TSC. Day-to-day management of the trial was undertaken by the chief investigators and their support staff. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the Research Governance Framework.[18,19] The trial protocol was approved by a research ethics committee in the United Kingdom (15/LO/1595) and by the local ethics committees or institutional review boards in other participating countries. The trial was registered with a public registry (ISRCTN 56012545). The trial protocol was published in a peer-reviewed scientific journal (Supplementary appendix, page 62).[20]

Patients

Eligible patients were aged 50 years or over and undergoing elective major intra-peritoneal surgery using an open surgical technique. Open technique was defined as a

surgical procedure where the incision was larger than that required to remove the surgical specimen. Patients were excluded if (a) they refused or were unable to provide written informed consent; (b) they had an anticipated requirement for invasive or non-invasive mechanical ventilation for at least four hours after surgery as part of routine care; (c) the patient was pregnant; (d) the patient was previously enrolled in the PRISM trial; or (e) if there was pre-existing participation in another clinical trial of a treatment with a similar biological mechanism or related primary outcome.[20] Patients were screened and approached by a local investigator, in most cases, before the day of surgery. A detailed and standardised data set was collected before, during and after surgery using an online database.

Randomisation and masking

Patients were allocated to either intervention or usual care groups in a 1:1 ratio by a computer-generated dynamic procedure (minimisation) with a random component. The randomisation system was accessed by investigators via a secure website, which concealed the allocation sequence. Minimisation variables were country, planned surgical procedure category and planned use of epidural anaesthesia. The surgical procedure categories were resection of colon, rectum or small bowel; resection of liver, pancreas or gall bladder; resection of stomach (non-obesity surgery); resection of oesophagus (non-obesity surgery); obesity surgery; vascular surgery; or other intra-peritoneal surgery. Each patient was allocated with 80% probability to the group that minimised between-group differences in these factors among all participating patients recruited to the trial to date, and to the alternative group with 20% probability. It was not possible to blind either patients or clinicians delivering the intervention to the study group allocation, however,

investigators collecting follow-up data were unaware of this. To quantify the degree of blinding, each investigator collecting primary outcome data completed a self-assessment of blinding.

Trial interventions

Patients were assigned to receive CPAP for at least four hours duration and started within four hours after the end of surgery, or to usual postoperative care. The duration of CPAP was chosen through expert consensus, balancing the evidence from previous research against the need to test an intervention, which was feasible for routine use in high-volume post-anaesthetic recovery units with variable skillsets amongst nursing staff. The airway pressure was started at 5 cm H_2O and then increased to a maximum of 10 cm H_2O at the discretion of the treating clinician. The fraction of inspired oxygen was at the discretion of the treating clinician. Patients in the usual care group received standard care for the participating hospital, consisting of supplemental oxygen therapy but not supplementary respiratory support unless clinically indicated.

Patient outcomes

The primary outcome was a composite of pneumonia, endotracheal re-intubation or death within 30 days of randomisation. Pneumonia was defined according to the United States Centres for Disease Control Definition, requiring three criteria.[21] The first criterion was two or more serial chest radiographs with at least one of the following features: new or progressive and persistent infiltrate; consolidation; or cavitation. For patients with no underlying pulmonary or cardiac disease one chest radiograph was considered sufficient. Second, one of the following features: fever (>38°C) with no other recognised cause;

leucopenia (< 4 x 10^9/L) or leucocytosis (>12 x 10^9/L); or for adults >70 years old, altered mental status with no other cause. Third, at least two of the following features: new onset of purulent sputum or change in character of sputum *or* increased respiratory secretions *or* increased suctioning requirements; new onset *or* worsening cough *or* dyspnea, or tachypnea; rales *or* bronchial breath sounds; or worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand). Endotracheal re-intubation was defined as re-insertion of an endotracheal tube after the patient had been extubated following the completion of the index surgical procedure. Endotracheal extubation was defined as an intentional clinical decision to remove an endotracheal tube, which did not include accidental or inadvertent removal of an endotracheal tube. Re-intubation did not include intubation for anaesthesia due to subsequent surgical procedures within the follow-up period. Secondary outcomes were pneumonia within 30 days of randomisation, endotracheal re-intubation within 30 days of randomisation, all-cause mortality within 30 days of randomisation, infection within 30 days of randomisation, postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation and mortality within one year of randomisation. Postoperative infections were assessed according to pre-specified and standardised definitions (supplementary appendix, page 33). Process outcomes were re-admission to hospital within 30 days of randomisation, days in critical care (both high dependency and intensive care) and duration of primary hospital stay. Adverse events were reported only in the CPAP group and only where considered to be at least possibly related to the trial intervention.

Sample size calculation

We determined that a sample of 4800 patients would provide the trial with 90% power to detect a reduction from 11·7% to 8·8% in the 30-day composite outcome of pneumonia, endotracheal re-intubation or death, at an alpha level of 0·05. This calculation allowed for a rate of withdrawal and loss to follow up of 4%.[20]

Statistical analysis

The statistical analysis was undertaken in accordance with a pre-specified statistical analysis plan (appendix, page 63) along with a schedule of amendments. We used STATA version 14 (STATACorp LP, Texas, USA) to analyse the data. We used an intention-to-treat approach. All patients with a recorded primary outcome were included in the analysis according to the treatment to which they were allocated. Patients with missing outcome data were excluded from the analysis.[22] The magnitude of the treatment effect estimate was reported as an adjusted odds ratio with 95% confidence intervals for primary and secondary outcomes. All p-values were two-sided with a significance level of 5%. Summary statistics are presented as mean (SD), median (IQR) or number (%) for each treatment arm. Baseline demographic and clinical data are summarised but not subjected to statistical testing. The primary analysis is presented as a mixed-effect logistic regression model, with a random intercept for centre.[23] We adjusted the model for the minimisation variables as fixed factors: country, planned use of epidural and planned surgical category,[24] and for the following pre-specified baseline covariates: age, sex, presence of comorbid disease, current smoker and American Society of Anesthesiologists (ASA) Physical Status Classification.[25] Missing data for baseline covariates were handled using mean imputation for age, and a missing indicator was added for missing data for

categorical variables (sex, co-morbid disease, smoking status and ASA score).[26] Secondary outcomes were analysed using the same approach as the primary outcome, except they were adjusted only for minimisation variables, excluding country, to avoid over-stratification, as the expected event rate for these outcomes was lower. We performed a time to event analysis for the primary and secondary outcomes on a complete case basis and presented these as Kaplan-Meier plots.

We performed a pre-specified subgroup analysis for the primary outcome, by surgical procedure category (lower gastrointestinal, hepatobiliary, upper gastrointestinal) and other (obesity surgery, vascular surgery or other intra-peritoneal surgery). For the subgroup analysis we used the same analysis model as the primary analysis, including an interaction term between planned surgical procedure and treatment arm. Since this was a pragmatic trial of a real-world intervention, it was plausible that some patients may not receive the treatment they were allocated. To investigate the effect of the intervention the patients received, we undertook a pre-specified per-protocol analysis using inverse probability-weighting (IPW) was performed for the primary outcome and the following secondary outcomes: (a) pneumonia within 30 days of randomisation; (b) endotracheal re-intubation within 30 days of randomisation; (c) all-cause mortality within 30 days of randomisation. As post-randomisation exclusions can cause bias, we used weighting to account for baseline risk factors that we expected to be joint determinants of adherence and the outcome (full list in supplementary appendix, page 63). This analysis estimates the effect of treatment if all participants in the group had started CPAP as intended by using a hypothetical strategy to handle non-adherence.[27] We used the same analysis models as for the primary and secondary outcomes. In addition, a post-hoc per-protocol

analysis using IPW was performed with a slight variation so that we defined patients in the intervention group who did not receive any CPAP due to being too unwell or remained intubated as having received the intervention. To assess whether the results were consistent for patients at high-risk of postoperative pulmonary complications, we undertook a post-hoc subgroup analysis for patients with a preoperative ARISCAT score of greater than 45.

Process evaluation

To better understand the delivery of the trial intervention we embedded a prospective mixed methods process evaluation within the PRISM trial. This combined data from ethnographic case studies in four hospitals (observations in areas where the intervention was delivered, staff focus groups [n=29 staff], patient telephone interviews [n=8]) and patient data. Principal investigators completed a 16-question trial exit questionnaire (54/70 hospitals responded). Case-study hospitals were chosen according to size, volume of patients recruited and intervention compliance. Thematic analysis was used to generate emergent themes from the qualitative data and descriptive statistics were used to analyse protocol deviations and questionnaire responses. All data were collected by an independent researcher and analysed prior to the main trial analysis.

Trial registration

This study is registered as an International Standard Randomised Controlled Trial number ISRCTN56012545.

Role of the funding source

The PRISM trial was an investigator-initiated trial and funding sources had no role in the design and conduct of the trial; collection, management, analysis or interpretation of the data; or preparation and approval of this report. The trial data were verified by the trial statisticians (AP, BK). The corresponding author had full access to trial data and takes final responsibility for the decision to submit for publication.

Results

From 8th February 2016 to 11th November 2019, we assessed 24586 patients for eligibility, of whom 4806 were enrolled in the trial at 70 hospitals (Figure 1). The hospitals were in United Kingdom (42), Italy (17), Spain (3), Norway (3), South Africa (3) and Sweden (2). Patient recruitment was stopped once the target sample size had been reached. 2405 patients were allocated to the intervention group and 2401 patients were allocated to the usual care group. Seven patients (0·1%) were missing data for the primary outcome and six patients (0·1%) withdrew consent for the use of their data, leaving 2396/2405 (99·6%) patients in the intervention group and 2397/2401 (99·8%) patients in the usual care group that were included in the primary intention to treat analysis (Figure 1). Four patients (<0·1%) withdrew from the trial but gave us permission to include their data and were included in the primary analysis. Baseline patient characteristics are described in Table 1 and Supplementary table 1 (appendix, page 12). The mean age was 67·8 (9·2) years and 2230/4793 (46·5%) patients were female. Patient care is described in Table 2 and Supplementary table 2 (appendix, page 14).

2241/2396 (93·5%) patients allocated to the trial intervention received CPAP (Supplementary table 3, appendix, page 16). The mean and median duration of CPAP was 194·2 (97·4) and 240 (149-240) minutes respectively. 1564/2241 (69·8%) patients received CPAP using a facemask, 568/2241 (25·3%) received CPAP via a hood device, 28/2241 (1·2%) received CPAP using a nasal mask and 81/2241 (3·6%) patients did not have a CPAP delivery method recorded. The median interval between the end of surgery and the start of CPAP was 90 (45-165) minutes. 157/2396 (6·5%) patients allocated to the intervention group did not receive CPAP and 686/2241 (30·6%) of patients that did receive

CPAP, received less than four hours duration (Supplementary tables 3, 4 and 5, appendix, pages 16-17).

At 30 days after randomisation we found no difference in the incidence of the primary outcome of pneumonia, endotracheal re-intubation or death, or any of the secondary outcomes, including the individual components of the primary outcome, infection or postoperative mechanical ventilation between patients allocated to CPAP or routine postoperative care (Table 3, Supplementary table 6 [appendix, page 18] and Figure 2). There was no difference in the incidence of death at one year after randomisation between treatment groups (table 3). Details of other postoperative complications stratified by treatment group are provided in Supplementary tables 8, 9 and 10 (appendix, pages 19-22). The median duration of the primary hospital admission was 9 (6-13) days. 2977/4793 (62·1%) patients were admitted to a critical care unit after surgery, with a median duration of 2 (2-3) days. 470/4793 (9·8%) patients were re-admitted to hospital after initial hospital discharge within 30 days after randomisation. (Supplementary tables 11 and 12, appendix, page 23).

A total of 276 adverse events occurred in 200/2241 (8·9%) patients who received CPAP (Supplementary tables 13, 14 and 15, appendix, pages 24-25). The most common adverse events associated with CPAP were claustrophobia (78/276), oro-nasal dryness (43/276), intolerance due to excessive air leak (36/276), vomiting (26/276) and pain (24/276). 7/276 patients experienced breathing difficulty associated with CPAP. One patient suffered significant hearing loss lasting for four days after CPAP delivered using a hood device and

one patient's central venous catheter was obstructed by a CPAP hood impeding a vasopressor infusion resulting in transient haemodynamic instability.

A planned per-protocol analysis using inverse probability weighting was conducted in accordance with the intervention that patients actually received (Supplementary tables 16 and 17, appendix, pages 26-27). In a pre-specified sub-group analysis there was no difference in the incidence of primary outcome between intervention and control groups when stratified by surgical procedure category (Supplementary table 18, appendix, page 28). The incidence of the primary outcome was similar in patients who received CPAP compared to usual care (adjusted odds ratio: 0·95 [0·77-1·18]; p=0·66). Secondary outcomes were also similar between groups. In a post hoc per protocol analysis including patients that were too unwell to receive CPAP or those who remained intubated after surgery and could not receive CPAP, the incidence of the primary and secondary outcomes remained similar between groups. In a post hoc per protocol analysis, comparing patients that received CPAP for at least four hours to those receiving usual care, the incidence of the primary and secondary outcomes remained similar between groups (Supplementary table 19, appendix, page 29). Investigator self-assessment of blinding for determination of outcomes indicated a high rate of adherence to masking procedures (Supplementary table 7, appendix, page 18). A post-hoc subgroup analysis for patients with an ARISCAT score of >45, indicating high-risk for pulmonary complications did not identify an effect of the intervention (odds ratio 0.97 [0.65-1.46]; p=0.91, Supplementary table 21, appendix, page 31).

A single unscheduled interim analysis was undertaken at the request of the independent DMEC to establish whether there was any value in increasing the trial sample size in light

of a lower than expected primary outcome event rate in the usual care group. Because we had decided to recruit no fewer the pre-specified sample of 4800 patients, we did not apply any adjustment to the significance thresholds in the final analysis. The results of the interim analysis were reviewed solely by members of the DMEC, who recommended we continue recruitment without increasing the trial sample size.

In the process evaluation, we found wide variations in the experiences of patients receiving CPAP and the clinical staff delivering it. The main influences on this variability were the characteristics of the intervention itself and the local context e.g. hospital culture, systems and resources. We found that a substantial proportion of patients did not like or were unable to tolerate CPAP. Claustrophobia, nausea, pain, feeling too hot, excessive dryness of the mouth or eyes and inability to communicate with relatives were the most commonly barriers to CPAP delivery. Patient accounts ranged from vague recollections of receiving CPAP to vivid descriptions of how unpleasant they found it. Of those who could recall receiving the intervention clearly, none completed four hours of treatment. Hospitals that were more successful in delivering the intervention tended to have integrated CPAP into postoperative care at the perceived optimal time, early after surgery when patients were often still drowsy. Additionally, staff appeared highly invested in delivering the intervention and helping patients tolerate CPAP.

Discussion

The principal finding of the PRISM trial was that preventative CPAP started early after major open abdominal surgery, lasting for at least four hours duration, did not reduce the incidence of postoperative pneumonia, endotracheal re-intubation or death at 30 days. This effect did not differ in any of the pre-specified subgroups or the per-protocol analysis conducted according to the intervention patients received. These results do not support the widespread adoption of postoperative CPAP as a preventative measure to prevent postoperative respiratory complications. When comparing these findings to those of smaller efficacy trials, it seems likely that various barriers to the successful routine delivery of CPAP to all patients after major abdominal surgery limit the real-world clinical effectiveness of this approach.

Previous research, mostly from small single-centre trials, suggests that preventative CPAP early after major surgery may prevent subsequent respiratory complications, perhaps by reducing atelectasis and pulmonary collapse.[15-17] This previous evidence also suggest that CPAP may improve outcomes amongst patients who develop respiratory failure after major surgery.[16,17] The findings of a Cochrane review, which identified ten trials including just over 700 patients, suggest that preventative CPAP may prevent pneumonia, re-intubation and invasive ventilation after major surgery. However, the authors of this systematic review concluded that further high quality research was needed to confirm this.[15] There is also previous evidence that CPAP may improve outcomes amongst patients that develop respiratory failure after major surgery.[17] One of the largest previous trials, by Squadrone and colleagues, evaluated the efficacy of CPAP in preventing re-intubation among 209 patients who developed respiratory failure following major abdominal surgery

across 15 hospitals.[16] The investigators found that patients receiving CPAP had a lower incidence of pneumonia and re-intubation. In a multi-centre trial of non-invasive ventilation in 293 patients who had undergone abdominal surgery, Jaber and colleagues reported an increase in ventilator-free days compared with standard oxygen therapy and a reduction in health care associated infections.[28] The results of these studies contrast with our current findings, perhaps because they relate to the focused use of respiratory support amongst patients who are already hypoxaemic. In the PRISM trial, we evaluated CPAP as a preventative measure to prevent respiratory failure, and so recruited a much wider patient population than previous trials where this approach has been used as a therapeutic measure to treat postoperative hypoxaemia.[16] These studies, which were phase two trials where the intervention was tightly controlled, are not readily comparable to PRISM, which is a pragmatic clinical effectiveness trial testing the real-world implementation of CPAP in post anaesthesia care units.

The trial protocol allowed for CPAP to be commenced within four hours after the end of surgery as some centres had to transfer patients to a critical care unit to deliver this as a local standard of care. This reflects the reality of intervention delivery. The median interval between the end of surgery and the start of CPAP was 90 minutes. Most recently, the iPROVE investigators evaluated the effectiveness of three intraoperative ventilation strategies in combination with postoperative CPAP to prevent postoperative complications in 967 patients of whom 723 received CPAP. Similar to the results of our trial, CPAP was not associated with any reduction in the incidence of postoperative complications compared to standard care.[29]

CPAP is a familiar and commonly used treatment for acute respiratory failure, but there is little data regarding its safety.[30-32] The results of the PRISM trial suggest that CPAP is a safe treatment, with no serious adverse events in 2241 administrations. Our data suggest that one in ten patients will experience minor problems with CPAP delivery that may require adjustment or discontinuation of the treatment. We observed that patients in the CPAP group often received non-invasive mechanical ventilation during the intervention period. However, there were very few adverse reports indicating respiratory failure amongst CPAP group patients during the intervention period. The likely explanation for this observation is that clinicians chose to administer non-invasive ventilation in preference to CPAP given the ease of switching between CPAP and non-invasive ventilation on many delivery devices.

Our trial had several strengths. We included a large sample of patients, representative of a broad spectrum of contemporary surgical and perioperative practice making the results widely generalisable. We used clearly defined outcome definitions and collected data using a standardised case report form. The statistical analysis was undertaken according to intention-to-treat principles using a pre-specified analysis plan. The pragmatic nature of the trial takes into account barriers to intervention delivery encountered in routine clinical practice, which we assessed through an embedded mixed methods process evaluation. The majority of patients underwent lower gastrointestinal, hepatobiliary or other intra-peritoneal surgery, while a much smaller proportion of patients underwent upper gastrointestinal surgery. This is likely due to concerns about the effects of positive pressure on anastomotic healing following this type of surgery, although there is no evidence that CPAP is harmful in this situation.[33] In the PRISM trial, the incidence of

anastomotic leak was similar in all patient sub-groups. Our trial also had some limitations. We allowed clinicians to choose from three CPAP interface devices, the facemask, hood and nasal mask, to represent the range of CPAP devices currently available for clinical use. Clinicians selected an interface device after discussion with individual patients, although not every device was available in every hospital. While training was offered on the range of interface devices, the choice of device may have been influenced by staff familiarity with certain types of equipment. Consequently, there was an unequal division of CPAP interface devices. The delivery devices also differed between hospitals, according to local policy and equipment availability. At the beginning of the trial local investigators were permitted to randomise patients at any point before the end of surgery. However, in some cases patients in the intervention group did not receive CPAP because they were either too unwell to receive CPAP in the immediate postoperative period or in some cases remained intubated immediately after the end of surgery. Therefore, we amended the protocol after the trial started to ensure investigators randomised patients at the end of surgery. PRISM was a pragmatic trial testing the clinical effectiveness of CPAP in a real-world context. We did not therefore expect 100% compliance with the trial intervention and we made allowance for this in our sample size calculation, anticipating a smaller treatment effect than anticipated under perfect circumstances. More than nine out of ten patients allocated to the intervention received CPAP. Examples of situations when patients did not receive the intervention include remaining intubated after surgery and patient refusal. Two thirds of patients who received CPAP received the full four-hour treatment. It seems likely that these findings represent the proportion of patients who would receive the full course of CPAP in routine practice. However, the observation that one third of patients were unable to tolerate four hours of CPAP is an important finding which may impact the future

use of CPAP in this setting. To test the impact of intervention compliance on clinical effectiveness, we conducted a post hoc per protocol analysis including only those patients that received CPAP for four hours. The treatment effect in this analysis was very similar to our primary analysis including all patients confirming that the lack of clinical effectiveness was not due to poor intervention compliance. This interpretation is further supported by the findings of our process evaluation, which revealed that the delivery of the trial intervention within the complex system of postoperative care was difficult in many hospitals. The ability to deliver the CPAP early after surgery, when patients were still drowsy, giving careful attention to patient tolerance and comfort appeared to improve trial intervention compliance. It was not feasible to blind patients and clinicians involved in the delivery of CPAP to intervention group, due to the nature of the intervention. However, we controlled this bias through blinded outcome assessment and we achieved good compliance with these procedures. Finally, we note that the primary outcome event rate of 8·2% was lower than the estimate we used in our sample size calculation (11·7%). The trial was very well powered with strong external generalisability, and it is highly unlikely that a larger sample size would alter our findings. In addition, while the observed incidence of complications is lower than expected, the preoperative ARISCAT score, which predicts postoperative respiratory morbidity, classifies the trial population as intermediate to high risk of respiratory complications. It is possible that a trial of very high-risk patients may return a different result.

Conclusions

In patients aged ≥50 years undergoing major open abdominal surgery, the application of CPAP within four hours after the end of surgery did not result in lower rates of pneumonia,

re-intubation or death at 30 days. These results do not support the widespread adoption of routine postoperative CPAP as a preventative measure to prevent early postoperative respiratory complications.

Contributors

Trial concept: RMP, MR, AR

Trial design: RMP, TEFA, AR, BK, SP, NP, MR

Data acquisition: all authors.

Analysis and interpretation of data: AP, BK, TEFA, RMP, MR.

Writing first draft of manuscript: TEFA, RMP.

Critical revision of manuscript for important intellectual content: writing committee

Approval of the final version of manuscript: all authors.

Access and verification of data: AP, BK

Trial guarantor: RMP

Declaration of interests

Dr. Pearse reports grants from NIHR, grants and non-financial support from Intersurgical UK, during the conduct of the study; grants and personal fees from Edwards Life Sciences, outside the submitted work; and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Intersurgical, GlaxoSmithKline and Edwards Lifesciences, and holds editorial roles with the British Journal of Anaesthesia, and the British Journal of Surgery. Dr. Abbott reports grants from Medical Research Council, during the conduct of the study; has performed consultancy work for MSD, outside the submitted work; and is a member of the associate editorial board of the British Journal of Anaesthesia. Dr Aldecoa is a member of the associate editorial board of the Revista Española de Anestesiologia y Reanimación and Frontiers. Dr. Szakmany reports and Associate editorial board member for the following journals: Trials, Frontiers in Microbiology, Medicine (Baltimore) and Critical Care Explorations. Dr Chew reports consultancy and speaker's fees from B Braun and Edwards Lifesciences; and is deputy editor-in-chief for the European Journal of Anaethesiology. All other members of the writing committee report no relevant interests.

Acknowledgements

The PRISM trial was funded by peer-reviewed grants from Barts Charity, the Association of Anaesthetists, Sapienza Università di Roma and by an unrestricted research grant from Intersurgical Ltd. RP was supported by a UK National Institute for Health Research

Professorship; TEFA was supported by a Medical Research Council and British Journal of Anaesthesia clinical research training fellowship (MR/M017974/1). The trial was sponsored by Queen Mary University of London.

Data sharing

The trial steering committee will consider requests for access to deidentified trial data by *bona fide* researchers, according to a prespecified statistical analysis plan and with a data sharing agreement. Data will be available at the time of publication. Data access requests should be made to admin@prismtrial.org The full set of trial documents, including the trial protocol, statistical analysis plan and informed consent forms are available on the trial website (prismtrial.org).

References

1. International Surgical Outcomes Study g. Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries. *British journal of anaesthesia* 2016; **117**(5): 601-9.
2. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Annals of surgery* 2005; **242**(3): 326-41; discussion 41-3.
3. Ackland GL, Iqbal S, Paredes LG, et al. Individualised oxygen delivery targeted haemodynamic therapy in high-risk surgical patients: a multicentre, randomised, double-blind, controlled, mechanistic trial. *The Lancet Respiratory medicine* 2015; **3**(1): 33-41.
4. Pearse RM, Harrison DA, MacDonald N, et al. Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systematic review. *Jama* 2014; **311**(21): 2181-90.
5. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015; **385 Suppl 2**: S11.
6. Abbott TEF, Fowler AJ, Dobbs TD, Harrison EM, Gillies MA, Pearse RM. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. *British journal of anaesthesia* 2017; **119**(2): 249-57.
7. Fowler AJ, Abbott TEF, Prowle J, Pearse RM. Age of patients undergoing surgery. *The British journal of surgery* 2019; **106**(8): 1012-8.
8. Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391**(10140): 2631-40.
9. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *British journal of anaesthesia* 2018; **120**(5): 1066-79.
10. Miskovic A, Lumb AB. Postoperative pulmonary complications. *British journal of anaesthesia* 2017; **118**(3): 317-34.
11. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *The New England journal of medicine* 1991; **325**(26): 1825-30.
12. Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. *The New England journal of medicine* 2014; **370**(24): 2276-85.
13. Martinez-Garcia MA, Capote F, Campos-Rodriguez F, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. *Jama* 2013; **310**(22): 2407-15.
14. McMillan A, Bratton DJ, Faria R, et al. Continuous positive airway pressure in older people with obstructive sleep apnoea syndrome (PREDICT): a 12-month, multicentre, randomised trial. *The Lancet Respiratory medicine* 2014; **2**(10): 804-12.
15. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the postoperative period for prevention of postoperative morbidity and mortality following major abdominal surgery. *The Cochrane database of systematic reviews* 2014; (8): CD008930.
16. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *Jama* 2005; **293**(5): 589-95.
17. Faria DA, da Silva EM, Atallah AN, Vital FM. Noninvasive positive pressure ventilation for acute respiratory failure following upper abdominal surgery. *The Cochrane database of systematic reviews* 2015; (10): CD009134.
18. World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *Jama* 2013; **310**(20): 2191-4.

19. Health Research Authority. UK policy framework for health and social care research. In: Health Do, editor.; 2017.
20. Pearse RM, Abbott TE, Haslop R, et al. The Prevention of Respiratory Insufficiency after Surgical Management (PRISM) Trial. Report of the protocol for a pragmatic randomized controlled trial of CPAP to prevent respiratory complications and improve survival following major abdominal surgery. *Minerva anestesiologica* 2017; **83**(2): 175-82.
21. Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *American journal of infection control* 2008; **36**(5): 309-32.
22. White IR, Horton NJ, Carpenter J, Pocock SJ. Strategy for intention to treat analysis in randomised trials with missing outcome data. *Bmj* 2011; **342**: d40.
23. Kahan BC. Accounting for centre-effects in multicentre trials with a binary outcome - when, why, and how? *BMC medical research methodology* 2014; **14**: 20.
24. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Statistics in medicine* 2012; **31**(4): 328-40.
25. Hurwitz EE, Simon M, Vinta SR, et al. Adding Examples to the ASA-Physical Status Classification Improves Correct Assignment to Patients. *Anesthesiology* 2017; **126**(4): 614-22.
26. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Statistics in medicine* 2005; **24**(7): 993-1007.
27. Agency EM. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the giudeline on statistical principles for clinical trials., 2020.
28. Jaber S, Lescot T, Futier E, et al. Effect of Noninvasive Ventilation on Tracheal Reintubation Among Patients With Hypoxemic Respiratory Failure Following Abdominal Surgery: A Randomized Clinical Trial. *Jama* 2016; **315**(13): 1345-53.
29. Ferrando C, Soro M, Unzueta C, et al. Individualised perioperative open-lung approach versus standard protective ventilation in abdominal surgery (iPROVE): a randomised controlled trial. *The Lancet Respiratory medicine* 2018; **6**(3): 193-203.
30. Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *The Cochrane database of systematic reviews* 2013; (5): CD005351.
31. Soares SM, Oliveira RA, Franca SA, et al. Continuous positive airway pressure increases inspiratory capacity of COPD patients. *Respirology* 2008; **13**(3): 387-93.
32. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *Lancet* 2014; **383**(9918): 736-47.
33. Charlesworth M, Lawton T, Fletcher S. Noninvasive positive pressure ventilation for acute respiratory failure following oesophagectomy: Is it safe? A systematic review of the literature. *Journal of the Intensive Care Society* 2015; **16**(3): 215-21.

Figure legends

Figure 1. Flow diagram showing the inclusion of patients in the PRISM trial.

Figure 2a. Time to event curves for the primary outcome of pneumonia, endotracheal re-intubation or death within 30 days after randomisation in 4793 patients. **Continuous positive airways pressure (blue). Usual postoperative care (red).**

Figure 2b. Time to event curves for all-cause mortality with one year after randomisation in 4795 patients (bottom panel).
Continuous positive airways pressure (blue). Usual postoperative care (red).

Table 1. Baseline patient characteristics

Baseline Characteristics*	Summary measure*	
	Usual Care n=2397	CPAP n=2396
Gender - no. (%)		
Male	1278 (53·3)	1292 (53·8)
Female	1122 (46·8)	1108 (46·2)
Age (years)		
Mean (SD)	67·9 (9·2)	67·8 (9·2)
Median (IQR)	68·6 (60·6-74·6)	68·1 (60·6-74·5)
Current smoker - no. (%)	318 (13·3)	338 (14·1)
American Society of Anaesthesiology grade[a] - no. (%)		
I	126 (5·3)	129 (5·4)
II	1284 (53·8)	1298 (54·3)
III	955 (40·0)	932 (39·0)
IV	21 (<1)	31 (1·3)
V	1 (<1)	0 (0·0)
Chronic comorbid disease[b] - no. (%)		
COPD	228 (9·5)	233 (9·7)
Asthma	185 (7·7)	213 (8·9)
Interstitial lung disease or pulmonary fibrosis	22 (<1)	26 (1·1)
Bronchiectasis	11 (<1)	19 (<1)
Ischaemic heart disease	235 (9·8)	230 (9·6)
Diabetes mellitus	437 (18·2)	395 (16·5)
Heart failure	60 (2·5)	64 (2·7)
Liver cirrhosis	82 (3·4)	77 (3·2)
Active cancer	1924 (80·3)	1926 (80·3)
Previous stroke or transient ischaemic attack	129 (5·4)	105 (4·4)
Primary respiratory infection with the previous month	50 (2·1)	52 (2·2)
HIV infection	19 (<1)	23 (<1)
Planned surgical procedure - no. (%)		
Resection of colon, rectum or small bowel	924 (38·5)	922 (38·4)
Resection of liver, pancreas or gall bladder	630 (26·3)	631 (26·3)
Resection of stomach (non-obesity surgery)	68 (2·8)	67 (2·8)
Obesity surgery	1 (<1)	0 (0·0)
Vascular procedure	69 (2·9)	71 (3·0)
Other intra-peritoneal surgery	708 (29·5)	706 (29·4)
Resection of oesophagus (non-obesity surgery)	0 (0·0)	3 (<1)
Planned use of epidural anaesthesia - no. (%)	1134 (47·3)	1131 (47·1)
Country - no. (%)		
Italy	574 (23·9)	573 (23·9)
Spain	37 (1·5)	36 (1·5)
Sweden	63 (2·6)	65 (2·7)
United Kingdom	1421 (59·2)	1421 (59·2)
South Africa	99 (4·1)	99 (4·1)

Norway	206 (8·6)	206 (8·6)
ARISCAT Score[c]		
Mean (SD)	40·8 (9·3)	41·1 (9·0)

Abbreviations: SD, standard deviation; IQR, Interquartile range; COPD, chronic obstructive pulmonary disease; HIV, Human Immunodeficiency Virus.

*A full summary of baseline characteristics is provided in supplementary table 1 (appendix, page 12) along with the 'number of patients with available data' used for each summary measure.

[a] American Society of Anesthesiology grades are defined as follows: 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; 4, a patient with severe systemic disease that is a constant threat to life; 5, a moribund patient who is not expected to survive without the operation

[b] Patient may have more than one chronic co-morbid disease

[c] Components of the ARISCAT score are provided in supplementary table 20 (appendix, page 30)

Table 2. Patient care

Patient care	Summary measure*	
	Usual Care n=2397	CPAP n= 2396
Open surgical technique used during surgery - no. (%)	2389 (99·7)	2387 (99·5)
Anaesthetic technique - no. (%)		
General anaesthesia	2394 (99·9)	2394 (99·8)
Epidural anaesthesia	1053 (44·0)	1035 (43·2)
Spinal anaesthesia	436 (18·2)	456 (19·0)
Endotracheal tube inserted	2346 (98·0)	2343 (97·7)
Mechanical ventilation during surgery		
Recruitment manoeuvre - no. (%)	430 (18·4)	446 (19·0)
Mechanical ventilation - no. (%)	2381 (99·5)	2388 (99·7)
Intravenous fluids during surgery (excluding blood products)		
Mean (SD)	2872.1 (1659·4)	2871.9 (1536·4)
Total volume of blood products administered (mL)		
Mean (SD)	120.0 (465·8)	101.4 (385·1)
Planned level of care on the first night after surgery - no. (%)		
Critical care unit level 3	231 (9·6)	231 (9·6)
Critical care unit level 2	1173 (48·9)	1193 (49·7)
Post-anaesthesia care unit	220 (9·2)	228 (9·5)
Surgical ward	776 (32·3)	748 (31·2)
Level of care on the first night after surgery - no. (%)		
Critical care unit level 3	225 (9·4)	238 (9·9)
Critical care unit level 2	1144 (47·8)	1204 (50·2)
Post-anaesthesia care unit	208 (8·7)	213 (8·9)
Surgical ward	818 (34·2)	743 (31·0)
Respiratory support after surgery (within 4 hours of the end of surgery) - no. (%)		
Invasive mechanical ventilation	125 (5·2)	118 (4·9)
Non-invasive mechanical ventilation	19 (0·8)	190 (7·9)
High flow nasal oxygen therapy	49 (2·0)	42 (1·8)

Abbreviations: SD, standard deviation; IQR, Interquartile range

*A full summary of patient care characteristics is provided in supplementary table 2 (appendix, page 14) along with the 'number of patients with available data' used for each summary measure.

Table 3. Primary and secondary patient outcomes at 30 days after randomisation

Outcomes	Summary measure*		Adjusted odds ratio (95% CI)	p-value
	Usual Care n= 2397	CPAP n= 2396		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)	197 (8·2)	195 (8·1)	1·01 (0·81, 1·24)	0·95
Pneumonia within 30 days of randomisation	117 (4·9)	123 (5·1)	1·06 (0·82, 1·38)	0·66
Endotracheal re-intubation within 30 days of randomisation	90 (3·8)	80 (3·3)	0·89 (0·65, 1·21)	0·45
All-cause mortality within 30 days of randomisation	33 (1·4)	30 (1·3)	0·91 (0·55, 1·50)	0·71
Postoperative infection within 30 days of randomisation	741 (31·0)	738 (30·8)	0·99 (0·87, 1·12)	0·89
Postoperative mechanical ventilation within 30 days of randomisation[a]	210 (8·8)[b]	230 (9·6)[c]	1.17 (0·94, 1·45)	0·16
All-cause mortality within one-year of randomisation	230 (9·7)	213 (9·0)	0·91 (0·75, 1·11)	0·37

[a] This outcome was recorded as receiving postoperative invasive and/or non-invasive mechanical ventilation within 30 days of randomisation but does not include data from the process measure related to ventilation in the four-hour period after the end of surgery

[b] In the usual care group, 168/2393 (7·0%) patients received invasive mechanical ventilation, 21/2393 (0·9%) patients received non-invasive mechanical ventilation and 21/2393 (0·9%) patients received both invasive and non-invasive mechanical ventilation

[c] In the intervention group, 166/2395 (6·9%) patients received invasive mechanical ventilation, 38/2395 (1·6%) patients received non-invasive mechanical ventilation and 26/2395 (1·1%) patients received both invasive and non-invasive mechanical ventilation

*The 'number of patients with available data and included in analysis' is provided in supplementary table 6 (appendix, page 18) for each summary measure.

**Covariates are surgical procedure category, ASA grade, age, current smoker, at least one comorbid disease, country, planned use of epidural and sex. These are listed in the statistical analysis plan, which is in the supplementary appendix (appendix, page 63).

Figure 1. Flow diagram showing the inclusion of patients in the PRISM trial.

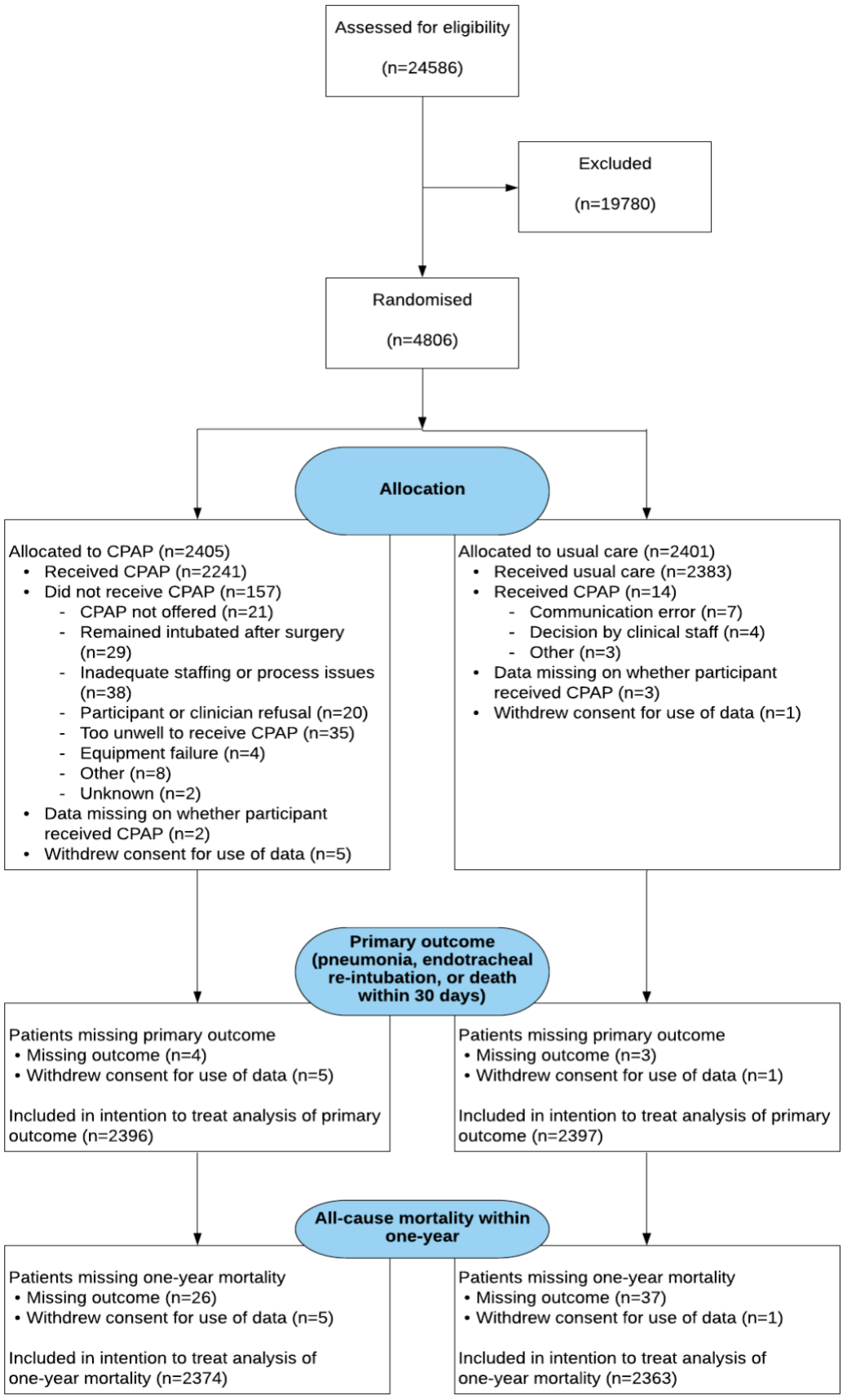


Figure 2a. Time to event curves for the primary outcome of pneumonia, endotracheal re-intubation or death within 30 days after randomisation in 4793 patients. **Continuous positive airways pressure (blue). Usual postoperative care (red).**

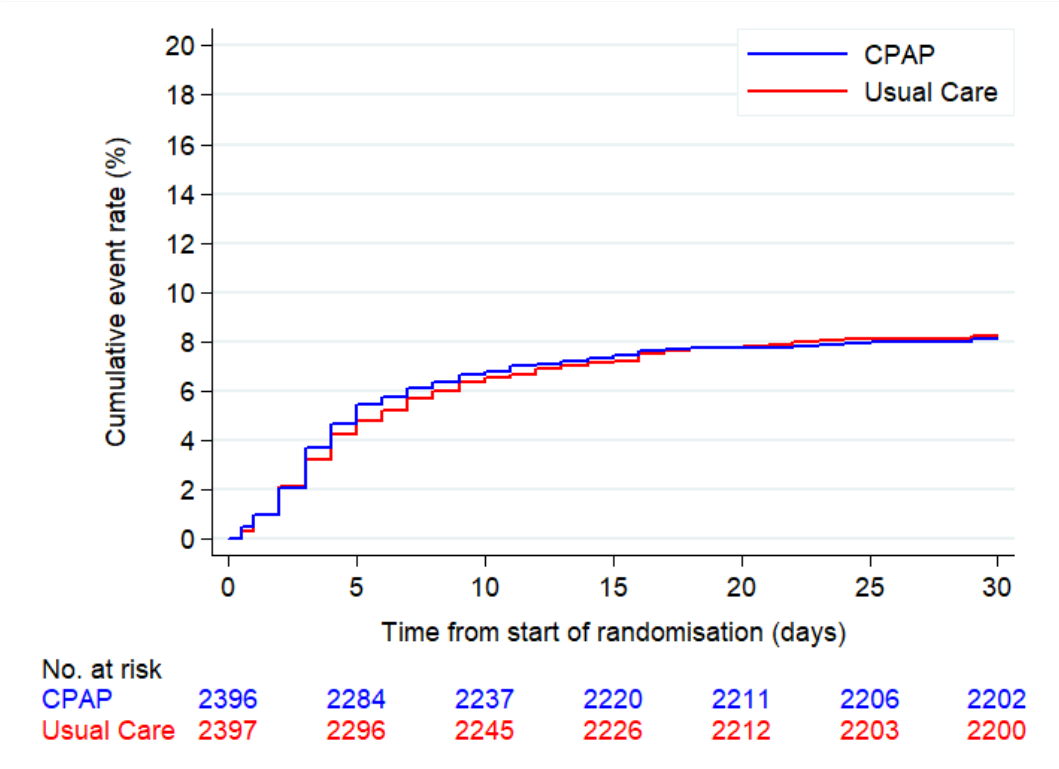
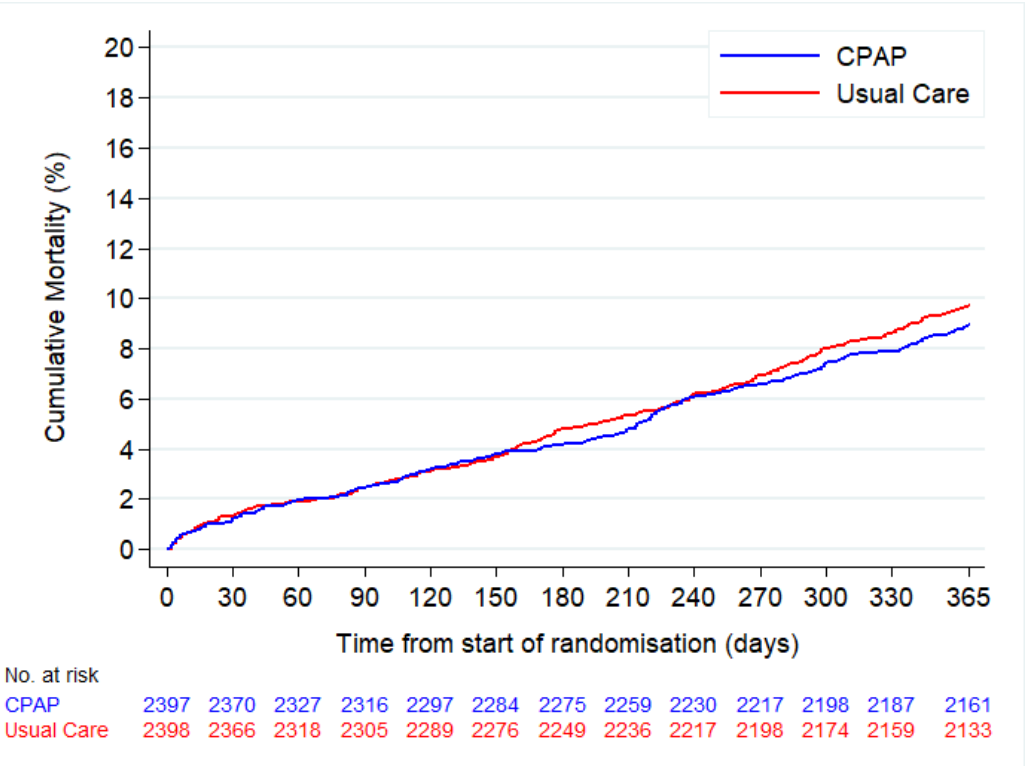


Figure 2b. Time to event curves for all-cause mortality with one year after randomisation in 4795 patients. **Continuous positive airways pressure (blue). Usual postoperative care (red).**



Postoperative continuous positive airway pressure to prevent pneumonia, re-intubation and death after major abdominal surgery: a pragmatic international randomised trial.

Supplementary appendix

Investigator list

Writing committee
Rupert M. Pearse, V. Marco Ranieri, Tom E.F. Abbott, Mari-Liis Pakats, Edoardo Piervincenzi, Akshaykumar Patel, Brennan C. Kahan, Andrew Rhodes, Priyanthi Dias, Russell Hewson, Ib Jammer, Michelle Chew, Cesar Aldecoa, Reitze Rodseth, Bruce Biccard, Tim Stephens, Sara Payne, David Hepworth, Soeren E. Pischke, Joerund Asvall, John Hausken, Shaman Jhanji, Martin Rooms, Neil Flint, Dawn Hales, Tamas Szakmany, Andrew Leitch, Savino Spadaro, Davide Chiumello, Paul Johnston, Joyce Yeung, Guglielmo Tellan, Tonny Veenith, Josep Macmillan, Pierpaolo Terragni, Caroline Hallsjo Sander, Vidya Kasipandian

Trial management group
Rupert M. Pearse, Mari-Liis Pakats, Tom E. F. Abbott, Priyanthi Dias, Edoardo Piervincenzi, Akshaykumar Patel, Brennan C. Kahan, Tahania Ahmad, Russell Hewson, Aaron Lee, Marcello Tammaro, V. Marco Ranieri

Data Management and Ethics committee
Danny McAuley (Chair, independent), Simon Skene (Statistician), Ravinder Vohra (Independent member)

Trial steering committee
Matt Wilson (Independent chair), Mark Edwards (Independent member), Ewen A. Griffiths (Independent member), Rupert M. Pearse (Chief investigator), V. Marco Ranieri (Co-chief investigator), Andrew Rhodes, Tom E. F. Abbott, Sara Payne, Naomi Pritchard, David Hepworth, Mari-Liis Pakats, Priyanthi Dias, Brennan C. Kahan, Akshaykumar Patel, Claudia Filippini, Russell Hewson, Edoardo Piervincenzi, Ib Jammer, Michelle Chew, Cesar Aldecoa, Reitze Rodseth, Bruce Biccard

National leads
United Kingdom: Rupert M. Pearse, Italy: V. Marco Ranieri, Sweden: Michelle Chew, Norway: Ib Jammer, Spain: Cesar Aldecoa, South Africa: Reitze Rodseth, Bruce Biccard

Local PRISM investigators:

Oslo University Hospital
Joerund Asvall (Local Co-ordinator), Soeren Pischke (Local Co-ordinator), Tor Aasmundstad, Einar Aksnes, Lise-Merete Alpers, Andreas Barratt-Due, Anita Dahl, Linda Sveen Feldt, Elisa Figari, Eva Jeanette Flåten, Karen Granheim, Minna Marie Hagring, Håkon Haugaa, John Hausken, Gisle Kjoesen, Inge Klaevahaugen, Harald Lenz, Marianne Myhre, Hilde Lang Orrem, Emily Stitt, Tor Inge Toennessen

The Royal Marsden NHS Foundation Trust
Shaman Jhanji (Local Co-ordinator), Martin Rooms (Local Co-ordinator), Samuel Al-Kadhimi, Robert Anker, Mihaela Alina Balint, Lauren Barraclough, Ethel Black, Matt Clayton, Leonora Conneely, Zara Edwards, Alex Eeles, Matthew Evans, Michelle Gerstman, Nicole Greenshields, Eleanor Harvey, Aoife Hegarty, Natalie Hester, Jenna Hutchinson, Ramanathan Kasivisvanathan, Helen Lawrence, Veronica Marsh, Laura Matthews, Francesca Mazzola, Jamie McCanny, Ben Morrison, Michelle O'Mahony, Ching Ling Pang, David Parkinson, Katrina Pirie, Ravishankar Rao Baikady, Louisa Shovel, Lorna Smith, Kate Tatham, Peter Thomas, Sophie Uren, Susanna Walker, Alasdair Wills

Leicester Royal Infirmary
Neil Flint (Local Co-ordinator), Prematie Andreou, Dawn Hales, Alex Howson, Jasmin Kaur, Adam Lewszuk, Esther Vergara Molina, Nirmalabaye Leanessa Ramsamy, Emma Roberts

The Royal London Hospital
Andrew Leitch (Local Co-ordinator), Tom E.F. Abbott, Vanessa Da Silva Amaral, Salma Begum, Soliana Bekele, Richard Cashmore, Carmen Correia, Priyanthi Dias, Steven Dunkley, Maria Fernandez, Alexander J. Fowler, Amaia Arrieta Garcia, Maria Della Giovampaola, Kathryn Greaves, Bethan Griffiths, Ryan Haines, Richard Haslop, Ying Hu, Sarah Hui, Marta Januszewska, Vasi Manon, Tim Martin, Shaun May, Annamaria Minicozzi, Edyta Niebrzegowska, Monica Oliveira, Mari-Liis Pakats, Katherine Pates, Filipa Santos, Tasnin Shahid, Paolo Simili, Alastair Somerville, Tim Stephens, Emily Subhedar, Ruzena Uddin, Sophie Walker, Yize Wan, Jan Whalley, Parjam Zolfaghari

Royal Gwent Hospital
Tamas Szakmany (Local Co-ordinator), Una Gunter, Gemma Hodkinson, Gwenllian Howe

Università degli Studi di Milano, Ospedale San Paolo - Polo univeristario
Davide Chiumello (Local Co-ordinator), Valentina Baratozzi, Giulia Casotto, Giulia Darai, Erica Ferrari, Giovanni Mistraletti, Valentina Palmaverdi

Arcispedale Sant'Anna University Hospital
Savino Spadaro (Local Co-ordinator), Stefano Furlani, Paolo Priani, Riccardo Ragazzi, Marco Salmaso, Marco Verri, Carlo Alberto Volta

Antrim Area Hospital
Paul Johnston (Local Co-ordinator), Chris Nutt (Local Co-ordinator), Emma McKay, Orla O'Neill

Heart of England NHS Foundation Trust
Jaimin Patel (Local Co-ordinator), Joyce Yeung (Local Co-ordinator), Katie Atterbury, Sarah Ballinger, Natalie Carling, Kaytie Ellis, Jo Gresty, Teresa Melody, Jade Monk, Chloe Norman, Eleanor Reeves, Julia Sampson, Peter Sutton, Marie Thomas

University Hospitals Birmingham NHS Foundation Trust
Tonny Veenith (Local Co-ordinator), Amy Bamford, Colin Bergin, Ronald Carrera, Lauren Cooper, Liesl Despy, Karen Ellis, Emma Fellows, Stephanie Goundry, Samantha Harkett, Peter Ip, Tracy Mason, Christopher McGhee, Aisling McLaughlin, Aoife Neal, Martin Pope, Stephanie Porter, Hazel Smith, Catherine Snelson, Elaine Spruce, Ylenia Vigo, Arlo Whitehouse, Tony Whitehouse

Sapienza Università di Roma, Policlinico Umberto I
Guglielmo Tellan (Local Co-ordinator), Maria Grazia Donatiello, Sergio Gazzanelli, Mario Mezzapesa, Edoardo Piervincenzi, V. Marco Ranieri, Martina Savino, Giacomo Settesoldi

King's College Hospital NHS Foundation Trust
Gudrun Kunst (Local Co-ordinator), Josep Macmillan (Local Co-ordinator), Sian Birch, Louise Greig, Harriet Noble, Evita Pappa, Bethany Penhaligon

Università degli Studi di Sassari
Pierpaolo Terragni (Local Co-ordinator), Andrea Pasquale Cossu, Leda Floris, Davide Piredda, Alberto Racca

Karolinska University Hospital
Olof Brattstrom (Local Co-ordinator), Caroline Hallsjo Sander (Local Co-ordinator), Bente Heggelund, Magnus Flodberg, Sandra Månsson

The Christie NHS Foundation Trust
Vidya Kasipandian (Local Co-ordinator), Mamoona Ahmed, Jonathan Allen, Paula Bell, Roman Genetu, Julia Glennon, Janice Hanley, Katy Jenner, Summayyah Jogi, Parisa Mahjoob, Clare McGovern, Anthony Murphy, Roonak Nazari, Jacki Routledge, Trishna Uttamlal, Sinead Ward,

Fondazione IRCCS Policlinico San Matteo
Giorgio Antonio Iotti (Local Co-ordinator), Raffaella Picchioni, Silvia Poma

A.O.U. Mater Domini
Paolo Navalesi (Local Co-ordinator), Andrea Bruni, Brunella De Leonardis, Eugenio Garofalo

Furness General Hospital
Panna Patel (Local Co-ordinator), Carol McArthur, Karen Burns, Steven Peters
Università Milano Bicocca - ASST Monza: Giuseppe Foti (Local Co-ordinator), Serena Calcinati, Alice Grassi, Silvia Villa

York Hospital
John Berridge (Local Co-ordinator), Muthuraj Kanakaraj (Local Co-ordinator), Hazel Cahill, Greg Forshaw, Andy Gibson, Lia Grainger, Kate Howard, Katherine James, Zoe Murphy, Helen Sweeting, Rebecca Tait, Danielle Wilcock, David Yates

Sunderland Royal Hospital
Sean Cope (Local Co-ordinator), Ashley Allan, Rebecca Betts, Sarah Cornell, Julie Sheriff, Lindsey Woods

Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico
Giacomo Grasselli (Local Co-ordinator), Matteo Brioni, Luigi Castagna

Grey's Hospital
Richard Peter von Rahden (Local Co-ordinator), Reitze Rodseth (Local Co-ordinator), Zane Farina, Samantha Green, Simphiwe Gumede, Chantal Rajah, Arisha Ramkillawan

Royal Alexandra Hospital (Paisley)
Susan Moug (Local Co-ordinator), David Alcorn, Carol Dalton, Natalie Dickinson, Jennifer Edwards, Steven Henderson, Erin McIlveen

Royal Liverpool University Hospital
Richard Ramsaran (Local Co-ordinator), Joanne Bell, Lorna Fleming, Kathleen Monks, Jane Parker, Sean Stamper, Jo Stokes-Denson

Hospital Universitario Rio Hortega
Cesar Aldecoa (Local Co-ordinator), Elisa Fernández Elías, Yessica Guerra, Jesus Rico-Feijoo

Royal Free London NHS Foundation Trust
Carlos Kidel (Local Co-ordinator), Helder Filipe (Local Co-ordinator), Gretchelle Asis, Yvonne Gleeson, Alice Harvey, Christine Eastgate Jackson, Margaret McNeil, Sara Mingo, Glykeria Pakou, Manuel Pinto

The Freeman Hospital
Stephen Wright (Local Co-ordinator), Maite Babio-Galan, David Buckley, Verity Calder, Ahmad Chishti, Joseph Cosgrove, Katherine Cullen, Leigh Dunn, Matthew Faulds, Jonathan Fortune, Matthew Gardner, Abigail Harrison, Carole Hays, Gerry Jones, Caroline Macfie, Iain Mccullagh, Ian Nesbitt, Suzanne O'Neil, Catherine Phoenix, Girish Rangaswamy, Craig Samson, Carmen Scott, Tara Shrestha, Rita Singh, Graham Soulsby, Jon Walton, Kimberley Zwiggelaar

Royal Glamorgan Hospital
Ceri Lynch (Local Co-ordinator), Heidi Clarke, Bethan Deacon, Helen Ivatt, Leanne Janine Jones, Ahmed Latif, Shaun Oram, Chris Perman, Lisa Roche

Groote Schuur Hospital
Rowan Duys (Local Co-ordinator), Margot Flint (Local Co-ordinator), Kamal Bhagwan, Ettienne Coetzee, Ivan Joubert, Felipe Montoya-Pelaez, Pradeep Navsaria, Guy Picken, Owen Porrill, Grant Strathie, Thembinkosi Zungu

Barnsley Hospital NHS Foundation Trust
Sireesha Aluri (Local Co-ordinator), Simon Chau (Local Co-ordinator), Deborah Cooper, Mishell Cunningham, Allison Daniels, Susan Hope, Alice Nicholson, Laura Walker

Azienda Ospedaliera Universitaria Policlinico "P. Giaccone"
Antonino Giarratano (Local Co-ordinator), Giuseppe Accurso, Santi Maurizio Raineri, Giuseppe Tricoli

Musgrove Park Hospital
Richard Innes (Local Co-ordinator), Patricia Doble, Joanne Hutter, Corinne Pawley, Moira Tait

St. George's Hospital
Mark Hamilton (Local Co-ordinator), Edward Andrade, Veronica Barnes, Claire Dalton, Carlos Castro Delgado, Sarah Farnell-Ward, Helen Farrah, Geraldine Gray, Aoife Hegarty, Luisa Howlett, Gipsy Joseph, Monika Krupa, Susannah Leaver, Joao Macedo, Karen Maher, Johannes Mellinghoff, Rachel Oguntimehin, Joel Cardoso Pereira, Frances Robinson, Christine Ryan, Nirav Shah, Paula Shirley
Inkosi Albert Luthuli Hospital: Alexandra Torborg (Local Co-ordinator), Thuli Biyase, Leanne Drummond, Belinda Kusel, Mbalenhle Mbuyisa, Sivuyisiwe Solala, Jenna Taylor

Guy's & St Thomas' NHS Foundation Trust
Adanma Ezihe-Ejiofor (Local Co-ordinator), Maame Aduse-Poku, Gary Colville, Louise Davies, Soo Jin Kang, Alex Phillips

Royal Surrey County Hospital NHS Foundation Trust
Justin Kirk-Bayley (Local Co-ordinator), Leigh Kelliher (Local Co-ordinator), Paula Carvelli, Gokce Daysal, Matthew Dickinson, Nancileigh Doyle, Christina Hughes, Laura Montague, Elizabeth Potter, Armorel Salberg, Sheena Jane Sibug, Sinduja Sivarajan, Milo Thomson, Nichola Wakeford

Ospedale Sant'Andrea: Monica Rocco (Local Co-ordinator) Daniela Alampi
Central Manchester Foundation Trust: Daniel Conway (Local Co-ordinator), Richard Clark, Jashmin Maria, Fiona Pomeroy, Tanviha Quraishi, Abigail Williams

Royal Blackburn Hospital
Srikanth Chukkambotla (Local Co-ordinator), Caroline Aherne, Donna Harrison-Briggs, Jill Fitchett, Stephen Duberley

Policlinico Sant Orsola Malpighi
Andrea Zanoni (Local Co-ordinator), Daniela Cardinale, Claudia Isabella Monroy Righi

Queen Elizabeth Hospital, King's Lynn
Mark Blunt (Local Co-ordinator), Tracy Fuller, Ruth Hodgson, Melissa Rosbergen

Bradford Teaching Hospitals NHS Foundation Trust
Andrew Brennan (Local Co-ordinator), Louise Akeroyd, Victoria Boardman, Christopher Bull, Mike Carrick, Ian Chadderton, Sarah Cooper, Sarah Goellner, Laura Graham, Carl Ilyas, James King, Muhammad Laklouk, Tom Lawton, Christopher Macrow, Michael Munro, Adam Neep, Martin Northey, Victoria Peacock, Kate Pye, Lydia Radley, James Sira, Beth Smithson, Stuart Syddall, David Tooth, Thomas White
Haukeland University Hospital: Sindre Hoel (Local Co-ordinator), Elin Kismul Aakre, Monica Totland Bakke, Tone Hoivik

Medway Maritime Hospital
Arystarch Makowski (Local Co-ordinator), Harry Alcock, Sean Cardoso, Samantha Coetzee, Mary Everett, Mohamed Ibrahim, Christina Kouridaki, Vongayi Ogbeide

AOU - University Hospital of Modena
Elisabetta Bertellini (Local Co-ordinator), Valentina Bertolotti, Antonio Buono, Maria Antonietta Fanigliulo
Kingston Hospital: Ram Kumar (Local Co-ordinator), Nicole Richards (Local Co-ordinator), Alisha Allana, Samantha Bacciarelli, Helen Barker, Jessica De Bois, Isabel Bradley, Jennifer Crooks, Peter Daum, Alex Feben, Lizzie Gannon, Sarah Kipling, Andrew Peetamsingh, Charlotte Quamina, Sahiba Sethi, Harry Sivadhas, Kathryn Sollesta, Andrew Swain, Evalyn Tan, Joan Willis, Maggie Zou

Royal Bournemouth Hospital
Julius Cranshaw (Local Co-ordinator), Nina Barratt, Katie Bowman, Debbie Branney, Maria Letts, Sally Pitts

Royal Devon and Exeter Hospital
Christopher Day (Local Co-ordinator), Sarah Benyon, Sara Eddy, Adam Green, Anna Grice, Sinéad Kelly, Daisy Mackle, Victor Mariano, Linda Park, Pauline Sibley, William Spencer

Azienda Ospedaliero-Universitaria di Parma
Elena Giovanna Bignami (Local Co-ordinator), Valentina Bellini

Azienda Universitario-Ospedaliera Pisana Nuovo Ospedale S.Chiara
Francesco Forfori (Local Co-ordinator), Maria Giovanna Curci, Alessandra Leo

Stepping Hill Hospital
Matthew Jackson (Local Co-ordinator), Jennifer Awolesi, Sheila Hodgkinson, Alissa Kent, Dee Leonard, Claire Stapleton, Clare Tibke

Northampton General Hospital NHS Trust
Farhad Alexander-Sefre (Local Co-ordinator), Lorraine Campey, Kathryn Hall, Jennifer Spimpolo

Linköping University Hospital
Malin Nilsson (Local Co-ordinator), Helen Didriksson

Shrewsbury and Telford Hospitals NHS Trust
Emma Hamilton (Local Co-ordinator), Mandy Carnahan, Chris Mowatt, Jo Stickley

Azienda Ospedaliera dei Colli Monaldi
Antonio Corcione (Local Co-ordinator), Giuseppe Rossi (Local Co-ordinator)

Stavanger University Hospital
Hege Fladby (Local Co-ordinator), Nina Gjerde Andersen, Gunhild Bjoernå, Mads Reite, Linda Roertveit, Philipp Seidel

St. Mary's Hospital - Imperial College
Glenn Arnold (Local Co-ordinator), Melissa Benavente, Anjalee Chattersingh, Nyasha Chironga, Gillian Hornzee, Joyce Kibaru, Ihtisham Malik, Laura McLeavy, Byiravey Pathmanathan, Florence Prior, Rhea Strudwick, Marios Vezyrgiannis,

Queen Alexandra Hospital
Aneeta Sinha (Local Co-ordinator), Sheeba Babu, Bisanth Batuwitage, Zoe Daly, Katharine Ellinor, Elizabeth Hawes, Ann Holmes, Karen Hudson, Jeremy Nightingale, Alison Le Poidevin, Lindsey Roberts

Yeovil District Hospital NHS Foundation Trust
Agnieszka Kubisz-Pudelko (Local Co-ordinator), Joanna Allison, Lucy Pippard

Nevil Hall Hospital
Vincent Hamlyn (Local Co-ordinator), Angie Organ

North Middlesex Hospital NHS Trust
Adanma Ezihe-Ejiofor (Local Co-ordinator), Thaventhran Prabhahar (Local Co-ordinator), Hayley Bridger, Lee Dvorkin, Vitul Manhas, Rachel Vincent

Royal Preston Hospital
Shondipon Laha (Local Co-ordinator), Terri-Louise Cromie, Donna Doyle, Rachel Howarth, Mark Verlander, Ailsa Watt, Alexandra Williams

Fondazione Policlinico Universitario A. Gemelli
Massimo Antonelli (Local Co-ordinator), Salvatore Cutuli, Luca Montini

Royal Cornwall Hospital
Juan Graterol (Local Co-ordinator), Benita Adams, Sarah Bean, Karen Burt, Fiona Hammonds

Whipps Cross Hospital
Suyogi Jigajinni (Local Co-ordinator), Laura Fulton (Local Co-ordinator), Stephen Kinghorn, Maria Fernandez, Amaia Arrieta Garcia, Tim Martin, Filipa Santos

James Cook University Hospital
Jost Mullenheim (Local Co-ordinator), Kirsty Baillie, Martyn Cain, Kerry Colling, Carol Hannaway

GB Morgagni-L Pierantoni Hospital
Ruggero Corso (Local Co-ordinator), Morena Calli

Hospital Clínico Universitario Valencia
Carlos Ferrando (Local Co-ordinator), Esther Romero

Hospital Clínico Universitario de Valladolid
Pablo Jorge-Monjas (Local Co-ordinator), María Susana Soria-García, José Ignacio Gómez-Herreras, Rita Pilar Rodríguez-Jiménez, Blanca De Prada-Martín

Supplementary methods

Database cleaning and analysis decisions
This describes the database cleaning process, analysis decisions, or any changes to the statistical analysis plan.

Section 1: Data Cleaning

Online database
This describes the data cleaning decisions for the eCRF database which includes data on randomisation, baseline, intraoperative period, intervention period, clinical outcomes within 30 days of randomisation and clinical outcomes within one-year of randomisation.

- Flagged data
    - Removed all flagged data (free text, 9999 etc.) from all variables and set to missing
- Active cancer (page 2 of CRF)
    - Set "is cancer the indication for surgery?" to missing if "Active Cancer" marked as "no"
    - Set "is the surgery intended to be curative or palliative" to missing if "Active Cancer" marked as "no"
    - Set "is the surgery intended to be curative or palliative" to missing if "cancer is the indication for surgery" is marked as "no"
- BMI (page 2 of CRF)
    - 2 Participants thought to have implausible values for BMI based on their height and weight were set to missing
- Resting oxygen saturation (SpO_2) (page 2 of CRF)
    - Set to missing if equal to 0 or greater than 100
- Anaesthetic technique (Page 4 of the CRF)
    - Set "was the patient extubated before leaving the operating room" to missing if "Did the patient have an endotracheal tube inserted" is marked as "no"
- Mechanical ventilation during surgery (page 4 of CRF)
    - Set maximum PEEP, maximum tidal volume, maximum respiratory rate, maximum FiO_2 to missing if "did the patient receive mechanical ventilation during surgery" is marked as "no"
    - Set maximum respiratory rate to missing if respiratory rate is equal to 0
- CPAP After Surgery (page 5 of CRF)
    - Set all items in the "CPAP After Surgery" section to missing if "Did the patient receive CPAP within twelve hours after the end of surgery" is marked as "no"
    - CPAP duration
        - 1 patient received 1465 mins of CPAP and was entered using STATA
        - Set to missing if CPAP duration is equal to 0
        - 1 patient received 180 mins of CPAP according to the protocol deviation for CPAP administered for less than 4 hours duration. However, on the database the duration was 240 mins. This was changed to 180 mins using STATA.
    - Maximum airway pressure received
        - Set to missing if max airway pressure is equal to 0
        - 1 patient had a max airway pressure of 7.5 and was entered using STATA
- Additional treatments (Page 7 of CRF)
    - Repeat Surgery
        - Set "Infection", "Bleeding", "Anastomotic leak" and "Other" to missing if Repeat surgery is marked as "No"
    - Invasive mechanical ventilation
        - Set "what was the total duration of invasive mechanical ventilation?" to missing if equal to 0 or if "Invasive mechanical ventilation after leaving the operating room" is marked as "no"
    - Non-invasive mechanical ventilation
        - Set "what was the total duration of non-invasive mechanical ventilation?" to missing if equal to 0 or if "Non-invasive mechanical ventilation after leaving the operating room" is marked as "no"
- Patient admitted to a critical care unit (page 8 of CRF)

    - If "Was the participant admitted to a critical care unit?" is marked as "No" then set the following questions to missing
        - Was the critical care admission to treat a complication?
        - Was a planned critical care admission prolonged by a postoperative complication?
        - What was the total duration of the level 2 critical care stay within 30 days of randomisation?
        - What was the total duration of the level 3 critical care stay within 30 days of randomisation?
    - If patient was admitted to a critical care unit and duration for level 2 and 3 is 0 days then duration for level 2 and 3 is set to missing
    - Total duration of level 2 and level 3 for a patient was calculated only if both level 2 and level 3 days were available
- Duration of primary hospital admission (page 8 of CRF)
    - Set to missing if patient is marked alive at 30 days and duration is equal to 0
    - If patient died on the day of randomisation then set duration to 0.5 days
- All date variables in string format were changed into a date variable that STATA recognised
- For the following events, the date of the event was set to missing if the event was marked as "no" or "alive" or missing
    - Pneumonia within 30 days of randomisation
    - Endotracheal re-intubation within 30 days of randomisation
    - All-cause mortality within 30 days of randomisation
    - All-cause mortality within one-year of randomisation
- Duration of surgery was calculated as date/time of end of surgery minus date/time start of surgery. Duration of surgery was set to missing if duration is equal to 0 or greater than 24 hours.
- Patients who have withdrew consent for use of data must have all data set to missing apart from PRISM ID and treatment allocation

Adverse Events Data

The data cleaning process for adverse events included the following:

- Adverse events categorised as 'Other' were reviewed and assigned a specific category
- Free-text for adverse events categorised as 'Other' were reviewed and reallocated to a pre-specified adverse event category if appropriate
- Adverse events categorised as 'Other' that did not count as an adverse event, as agreed within the TMG, were removed

Protocol Deviations

The data cleaning process for the protocol deviations collected using CRF versions 1.1, 1.2 and 1.3 included the following:

- The deviation 'CPAP administered for less than 4 hours and CPAP administered with significant interruption' was split into two individual deviations
- Going through free-text where no pre-specified deviation has been marked and to assign to a pre-specified/other deviation or to remove it if it does not count as a protocol deviation
- Duplicate protocol deviations were removed

The data cleaning process for the protocol deviations collected using the CRF version 1.4 included the following:

- Free text for protocol deviations categorised as 'Other' were reviewed and re-allocated to a pre-specified protocol deviation if appropriate
- Protocol deviations categorised as 'Other' that did not count as a protocol deviation, as agreed within the TMG, were removed
- Protocol deviations for two patients who according to the entered data did not receive CPAP were entered by the trial coordinator since the site did not complete electronic protocol deviation forms before data lock
- Protocol deviations related to CPAP for patients in the usual care arm were removed
- Protocol deviations for four patients who according to the entered data received less than 4h of CPAP were entered by the trial coordinator since the site did not complete electronic protocol deviation forms before data lock
- Duplicate protocol deviations were removed

Section 2: Primary analysis

Analysis
The primary outcome will be analyzed using a mixed-effect logistic regression model, with a random intercept for centre. The model will be adjusted for minimization variables as fixed factors which are country, planned use of epidural and planned surgical procedure. The model will also be adjusted for the following pre-specified baseline covariates: age, gender, at least one comorbid disease, smoking status and ASA grade (I & II vs III-V)

Changes from the SAP
- Typo in the analysis plan regarding the way ASA grade was adjusted for in the analysis model. SAP suggests ASA grade I-II vs III-IV but this should be defined as I-II vs III-V.

Decisions made according to pre-specified SAP
- Planned surgical procedure
    - Due to having fewer than 15 patients in each of the two categories (a) resection of oesophagus (non-obesity surgery), and (b) obesity surgery, these categories were combined with the category other intra-peritoneal surgery
- Country
    - Due to over stratification (no outcome events within one of the treatment groups within a category), Sweden was combined with Norway in the variable Country. This decision was made by the Chief Investigator who had no access to any trial data or results
- At least one comorbid disease.
    - Due to over stratification, the missing indicator category (those with missing data) for comorbid disease was merged with the 'yes' category. This decision was made by the Chief Investigator who had no access to any trial data or results
- Smoking status
    - Due to over stratification, the missing indicator category (those with missing data) for smoking status was merged with the 'no' category. This decision was made by the Chief Investigator who had no access to any trial data or results

Section 3: Secondary analyses

Analysis
Secondary outcomes will be analyzed using a mixed-effect logistic regression model, with a random intercept for center. The models will only be adjusted for the minimization variables, planned surgical procedure and planned use of epidural.

Changes from the SAP
- Secondary outcome for mechanical ventilation redefined
    - This outcome was recorded as receiving postoperative invasive and/or non-invasive mechanical ventilation within 30 days of randomisation (page 7 of CRF) but does not include data from the process measure related to ventilation in the 4 hour period after the end of surgery (page 5 of CRF) as opposed to including this data as originally planned in the SAP. This decision was made by the chief investigator.

Decisions made according to pre-specified SAP
- Planned surgical procedure (minimization variable)
    - Due to having fewer than 15 patients in each of the two categories (a) resection of esophagus (non-obesity surgery), and (b) obesity surgery, these categories were combined with the category other intra-peritoneal surgery. This step was taken for the analysis of all secondary outcomes.
- In addition to the above, due to over stratification, the vascular surgery category of planned surgical procedure was combined with other intra-peritoneal surgery category for the analysis of all-cause mortality within 30 days of randomization (but not for any other outcomes).

Section 4: Subgroup Analysis (primary outcome)

Analysis
The sub-group analysis model used was the same as that for the primary analysis model except planned surgical procedure was defined as in the SAP and included an interaction term between planned surgical procedure and treatment arm.

Changes from the SAP
- Typo in the analysis plan regarding the way ASA grade was adjusted for in the analysis model. SAP suggests ASA grade I-II vs III-IV but this should be defined as I-II vs III-V.

Decisions made according to pre-specified SAP
- Same as for the analysis of the primary outcome

Section 5: Per-protocol analysis

Analysis
A per-protocol analysis using inverse probability weighting (IPW) was performed for the primary outcome and the following secondary outcomes: (a) pneumonia within 30 days of randomization; (b) endotracheal re-intubation within 30 days of randomization, (c) all-cause mortality within 30 days from randomization. Participants who are non-adherent will be excluded from the analysis non-adherence is defined as (a) a participant in the intervention group who does receive any CPAP; or (b) a participant in the usual care group who does receive CPAP. We will use the following baseline covariates to calculate weights: age, current smoker, ASA grade, COPD, interstitial lung disease, bronchiectasis, heart failure, liver cirrhosis, active cancer, previous stroke, respiratory infection within the previous month, planned surgical procedure, planned use of epidural, and BMI. Missing data for these baseline covariates will be handled using mean imputation for continuous variables and the missing indicator approach for categorical variables. The probability of non-adherence will be estimated from on a logistic regression model with non-adherence as the outcome, and the covariates mentioned above as fixed terms. Age and BMI will be included as linear terms. The weight is calculated as $\frac{1}{1-P(non-adherence)}$; weights will be calculated separately in each treatment group. We will then use the same analysis model as for the main analysis, except we will include the Stata options [pw=weight], and vce(robust).

Note: A post-hoc per-protocol analysis was also conducted but the only variation is that we included patients who did not receive any CPAP due to being too unwell or remained intubated as adhering to the protocol.

Note: Another post-hoc per-protocol analysis was conducted where we included patients who did not receive any CPAP due to being unwell or remained intubated as adhering to the protocol. Also, we excluded those that received CPAP for less than 4 hours in the intervention group.

Decisions (model for non-adherence)
- Planned surgical procedure
    - Due to over stratification we merged the categories obesity surgery, vascular surgery, resection of esophagus (non-obesity surgery) and resection of stomach (non-obesity surgery) with the category other intra-peritoneal surgery
- Variables dropped
    - For the following variables, no outcome events occurred within one of the treatment groups across all categories: COPD, interstitial lung disease, bronchiectasis, hearts failure, liver cirrhosis, active cancer, respiratory infection within the previous month. These variables were dropped from the model.
- ASA grade
    - Due to over stratification, ASA grade I and II were combined and ASA grade III-V were combined
    - Due to over stratification, those in the missing indicator category for ASA grade were merged with the category ASA grade I-II
- Smoking status
    - Due to over stratification, those in the missing indicator category for smoking status were merged with the non-smoker category
- Previous stroke or TIA

  - Due to over-stratification, those in the missing indicator category for previous stroke or TIA were merged with the 'no' category.
- BMI
  - Mean imputation was used if BMI was missing

Decisions (primary and secondary outcomes analysis models)
All decisions made are the same as described in sections 2 & 3 for the primary and secondary outcome analysis models.

Supplementary tables

Supplementary table 1. Full summary of baseline characteristics

Baseline Characteristics	Number of patients with available data - no. (%)		Summary measure	
	Usual Care[c] (n=2401)	CPAP[d] (n=2405)	Usual Care	CPAP
Gender - no. (%)	2400 (>99.9)	2400 (99.8)		
Male			1278 (53.3)	1292 (53.8)
Female			1122 (46.8)	1108 (46.2)
Age (years)	2400 (>99.9)	2400 (99.8)		
Mean (SD)			67.9 (9.2)	67.8 (9.2)
Median (IQR)			68.6 (60.6-74.6)	68.1 (60.6-74.5)
Current smoker - no. (%)	2395 (99.8)	2397 (99.7)	318 (13.3)	338 (14.1)
American Society of Anaesthesiology grade[a] - no. (%)	2387 (99.4)	2390 (99.4)		
I			126 (5.3)	129 (5.4)
II			1284 (53.8)	1298 (54.3)
III			955 (40.0)	932 (39.0)
IV			21 (<1)	31 (1.3)
V			1 (<1)	0 (0.0)
Chronic comorbid disease[b] - no. (%)				
COPD	2395 (99.8)	2398 (99.7)	228 (9.5)	233 (9.7)
Asthma	2395 (99.8)	2398 (99.7)	185 (7.7)	213 (8.9)
Interstitial lung disease or pulmonary fibrosis	2395 (99.8)	2398 (99.7)	22 (<1)	26 (1.1)
Bronchiectasis	2395 (99.8)	2398 (99.7)	11 (<1)	19 (<1)
Ischaemic heart disease	2395 (99.8)	2398 (99.7)	235 (9.8)	230 (9.6)
Diabetes mellitus	2395 (99.8)	2398 (99.7)	437 (18.2)	395 (16.5)
Heart failure	2395 (99.8)	2398 (99.7)	60 (2.5)	64 (2.7)
Liver cirrhosis	2395 (99.8)	2398 (99.7)	82 (3.4)	77 (3.2)
Active cancer	2395 (99.8)	2398 (99.7)	1924 (80.3)	1926 (80.3)
Previous stroke or transient ischaemic attack	2395 (99.8)	2398 (99.7)	129 (5.4)	105 (4.4)
Primary respiratory infection with the previous month	2395 (99.8)	2397 (99.7)	50 (2.1)	52 (2.2)
HIV infection	2394 (99.7)	2398 (99.7)	19 (<1)	23 (<1)
Planned surgical procedure - no. (%)	2400 (>99.9)	2400 (99.8)		
Resection of colon, rectum or small bowel			924 (38.5)	922 (38.4)
Resection of liver, pancreas or gall bladder			630 (26.3)	631 (26.3)
Resection of stomach (non-obesity surgery)			68 (2.8)	67 (2.8)
Obesity surgery			1 (<1)	0 (0.0)
Vascular procedure			69 (2.9)	71 (3.0)
Other intra-peritoneal surgery			708 (29.5)	706 (29.4)
Resection of oesophagus (non-obesity surgery)			0 (0.0)	3 (<1)
Planned use of epidural anaesthesia - no. (%)	2400 (>99.9)	2400 (99.8)	1134 (47.3)	1131 (47.1)
Country - no. (%)	2400 (>99.9)	2400 (99.8)		
Italy			574 (23.9)	573 (23.9)
Spain			37 (1.5)	36 (1.5)
Sweden			63 (2.6)	65 (2.7)
United Kingdom			1421 (59.2)	1421 (59.2)
South Africa			99 (4.1)	99 (4.1)
Norway			206 (8.6)	206 (8.6)
Surgical procedure performed - no. (%)	2397 (99.8)	2398 (99.7)		
Resection of colon, rectum or small bowel			928 (38.7)	922 (38.4)
Resection of liver, pancreas or gall bladder			628 (26.2)	621 (25.9)
Resection of stomach (non-obesity surgery)			61 (2.5)	63 (2.6)

Obesity surgery			1 (<1)	0 (0.0)
Vascular procedure			70 (2.9)	73 (3.0)
Other intra-peritoneal surgery			708 (29.5)	717 (29.9)
Resection of oesophagus (non-obesity surgery)			1 (<1)	2 (<1)
Haemoglobin (g/dL)	2386 (99.4)	2381 (99.0)		
Mean (SD)			12.7 (1.9)	12.7 (1.8)
Median (IQR)			12.9 (11.5-14.1)	12.9 (11.5-14.0)
Creatinine (mmol/L)	2373 (98.8)	2374 (98.7)		
Mean (SD)			81.0 (37.5)	81.8 (55.6)
Median (IQR)			75.0 (63.6-89.0)	74.0 (63.0-88.4)
BMI (kg/m^2)	2395 (99.8)	2396 (99.6)		
Mean (SD)			27.3 (5.3)	27.1 (5.4)
Median (IQR)			26.7 (23.6-30.1)	26.4 (23.4-29.9)
ARISCAT Score	2352 (98.0)	2363 (98.3)		
Mean (SD)			40.8 (9.3)	41.1 (9.0)
Median (IQR)			41.0 (41.0-41.0)	41.0 (41.0-41.0)

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] American Society of Anesthesiology grades are defined as follows: 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; 4, a patient with severe systemic disease that is a constant threat to life; 5, a moribund patient who is not expected to survive without the operation

[b] Patient may have more than one chronic co-morbid disease

[c] 1 patient withdrew consent for use of data in the usual care group

[d] 5 patients withdrew consent for use of data in the CPAP group

[e] Components of the ARISCAT score are provided in supplementary table 20

Supplementary table 2. Full summary of patient care characteristics

Patient care	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
Open surgical technique used during surgery - no. (%)	2397 (99.8)	2398 (99.7)	2389 (99.7)	2387 (99.5)
Anaesthetic technique - no. (%)				
General anaesthesia	2397 (99.8)	2398 (99.7)	2394 (99.9)	2394 (99.8)
Epidural anaesthesia	2394 (99.7)	2398 (99.7)	1053 (44.0)	1035 (43.2)
Spinal anaesthesia	2394 (99.7)	2397 (99.7)	436 (18.2)	456 (19.0)
Endotracheal tube inserted	2394 (99.7)	2397 (99.7)	2346 (98.0)	2343 (97.7)
Mechanical ventilation during surgery				
Recruitment manoeuvre - no. (%)	2340 (97.5)	2350 (97.7)	430 (18.4)	446 (19.0)
Mechanical ventilation - no. (%)	2393 (99.7)	2396 (99.6)	2381 (99.5)	2388 (99.7)
Maximum positive end-expiratory pressure (cmH_2O)[a]	2328/2381 (97.8)	2338/2388 (97.9)		
Mean (SD)			5.9 (2.5)	5.8 (2.3)
Median (IQR)			5 (5-6)	5 (5-6)
Maximum set tidal volume (ml)[a]	2312/2381 (97.1)	2310/2388 (96.7)		
Mean (SD)			512.0 (92.9)	511.0 (88.4)
Median (IQR)			500 (450-550)	500 (450-550)
Maximum respiratory rate (min^{-1})[a]	2321/2381 (97.5)	2327/2388 (97.4)		
Mean (SD)			13.6 (2.5)	13.6 (2.5)
Median (IQR)			13 (12-15)	14 (12-15)
Maximum FiO_2 (%)[a]	2337/2381 (98.2)	2348/2388 (98.3)		
Mean (SD)			53.9 (14.9)	53.6 (14.9)
Median (IQR)			50 (45-60)	50 (45-60)
Intravenous fluids during surgery				
Total volume of intravenous fluid administered excluding blood products (mL)	2394 (99.7)	2392 (99.5)		
Mean (SD)			2872.1 (1659.4)	2871.9 (1536.4)
Median (IQR)			2500 (2000-3500)	2500 (2000-3500)
Total volume of blood products administered (mL)	2393 (99.7)	2391 (99.4)		
Mean (SD)			120.0 (465.8)	101.4 (385.1)

Median (IQR)			0 (0-0)	0 (0-0)
Planned level of care on the first night after surgery - no. (%)	2400 (>99.9)	2400 (99.8)		
Critical care unit level 3			231 (9.6)	231 (9.6)
Critical care unit level 2			1173 (48.9)	1193 (49.7)
Post-anaesthesia care unit			220 (9.2)	228 (9.5)
Surgical ward			776 (32.3)	748 (31.2)
Level of care on the first night after surgery - no. (%)	2395 (99.8)	2398 (99.7)		
Critical care unit level 3			225 (9.4)	238 (9.9)
Critical care unit level 2			1144 (47.8)	1204 (50.2)
Post-anaesthesia care unit			208 (8.7)	213 (8.9)
Surgical ward			818 (34.2)	743 (31.0)
Respiratory support after surgery (within 4 hours of the end of surgery) - no. (%)				
Invasive mechanical ventilation	2397 (99.8)	2397 (99.7)	125 (5.2)	118 (4.9)
Non-invasive mechanical ventilation	2397 (99.8)	2397 (99.7)	19 (0.8)	190 (7.9)
High flow nasal oxygen therapy	2397 (99.8)	2397 (99.7)	49 (2.0)	42 (1.8)

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] Only summarised for patients who received mechanical ventilation during surgery

Supplementary table 3. CPAP characteristics for patients in the CPAP group.

CPAP Characteristics	Number of patients with available data - no. (%)	Summary measure
	Allocated to CPAP group (n=2405)	CPAP
Number of patients who received CPAP - no. (%)	2398 (99.7)	2241 (93.5)
Total duration of CPAP within 12 hours of the end of surgery (minutes)	2239/2241 (99.9)	
Mean (SD)		194.2 (97.4)
Median (IQR)		240 (149-240)
Maximum airway pressure received within 12 hours of the end of surgery (cmH_2O)	2127/2241 (94.9)	
Mean (SD)		5.5 (1.4)
Median (IQR)		5 (5-5)
Primary method of CPAP delivery - no. (%)	2160/2241 (96.4)	
Face mask		1564 (72.4)
Helmet device		568 (26.3)
Nasal mask		28 (1.3)
Extra research staff present to help deliver CPAP - no. (%)	2160/2241 (96.4)	1007 (46.6)
Staff administering CPAP used equipment to monitor airway pressures - no. (%)	2155/2241 (96.2)	1271 (59.0)
Staff administering CPAP used equipment to monitor FiO_2 - no. (%)	2159/2241 (96.3)	1646 (76.2)
Patient had a nasogastric tube in situ during CPAP - no. (%)	2160/2241 (96.4)	744 (34.4)

Abbreviations: SD, standard deviation; IQR, Interquartile range

Supplementary table 4. Adherence and contamination

Adherence and contamination - no. (%)	Usual Care[a] (n=2397/2401)	CPAP[b] (n=2398/2405)
Patients with ≥1 treatment deviation	14 (0.6)	857 (35.7)
Total number of deviations	14	888
Number of treatment deviations per patient		
0	2383 (99.4)	1541 (64.3)
1	14 (0.6)	826 (34.4)
2	N/A	31 (1.3)
3	N/A	0 (0.0)
Type of deviation		
Participant in the intervention group did not receive CPAP	N/A	157 (6.5)
CPAP administered for less than 4 hours duration	N/A	686 (28.6)
CPAP administered with significant interruption	N/A	38 (1.6)
CPAP started at a dose other than 5cmH_2O	N/A	7 (0.3)
Participant in the usual care group received CPAP	14 (0.6)	N/A

[a] 3 patients missing data on whether they received CPAP and 1 patient withdrew consent for use of data
[b] 2 patients missing data on whether they received CPAP and 5 patients withdrew consent for use of data

Supplementary table 5. Adherence and contamination by CPAP delivery method

Adherence and contamination - no. (%)	CPAP[a] (n=2160/2405)		
	Face mask (n=1564)	Helmet device (n=568)	Nasal mask (n=28)
Patients with ≥1 treatment deviation	530 (33.9)	89 (15.7)	0 (0.0)
Total number of deviations	557	93	0
Number of treatment deviations per patient			
0	1034 (66.1)	479 (84.3)	28 (100.0)
1	503 (32.2)	85 (15.0)	0 (0.0)
2	27 (1.7)	4 (0.7)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)
Type of deviation			
CPAP administered for less than 4 hours duration	518 (33.1)	87 (15.3)	0 (0.0)
CPAP administered with significant interruption	32 (2.0)	6 (1.1)	0 (0.0)
CPAP started at a dose other than 5cmH_2O	7 (0.4)	0 (0.0)	0 (0.0)

[a] 5 patients withdrew consent for use of data, 157 patients did not receive CPAP, 2 patients missing data on whether they received CPAP and 81 patients missing data on CPAP method

Supplementary table 6. Primary and secondary outcomes within 30 days of randomization (includes the number of patients with available data and included in the analysis)

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Adjusted odds ratio (95% CI)	P-value
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)	2397 (99.8)	2396 (99.6)	197 (8.2)	195 (8.1)	1.01 (0.81, 1.24)	0.95
Pneumonia within 30 days of randomisation	2397 (99.8)	2396 (99.6)	117 (4.9)	123 (5.1)	1.06 (0.82, 1.38)	0.66
Endotracheal re-intubation within 30 days of randomisation	2398 (99.9)	2397 (99.7)	90 (3.8)	80 (3.3)	0.89 (0.65, 1.21)	0.45
All-cause mortality within 30 days of randomisation	2398 (99.9)	2397 (99.7)	33 (1.4)	30 (1.3)	0.91 (0.55, 1.50)	0.71
Postoperative infection within 30 days of randomisation	2393 (99.7)	2395 (99.6)	741 (31.0)	738 (30.8)	0.99 (0.87, 1.12)	0.89
Postoperative mechanical ventilation within 30 days of randomisation[a]	2393 (99.7)	2395 (99.6)	210 (8.8)[b]	230 (9.6)[c]	1.17 (0.94, 1.45)	0.16
All-cause mortality within one-year of randomisation	2363 (98.4)	2374 (98.7)	230 (9.7)	213 (9.0)	0.91 (0.75, 1.11)	0.37

[a] This outcome was recorded as receiving postoperative invasive and/or non-invasive mechanical ventilation within 30 days of randomisation but does not include data from the process measure related to ventilation in the four hour period after the end of surgery

[b] In the usual care group, 168/2393 (7.0%) participants received invasive mechanical ventilation, 21/2393 (0.9%%) participants received non-invasive mechanical ventilation and 21/2393 (0.9%) participants received both invasive and non-invasive mechanical ventilation

[c] In the intervention group, 166/2395 (6.9%) participants received invasive mechanical ventilation, 38/2395 (1.6%) participants received non-invasive mechanical ventilation and 26/2395 (1.1%) participants received both invasive and non-invasive mechanical ventilation

Supplementary table 7. Summary of investigators' self-assessment of blinding (patients followed-up by a member of research who are unaware of trial group allocation)

Investigator self-assessment of blinding - no. (%)	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
Suitably blinded	2394 (99.7)	2394 (99.5)	1813 (75.7)	1686 (70.4)
May have known the study group allocation			190 (7.9)	200 (8.4)
Definitely knew the study group allocation			391 (16.3)	508 (21.2)

Supplementary table 8. Complications within 30 days of randomization

Complication	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
Respiratory - no. (%)				
Pneumonia	2396 (99.8)	2397 (99.7)	117 (4.9)	124 (5.2)[a]
Pleural effusion	2394 (99.7)	2395 (99.6)	159 (6.6)	173 (7.2)
Pneumothorax	2394 (99.7)	2395 (99.6)	10 (<1)	16 (<1)
Bronchospasm	2394 (99.7)	2395 (99.6)	11 (<1)	12 (<1)
Aspiration pneumonitis	2394 (99.7)	2395 (99.6)	12 (<1)	13 (<1)
Acute respiratory distress syndrome	2394 (99.7)	2395 (99.6)	11 (<1)	6 (<1)
Infections - no. (%)				
Surgical site infection (superficial)	2393 (99.7)	2395 (99.6)	248 (10.4)	241 (10.1)
Surgical site infection (deep)	2393 (99.7)	2395 (99.6)	114 (4.8)	111 (4.6)
Surgical site infection (organ space)	2393 (99.7)	2395 (99.6)	149 (6.2)	139 (5.8)
Urinary tract infection	2393 (99.7)	2395 (99.6)	124 (5.2)	132 (5.5)
Infection, source uncertain	2394 (99.7)	2395 (99.6)	127 (5.3)	135 (5.6)
Laboratory confirmed blood stream infection	2394 (99.7)	2395 (99.6)	80 (3.3)	82 (3.4)
Cardiac - no. (%)				
Myocardial infarction	2394 (99.7)	2394 (99.5)	14 (<1)	18 (<1)
Arrhythmia	2394 (99.7)	2394 (99.5)	118 (4.9)	101 (4.2)
Cardiogenic pulmonary oedema	2394 (99.7)	2394 (99.5)	10 (<1)	14 (<1)
Cardiac arrest with successful resuscitation	2394 (99.7)	2394 (99.5)	8 (<1)	12 (<1)
Other - no. (%)				
Acute kidney injury	2394 (99.7)	2394 (99.5)	139 (5.8)	157 (6.6)
Pulmonary embolism	2394 (99.7)	2394 (99.5)	31 (1.3)	32 (1.3)
Stroke	2394 (99.7)	2394 (99.5)	2 (<1)	5 (<1)
Acute psychosis or delirium	2394 (99.7)	2394 (99.5)	102 (4.3)	107 (4.5)
Bowel infarction	2394 (99.7)	2394 (99.5)	9 (<1)	9 (<1)
Anastomotic leak	2394 (99.7)	2394 (99.5)	101 (4.2)	102 (4.3)
Perforation of viscus	2394 (99.7)	2394 (99.5)	21 (<1)	9 (<1)
Gastro-intestinal bleed	2394 (99.7)	2394 (99.5)	62 (2.6)	31 (1.3)
Other postoperative haemorrhage	2394 (99.7)	2394 (99.5)	53 (2.2)	54 (2.3)
Any other complication	2393 (99.7)	2394 (99.5)	415 (17.3)	406 (17.0)

[a] There is a discrepancy in the number of participants with pneumonia between supplementary tables 6 and 8. This is due to the way outcome measures for supplementary table 6 and complications in supplementary table 8 were collected and defined. For the secondary outcome of pneumonia (supplementary table 6), the date of pneumonia was collected, and the outcome was set to missing if the date was not recorded. The complication data in supplementary table 8 was collected as Clavien-Dindo grade I-V or No complication, with no date required. One patient was classified as having a secondary outcome of pneumonia, with the date of pneumonia missing, and as having a complication of pneumonia. Because we were unable to ascertain the date, we set the outcome in supplementary table 6 to missing, and set the complication in supplementary table 8 to the patient experiencing pneumonia.

Supplementary table 9. Complications within 30 days of randomisation in the intervention group by CPAP method

Complication	Number of patients with available data - no. (%)			Summary measure		
	CPAP[a] (n=2160/2405)			CPAP		
	Face mask (n=1564)	Helmet device (n=568)	Nasal mask (n=28)	Face mask	Helmet device	Nasal mask
Respiratory - no. (%)						
Pneumonia	1562 (99.9)	567 (99.8)	28 (100.0)	90 (5.8)	26 (4.6)	1 (3.6)
Pleural effusion	1562 (99.9)	567 (99.8)	28 (100.0)	96 (6.1)	57 (10.1)	1 (3.6)
Pneumothorax	1562 (99.9)	567 (99.8)	28 (100.0)	6 (<1)	3 (<1)	1 (3.6)
Bronchospasm	1562 (99.9)	567 (99.8)	28 (100.0)	9 (<1)	2 (<1)	0 (0.0)
Aspiration pneumonitis	1562 (99.9)	567 (99.8)	28 (100.0)	11 (<1)	1 (<1)	0 (0.0)
Acute respiratory distress syndrome	1562 (99.9)	567 (99.8)	28 (100.0)	6 (<1)	0 (0.0)	0 (0.0)
Infections - no. (%)						
Surgical site infection (superficial)	1562 (99.9)	567 (99.8)	28 (100.0)	181 (11.6)	33 (5.8)	1 (3.6)
Surgical site infection (deep)	1562 (99.9)	567 (99.8)	28 (100.0)	69 (4.4)	30 (5.3)	0 (0.0)
Surgical site infection (organ space)	1562 (99.9)	567 (99.8)	28 (100.0)	89 (5.7)	28 (4.9)	0 (0.0)
Urinary tract infection	1562 (99.9)	567 (99.8)	28 (100.0)	89 (5.7)	25 (4.4)	0 (0.0)
Infection, source uncertain	1562 (99.9)	567 (99.8)	28 (100.0)	87 (5.6)	30 (5.3)	0 (0.0)
Laboratory confirmed blood stream infection	1562 (99.9)	567 (99.8)	28 (100.0)	40 (2.6)	31 (5.5)	0 (0.0)
Cardiac - no. (%)						
Myocardial infarction	1562 (99.9)	567 (99.8)	28 (100.0)	9 (<1)	5 (<1)	0 (0.0)
Arrhythmia	1562 (99.9)	567 (99.8)	28 (100.0)	73 (4.7)	14 (2.5)	0 (0.0)
Cardiogenic pulmonary oedema	1562 (99.9)	567 (99.8)	28 (100.0)	8 (<1)	5 (<1)	0 (0.0)
Cardiac arrest with successful resuscitation	1562 (99.9)	567 (99.8)	28 (100.0)	7 (<1)	3 (<1)	0 (0.0)
Other - no. (%)						
Acute kidney injury	1562 (99.9)	567 (99.8)	28 (100.0)	102 (6.5)	27 (4.8)	2 (7.1)
Pulmonary embolism	1562 (99.9)	567 (99.8)	28 (100.0)	22 (1.4)	7 (1.2)	0 (0.0)
Stroke	1562 (99.9)	567 (99.8)	28 (100.0)	1 (<1)	3 (<1)	1 (3.6)
Acute psychosis or delirium	1562 (99.9)	567 (99.8)	28 (100.0)	71 (4.5)	21 (3.7)	1 (3.6)
Bowel infarction	1562 (99.9)	567 (99.8)	28 (100.0)	4 (<1)	4 (<1)	0 (0.0)
Anastomotic leak	1562 (99.9)	567 (99.8)	28 (100.0)	62 (4.0)	25 (4.4)	1 (3.6)
Perforation of viscus	1562 (99.9)	567 (99.8)	28 (100.0)	4 (<1)	4 (<1)	0 (0.0)
Gastro-intestinal bleed	1562 (99.9)	567 (99.8)	28 (100.0)	17 (1.1)	11 (1.9)	0 (0.0)
Other postoperative haemorrhage	1562 (99.9)	567 (99.8)	28 (100.0)	25 (1.6)	17 (3.0)	1 (3.6)
Any other complication	1562 (99.9)	567 (99.8)	28 (100.0)	293 (18.8)	74 (13.1)	1 (3.6)

[a] 5 patients withdrew consent for use of data, 157 patients did not receive CPAP, 2 patients missing data on whether they received CPAP and 81 patients missing data on CPAP method

Supplementary table 10. Complications within 30 days of randomization

Complication	Number of patients with available data - no. (%)		Summary measure					
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care			CPAP		
			I-II	III-V	Total	I-II	III-V	Total
Respiratory - no. (%)								
Pneumonia	2396 (99.8)	2397 (99.7)	94 (3.9)	23 (<1)	117 (4.9)	103 (4.3)	21 (<1)	124 (5.2)[a]
Pleural effusion	2394 (99.7)	2395 (99.6)	120 (5.0)	39 (1.6)	159 (6.6)	134 (5.6)	39 (1.6)	173 (7.2)
Pneumothorax	2394 (99.7)	2395 (99.6)	4 (<1)	6 (<1)	10 (<1)	10 (<1)	6 (<1)	16 (<1)
Bronchospasm	2394 (99.7)	2395 (99.6)	8 (<1)	3 (<1)	11 (<1)	10 (<1)	2 (<1)	12 (<1)
Aspiration pneumonitis	2394 (99.7)	2395 (99.6)	4 (<1)	8 (<1)	12 (<1)	8 (<1)	5 (<1)	13 (<1)
Acute respiratory distress syndrome	2394 (99.7)	2395 (99.6)	1 (<1)	10 (<1)	11 (<1)	2 (<1)	4 (<1)	6 (<1)
Infections - no. (%)								
Surgical site infection (superficial)	2393 (99.7)	2395 (99.6)	224 (9.4)	24 (1.0)	248 (10.4)	224 (9.4)	17 (<1)	241 (10.1)
Surgical site infection (deep)	2393 (99.7)	2395 (99.6)	69 (2.9)	45 (1.9)	114 (4.8)	66 (2.8)	45 (1.9)	111 (4.6)
Surgical site infection (organ space)	2393 (99.7)	2395 (99.6)	61 (2.5)	88 (3.7)	149 (6.2)	58 (2.4)	81 (3.4)	139 (5.8)
Urinary tract infection	2393 (99.7)	2395 (99.6)	120 (5.0)	4 (<1)	124 (5.2)	129 (5.4)	3 (<1)	132 (5.5)
Infection, source uncertain	2394 (99.7)	2395 (99.6)	114 (4.8)	13 (<1)	127 (5.3)	127 (5.3)	8 (<1)	135 (5.6)
Laboratory confirmed blood stream infection	2394 (99.7)	2395 (99.6)	60 (2.5)	20 (<1)	80 (3.3)	63 (2.6)	19 (<1)	82 (3.4)
Cardiac - no. (%)								
Myocardial infarction	2394 (99.7)	2394 (99.5)	7 (<1)	7 (<1)	14 (<1)	7 (<1)	11 (<1)	18 (<1)
Arrhythmia	2394 (99.7)	2394 (99.5)	108 (4.5)	10 (<1)	118 (4.9)	85 (3.6)	16 (<1)	101 (4.2)
Cardiogenic pulmonary oedema	2394 (99.7)	2394 (99.5)	6 (<1)	4 (<1)	10 (<1)	9 (<1)	5 (<1)	14 (<1)
Cardiac arrest with successful resuscitation	2394 (99.7)	2394 (99.5)	0 (0.0)	8 (<1)	8 (<1)	0 (0.0)	12 (<1)	12 (<1)
Other - no. (%)								
Acute kidney injury	2394 (99.7)	2394 (99.5)	114 (4.8)	25 (1.0)	139 (5.8)	129 (5.4)	28 (1.2)	157 (6.6)
Pulmonary embolism	2394 (99.7)	2394 (99.5)	24 (1.0)	7 (<1)	31 (1.3)	29 (1.2)	3 (<1)	32 (1.3)
Stroke	2394 (99.7)	2394 (99.5)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	5 (<1)
Acute psychosis or delirium	2394 (99.7)	2394 (99.5)	101 (4.2)	1 (<1)	102 (4.3)	103 (4.3)	4 (<1)	107 (4.5)
Bowel infarction	2394 (99.7)	2394 (99.5)	1 (<1)	8 (<1)	9 (<1)	3 (<1)	6 (<1)	9 (<1)
Anastomotic leak	2394 (99.7)	2394 (99.5)	30 (1.3)	71 (3.0)	101 (4.2)	27 (1.1)	75 (3.1)	102 (4.3)
Perforation of viscus	2394 (99.7)	2394 (99.5)	3 (<1)	18 (<1)	21 (<1)	0 (0.0)	9 (<1)	9 (<1)
Gastro-intestinal bleed	2394 (99.7)	2394 (99.5)	27 (1.1)	35 (1.5)	62 (2.6)	11 (<1)	20 (<1)	31 (1.3)
Other postoperative haemorrhage	2394 (99.7)	2394 (99.5)	20 (<1)	33 (1.4)	53 (2.2)	29 (1.2)	25 (1.0)	54 (2.3)
Any other complication	2393 (99.7)	2394 (99.5)	302 (12.6)	113 (4.7)	415 (17.3)	321 (13.4)	85 (3.6)	406 (17.0)

[a] There is a discrepancy in the number of participants with pneumonia between supplementary tables 6 and 10. This is due to the way outcome measures for supplementary table 6 and complications in supplementary table 10 were collected and defined. For the secondary outcome of pneumonia (supplementary table 6), the date of pneumonia was collected, and the outcome was set to missing if the date was not recorded. The complication data in supplementary table 10 was collected as Clavien-Dindo grade I-V or No complication, with no date required. One

patient was classified as having a secondary outcome of pneumonia, with the date of pneumonia missing, and as having a complication of pneumonia. Because we were unable to ascertain the date, we set the outcome in supplementary table 6 to missing, and set the complication in supplementary table 10 to the patient experiencing pneumonia

Supplementary table 11. Process measures

Process measures	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
Re-admission to hospital within 30 days of randomisation - no. (%)	2391 (99.6)	2395 (99.6)	242 (10.1)	228 (9.5)
Duration of primary hospital admission within 30 days of randomisation (days)	2390 (99.5)	2392 (99.5)		
Mean (SD)			11.3 (11.4)	11.4 (10.5)
Median (IQR)			8 (6-13)	9 (6-13)
Number of patients admitted to a critical care unit - no. (%)	2397 (99.8)	2397 (99.7)	1451 (60.5)	1526 (63.7)
Total duration of critical care stay within 30 days of randomisation (days)[a]	1448/1451 (99.8)	1521/1526 (99.7)		
Mean (SD)			3.3 (3.4)	3.0 (3.1)
Median (IQR)			2 (2-4)	2 (2-3)

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] Summarised only for patients admitted to a critical care unit

Supplementary table 12. Critical care stay within 30 days of randomization

Critical care stay within 30 days of randomisation	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
Number of patients admitted to a critical care unit - no. (%)	2397 (99.8)	2397 (99.7)	1451 (60.5)	1526 (63.7)
Duration of level 2 critical care stay (days)[a]	1449/1451 (99.9)	1521/1526 (99.7)		
Mean (SD)			2.5 (2.3)	2.3 (2.2)
Median (IQR)			2 (1-3)	2 (1-3)
Duration of level 3 critical care stay (days)[a]	1450/1451 (99.9)	1521/1526 (99.7)		
Mean (SD)			0.8 (2.7)	0.7 (2.5)
Median (IQR)			0 (0-0)	0 (0-0)

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] Summarised only for patients admitted to a critical care unit

Supplementary table 13. Safety outcomes in CPAP group

Adverse Events - no. (%)	CPAP[a] (2241/2405)
Patients with ≥1 adverse event	200 (8.9)
Total number of adverse events	276
Number of adverse events per patient	
0	2041 (91.1)
1	146 (6.5)
2	35 (1.6)
3	16 (0.7)
4	3 (0.1)
Type of adverse event	
Interface intolerance due to excessive air leak	36 (1.6)
Pain	24 (1.1)
Cutaneous pressure area	13 (0.6)
Claustrophobia	78 (3.5)
Oronasal dryness	43 (1.9)
Hypercapnia	11 (0.5)
Haemodynamic instability	15 (0.7)
Vomiting	26 (1.2)
Aspiration of gastric contents	0 (0.0)
Other	30 (1.3)

[a] 5 patients withdrew consent for use of data, 2 patients missing data on whether they received CPAP and 157 patients did not receive CPAP

Supplementary table 14. Other safety outcomes in CPAP group

Other Adverse Events - no. (%)	CPAP[a] (n=2241/2405)
Total number of other adverse events	30
Type of adverse event	
Discomfort associated with CPAP device	14
Breathing difficulty	7
Nausea without vomit	7
Hearing loss	1
Possible allergy	1

[a] 5 patients withdrew consent for use of data, 2 patients missing data on whether they received CPAP and 157 patients did not receive CPAP

Supplementary table 15. Safety outcomes by CPAP delivery method in the CPAP group

Adverse Events - no. (%)	CPAP[a] (n=2160/2405)		
	Face mask (n=1564)	Helmet device (n=568)	Nasal mask (n=28)
Patients with ≥1 adverse event	165 (10.5)	33 (5.8)	0 (0.0)
Total number of adverse events	234	40	0
Number of adverse events per patient			
0	1399 (89.5)	535 (94.2)	28 (100.0)
1	118 (7.5)	26 (4.6)	0 (0.0)
2	28 (1.8)	7 (1.2)	0 (0.0)
3	16 (1.0)	0 (0.0)	0 (0.0)
4	3 (0.2)	0 (0.0)	0 (0.0)
Type of adverse event			
Interface intolerance due to excessive air leak	35 (2.2)	1 (0.2)	0 (0.0)
Pain	21 (1.3)	3 (0.5)	0 (0.0)
Cutaneous pressure area	11 (0.7)	2 (0.4)	0 (0.0)
Claustrophobia	63 (4.0)	13 (2.3)	0 (0.0)
Oronasal dryness	36 (2.3)	7 (1.2)	0 (0.0)
Hypercapnia	10 (0.6)	1 (0.2)	0 (0.0)
Haemodynamic instability	12 (0.8)	3 (0.5)	0 (0.0)
Vomiting	20 (1.3)	6 (1.1)	0 (0.0)
Aspiration of gastric contents	0 (0.0)	0 (0.0)	0 (0.0)
Other	26 (1.7)	4 (0.7)	0 (0.0)

[a] 5 patients withdrew consent for use of data, 157 patients did not receive CPAP, 2 patients missing data on whether they received CPAP and 81 patients missing data on CPAP method

Supplementary table 16. Per-protocol analysis using inverse probability weighting

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Adjusted odds ratio (95% CI)	P-value
	Usual Care[a] (n=2383/2401)	CPAP[b] (n=2241/2405)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)	2380 (99.9)	2237 (99.8)	197 (8.3)	173 (7.7)	0.95 (0.77, 1.18)	0.66
Pneumonia within 30 days of randomisation	2380 (99.9)	2237 (99.8)	117 (4.9)	116 (5.2)	1.07 (0.81, 1.43)	0.63
Endotracheal re-intubation within 30 days of randomisation	2381 (99.9)	2238 (99.9)	90 (3.8)	66 (2.9)	0.78 (0.59, 1.04)	0.09
All-cause mortality within 30 days of randomisation	2381 (99.9)	2238 (99.9)	33 (1.4)	21 (0.9)	0.68 (0.41, 1.13)	0.13

[a] Excludes 1 patient who withdrew consent for use of data, 14 patients who received CPAP and 3 patients missing data on whether they received CPAP

[b] Excludes 5 patients who withdrew consent for use of data, 157 patients did not receive CPAP and 2 patients missing data on whether they received CPAP

Supplementary table 17. Post-hoc per-protocol analysis using inverse probability weighting (including those that did not receive CPAP due to being unwell or remained intubated to have been compliers)

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Adjusted odds ratio (95% CI)	P-value
	Usual Care[a] (n=2383/2401)	CPAP[b] (n=2305/2405)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)	2380 (99.9)	2301 (99.8)	197 (8.3)	190 (8.3)	1.02 (0.84, 1.23)	0.85
Pneumonia within 30 days of randomisation	2380 (99.9)	2301 (99.8)	117 (4.9)	121 (5.3)	1.08 (0.82, 1.42)	0.57
Endotracheal re-intubation within 30 days of randomisation	2381 (99.9)	2302 (99.9)	90 (3.8)	77 (3.3)	0.89 (0.66, 1.19)	0.42
All-cause mortality within 30 days of randomisation	2381 (99.9)	2302 (99.9)	33 (1.4)	29 (1.3)	0.91 (0.59, 1.42)	0.69

[a] Excludes 1 patient who withdrew consent for use of data, 14 patients who received CPAP and 3 patients missing data on whether they received CPAP

[b] Excludes 5 patients who withdrew consent for use of data, 93 patients who did not receive CPAP (for reasons other than being unwell or remaining intubated) and 2 patients missing data on whether they received CPAP

Supplementary table 18. Pre-specified subgroup analysis for primary outcome

Planned surgical procedure	Number of patients with available data and included in analysis - no. (%)		Pneumonia, endotracheal re-intubation or death within 30 days of randomisation - no. (%)		Adjusted odds ratio (95% CI)	P-value for interaction
	Usual Care[a] (n=2400/2401)	CPAP[b] (n=2400/2405)	Usual Care	CPAP		
Lower gastrointestinal (resection of colon, rectum, or small bowel)	922/924 (99.8)	921/922 (99.9)	72/922 (7.8)	65/921 (7.1)	0.88 (0.61, 1.25)	0.76
Hepatobiliary (resection of liver, pancreas, or gall bladder)	629/630 (99.8)	628/631 (99.5)	63/629 (10.0)	64/628 (10.2)	1.03 (0.71, 1.50)	
Upper gastrointestinal (resection of oesophagus, or resection of stomach (non-obesity surgery))	68/68 (100.0)	70/70 (100.0)	10/68 (14.7)	11/70 (15.7)	1.32 (0.50, 3.44)	
Other (obesity surgery, vascular procedure, or other intra-peritoneal surgery)	778/778 (100.0)	777/777 (100.0)	52/778 (6.7)	55/777 (7.1)	1.12 (0.75, 1.67)	

[a] 1 patient withdrew consent for use of data
[b] 5 patients withdrew consent for use of data

Supplementary table 19. Post-hoc Per-protocol analysis using inverse probability weighting (we included those that did not receive CPAP due to being unwell or remained intubated to have been compliers and excluded those in the intervention group that received CPAP for less than 4 hours)

Outcomes	Number of patients with available data and included in analysis - no. (%)		Summary measure		Adjusted odds ratio (95% CI)	P-value
	Usual Care[a] (n=2383/2401)	CPAP[b] (n=1619/2405)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)	2380 (99.9)	1617 (99.9)	197 (8.3)	135 (8.3)	1.02 (0.83, 1.25)	0.88
Pneumonia within 30 days of randomisation	2380 (99.9)	1617 (99.9)	117 (4.9)	85 (5.3)	1.10 (0.84, 1.44)	0.49
Endotracheal re-intubation within 30 days of randomisation	2381 (99.9)	1618 (99.9)	90 (3.8)	54 (3.3)	0.87 (0.62, 1.24)	0.45
All-cause mortality within 30 days of randomisation	2381 (99.9)	1618 (99.9)	33 (1.4)	22 (1.4)	0.91 (0.55, 1.49)	0.71

[a] Excludes 1 patient who withdrew consent for use of data, 14 patients who received CPAP and 3 patients missing data on whether they received CPAP

[b] Excludes 5 patients who withdrew consent for use of data, 93 patients who did not receive CPAP (for reasons other than being unwell or remaining intubated), 686 patients who received CPAP for less than 4 hours and 2 patients missing data on whether they received CPAP

Supplementary table 20. ARISCAT Score

ARISCAT	Number of patients with available data - no. (%)		Summary measure	
	Usual Care (n=2401)	CPAP (n=2405)	Usual Care	CPAP
ARISCAT Score	2352 (98.0)	2363 (98.3)		
Mean (SD)			40.8 (9.3)	41.1 (9.0)
Median (IQR)			41.0 (41.0-41.0)	41.0 (41.0-41.0)
Components				
Age (years) - no. (%)				
≤50			43 (1.8)	49 (2.1)
51-80			2123 (90.3)	2134 (90.3)
>80			186 (7.9)	180 (7.6)
Percentage of peripheral oxygen saturation (SpO_2) - no. (%)				
≥96%			2086 (88.7)	2118 (89.6)
91-95%			255 (10.8)	236 (10.0)
≤90%			11 (<1)	9 (<1)
Respiratory infection in the last month - no. (%)			50 (2.1)	52 (2.2)
Preoperative anemia (Hgb ≤10 g/dL) - no. (%)			220 (9.4)	218 (9.2)
Surgical incision - no. (%)				
Upper abdominal			2352 (100.0)	2360 (99.9)
Intrathoracic			0 (0.0)	3 (<1)
Peripheral			0 (0.0)	0 (0.0)
Duration of surgery - no. (%)				
≤ 2 Hours			236 (10.0)	192 (8.1)
>2-3 Hours			427 (18.2)	435 (18.4)
> 3 Hours			1689 (71.8)	1736 (73.5)
Emergency procedure[a] - no. (%)			0 (0.0)	0 (0.0)

Abbreviations: SD, standard deviation; IQR, Interquartile range

[a] All patients recruited in the trial were elective

Supplementary table 21 – Post-hoc subgroup analysis for primary outcome

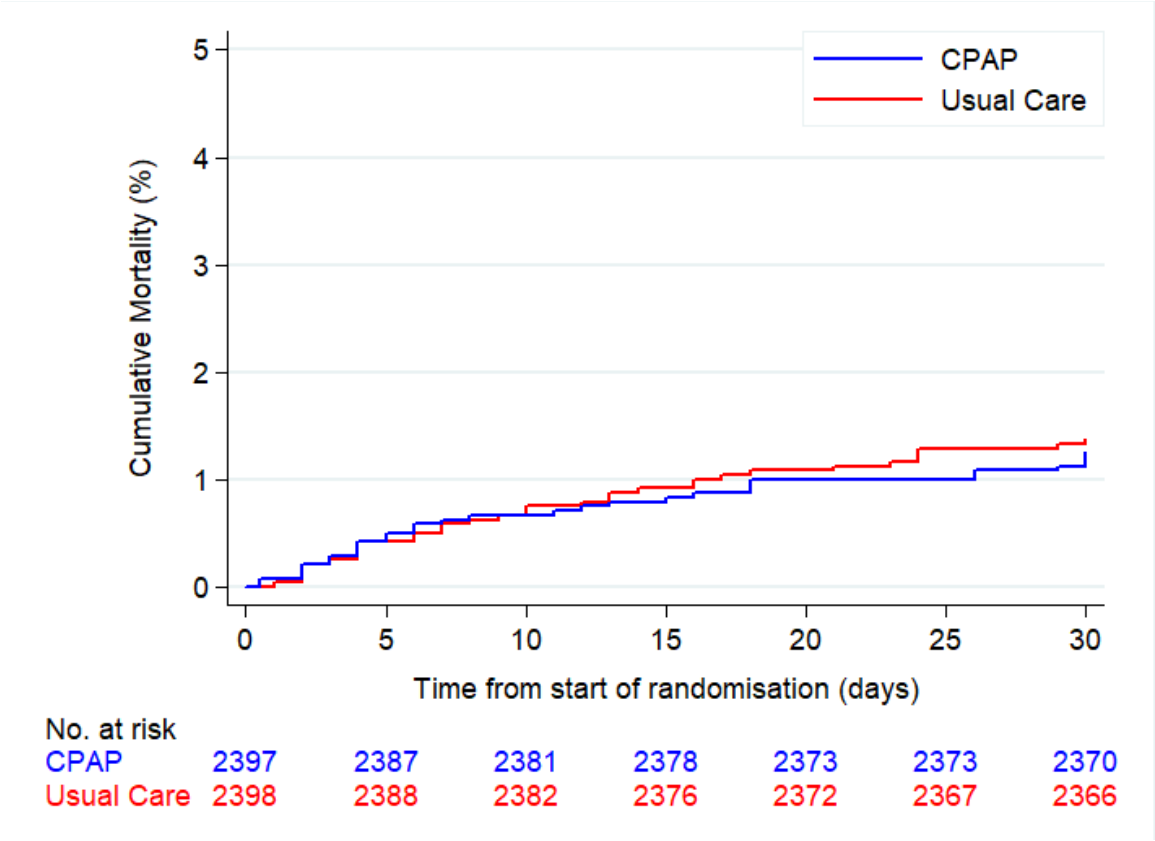
ARISCAT Score	Number of patients with available data and included in analysis - no. (%)		Pneumonia, endotracheal re-intubation or death within 30 days of randomisation - no. (%)		Adjusted odds ratio (95% CI)	P-value for interaction
	Usual Care[a] (n=2352/2401)	CPAP[b] (n=2363/2405)	Usual Care	CPAP		
ARISCAT Score ≤ 45	1847/1849 (99.9)	1869/1871 (99.9)	138/1847 (7.5)	138/1869 (7.4)	1.00 (0.78, 1.28)	0.91
ARSCAT Score > 45	502/503 (99.8)	490/492 (99.6)	58/502 (11.6)	54/490 (11.0)	0.97 (0.65, 1.46)	

[a] 1 patient withdrew consent for use of data in the usual care group and 48 patients were missing an ARISCAT Score

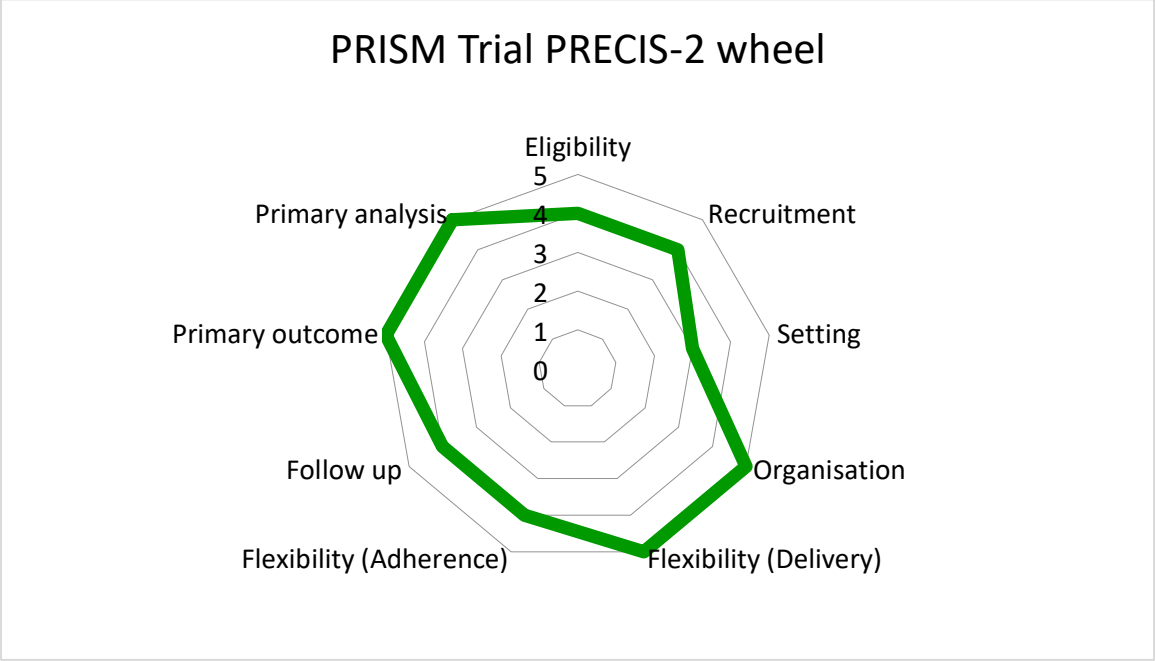
[b] 5 patients withdrew consent for use of data in the CPAP group and 37 patients were missing an ARISCAT Score

Supplementary figures

Supplementary figure 1. Kaplan-Meier survival curves by treatment allocation within 30 days of randomization.



Supplementary figure 2. PRECIS-2 diagram.



Trial definitions

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°C) with no other recognised cause
b) leucopaenia (< 4 x 10^9/L) or leucocytosis (>12 x 10^9/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 in not extubated at the end of the later surgical procedure.

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 ≥354 μmol/L (≥4.0 mg/dL) with an acute rise of > 44 μmol/L (0.5mg/dL)
c) or oliguria of < 0.5 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: PaO_2:FiO_2 26.7-40.0 kPa with PEEP or CPAP ≥ 5cmH_2O
    - Moderate: PaO_2:FiO_2 13.3-26.6 kPa with PEEP ≥ 5cmH_2O
    - Severe: PaO_2:FiO_2 ≤ 13.3 kPa with PEEP ≥ 5cmH_2O

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 or 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^{o}C or >38^{o}C
b) white cell count >12 x 10^9/L or <4 x 10^9/L
c) respiratory rate >20 breaths per minute or $PaCO_2$ < 4.5 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 ≥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 (>38ºC)
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 (>38ºC) 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 (>38ºC), chills, or hypotension and at least one of the following:

a. Common skin contaminant is cultured from two or more blood cultures drawn on separate occasions;
b. Common skin contaminant is cultured from at least one blood culture from a patient with an intravascular line, and the physician institutes appropriate antimicrobial therapy;
c. Positive antigen 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 grading[1]:

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 $PaCO_2$ 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 de-bulking 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 (SpO_2)
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 (Vt) 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.

Summary of protocol amendments

Date of amendment (Submission to REC)	Protocol version and date	Summary of changes	
20/08/15	Version 1.4 18.08.2015	Initial version submitted to the REC	
08/04/16	Version 1.5 01.03.2016	**Section:**	**Title Page (pg 1) and Chief Investigator Agreement (pg 4)**
		Formerly read:	Version 1.4 Date: 18 August 2015 **Principal Investigator** *[Insert local PI details]*
		Amended to:	Version 1.5 Date: 1 March 2016 ~~**Principal Investigator** *[Insert local PI details]*~~
		Section:	**4. INTRODUCTION (pg 6-7)**
		Formerly read:	Approximately 230 million surgical procedures are carried out worldwide each year. Whilst the results of these trials suggest that postoperative CPAP is efficacious, there has yet to be a large multi-centre trial to evaluate clinical effectiveness.
		Amended to:	Approximately 310 million surgical procedures are carried out worldwide each year. 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.
		Section:	**5.4 Secondary outcome measures (pg 8)**
		Formerly read:	• 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
		Amended to:	• 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

		Moved from later section
	Section:	**5.5 Safety objectives**
	Formerly read:	5.5 Tertiary objectives
	Amended to:	5.5 Safety objectives
	Section:	**5.6 Safety outcome measures (pg 9)**
	Formerly read:	5.6 Tertiary outcome measures Tertiary 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: • Interface intolerance due to excessive air leaks • Pain • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Hypercapnia • Haemodynamic instability • Vomiting • Other harm assessed as probably or definitely related to CPAP In addition, we will use the following process measures: • 30-day re-admission • Days in critical care • Duration of hospital stay A full list of definitions is available in the appendix.
	Amended to:	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.
	Section:	**6.2 Inclusion criteria**
	Formerly read:	Patients aged 50 years or over undergoing major intra-peritoneal surgery using an open surgical technique.
	Amended to:	Patients aged 50 years or over undergoing elective major intra-peritoneal surgery using an open surgical technique.
	Section:	**7.1 Recruitment and screening**
	Formerly read:	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……
	Amended to:	This is an international randomised controlled trial in several European countries. 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……
	Section:	**7.3 Randomisation**
	Formerly read:	Randomisation will occur after the participant has provided informed consent but before the surgical procedure is due to start. Participants will be centrally allocated to treatment groups (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 hosted by Queen Mary University of London and complete the patient's details to obtain a unique patient identification number and allocation to a treatment group.
	Amended to:	Randomisation will occur after the participant has provided informed consent and up to four hours after the end of surgery. 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.
	Section:	**7.4 Trial intervention**
	Formerly read:	The trial intervention period will commence immediately after the completion of surgery and continue for at least four hours. 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, started immediately after the patient has left the operating room after surgery. Administration of CPAP will only take place under the direct supervision of appropriately trained staff in an adequately equipped clinical area. The 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. Clinicians may only use commercially available CPAP equipment to deliver the intervention. The

		starting airway pressure should be 5cmH2O and the maximal permissible airway pressure is 10cmH2O. 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 7.9 for further details. **Usual care group** Patients in the *usual care group* will be managed by clinical staff according to local policy and guidelines. 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. 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 7.9 for further details.
	Amended to:	The trial intervention will commence immediately after the completion of surgery and continue for at least four hours. 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, started immediately after (within four 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. Clinicians may only use commercially available CPAP equipment to deliver the intervention. The starting airway pressure should be 5cmH2O and the maximal permissible airway pressure is 10cmH2O. 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.
	Section:	**7.7 Data collection**
	Formerly read:	The following data will be collected from all sites before and after the trial intervention.

		Randomisation data
		• Checklist to ensure the patient meets the eligibility criteria
		• Surgical procedure category
		• Centre ID
		
		Baseline data
		• Full name
		• Gender
		• Age/DOB
		• ASA grade
		• Planned surgical procedure
		• Diagnosis of chronic lung disease (COPD, Asthma, ILD)
		• Diagnosis of ischaemic heart disease
		• Diagnosis of diabetes
		• Diagnosis of stroke
		• Diagnosis of heart failure
		• Diagnosis of cirrhosis
		• 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
		• Extubated at the end of surgery (Y/N)
		
		24 hours postoperative
		• Patient received CPAP within four hours 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)

		• 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)
		
		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 (not including re-admission)
		• 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

	Amended to:	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) • Respiratory infection within the previous month • Diagnosis of ischaemic heart disease • Diagnosis of diabetes • Diagnosis of stroke • Diagnosis of heart failure

		• Diagnosis of cirrhosis
		• Diagnosis of active cancer
		• 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)
		  o Duration
		  o Maximum PEEP
		  o Maximum Vt
		  o Maximum FiO2 (excluding pre-oxygenation during induction of anaesthesia)
		  o Total IV fluid input (sum of crystalloid and colloid)
		  o 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 four hours of surgery? (Y/N)
		  o Total duration of CPAP within 12 hours of surgery
		  o Delivery method (mask, nasal, helmet)
		  o 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)
		  o Interface intolerance due to excessive air leaks (Y/N)
		  o Pain (Y/N)
		  o Cutaneous pressure sore or pressure area (Y/N)
		  o Claustrophobia (Y/N)
		  o Oro-nasal dryness (Y/N)
		  o Hypercapnia (Y/N and peak PaCO2)
		  o Haemodynamic instability (Y/N)
		  o Vomiting (Y/N)
		  o 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
	Section:	**7.8 Predefined protocol deviations**
	Formerly read:	• Failure to administer CPAP to patients in the intervention group. This includes patients that unexpectedly remain intubated after surgery • Starting CPAP at a dose other than 5cmH2O • Administration of CPAP to a patient in usual care group. • Administration of CPAP for less than 4 hours or 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.
	Amended to:	• 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 four hours after the end of surgery • Starting CPAP at a dose other than 5cmH2O • 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 or 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 prolonged.
	Section:	**7.9 Follow-up procedures**
	Formerly read:	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. To facilitate the health economic analysis, in terms of hospital episode data, and in cases where the participant is un-contactable during the follow-up period, we will request hospital episode statistics and mortality data from the HSCIC for UK participants or equivalent national database for other participating countries. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.
	Amended to:	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 the HSCIC for UK participants. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.

	Section:	**7.11 Self-assessment of blinding by research staff**
	Formerly read:	Research staff will complete a self-assessment to allow us to report the effectiveness of blinding procedures during the trial. They will grade themselves as one of the following options: • Suitably blinded • May have known study group allocation • Definitely knew study group allocation
	Amended to:	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
	Section:	**7.13 Schedule of assessment**
	Formerly read:	EQ5D questionnaire
	Amended to:	EQ5D questionnaire (UK only)
	Section:	**8.2 Statistical analysis**
	Formerly read:	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. The primary outcome (pneumonia, endotracheal reintubation, or death within 30 days of randomisation) will be analysed using a mixed-effect logistic regression model……..
	Amended to:	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…….
	Section:	**8.3 Health economic analysis**
	Formerly read:	The health economics 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……
	Amended to:	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……..
	Section:	**9. RESEARCH ETHICS**
	Formerly read:	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. 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.
	Amended to:	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.
	Section:	**12. SAFETY REPORTING**
	Formerly read:	**12.1 Adverse Events (AE)** An AE is any untoward medical occurrence in a subject who has received CPAP initiated as part of the PRISM trial. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the trial intervention. Adverse events must be related to CPAP; the Principle Investigator (or nominated deputy) is responsible for confirming this. **12.2 Notification and reporting Adverse Events or reactions** We will record all AEs in the CRF (supplementary form) and in the patient notes (where appropriate). SAEs will be reported to the national co-ordinating centre within 72 hours. **12.3 Serious Adverse Event (SAE)** A serious adverse event (SAE) is defined as an untoward occurrence that: (a) results in death; (b) is life-threatening; (c) requires hospitalisation or prolongation of existing hospitalisation; (d) results in persistent or significant disability or incapacity; An SAE occurring to a research participant should be reported to the sponsor where in the opinion of the Chief Investigator the event was: • Related – that is, it probably or definitely arose as a result of the trial intervention, and

		• Unexpected – that is, the type of event is not listed in the protocol as an expected occurrence. The PRISM trial is an investigation of a perioperative intervention. It is expected that patients undergoing major abdominal surgery will suffer medical complications, up to and including death. Only complications *related* to the use of CPAP in the intervention group should be reported as SAEs. Some complications of CPAP are expected. The following expected occurrences should be reported as AEs but not SAEs: • Interface intolerance due to excessive air leaks • Pain • Cutaneous pressure sore or pressure area • Claustrophobia • Oro-nasal dryness • Hypercapnia • Haemodynamic instability • Vomiting **12.4 Notification and reporting of Serious Adverse Events** Serious Adverse Event (SAEs) that are considered to be 'related' and 'unexpected' are to be reported to the sponsor and the sponsor's representative for that country within 72 hours of learning of the event. **12.5 Reporting an Adverse Event or Serious Adverse Event** Individual sites will notify the co-ordinating centre in that country of an SAE by emailing a scanned copy of the supplementary AE report form to the national co-ordinator. AEs will be reported by the eCRF. SAEs will be reported within 72 hours and will be forwarded to the sponsor via the UK co-ordinating centre. **12.5 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. **12.6 Annual safety reporting** The CI will send the annual progress report to the REC and to the sponsor. **12.7 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.
	Amended to:	**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.
	Section:	**13.1 Training of investigators**
	Formerly read:	**13.1 Monitoring the safety and well-being of trial participants**
	Amended to:	**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**
	Section:	**13.3 Monitoring the safety of investigators.**
	Formerly read:	**13.2 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 and consent training prior to start up
	Amended to:	**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.
	Section:	**14.2 Trial steering committee**
	Formerly read:	The Trial Steering Committee will oversee the trial and will consist of: • several independent clinicians and trialists • lay representation • co-investigators • an independent Chair
	Amended to:	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
	Section:	**14.3 Data monitoring and ethics committee**

	Formerly read:	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. During the period of recruitment into the trial the DMEC will perform a single interim analysis as it sees fit. The trial will be terminated early if there is evidence of harm in the intervention group or if recruitment is futile. The DMEC functions primarily as a check for safety by reviewing adverse events.
	Amended to:	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.
	Section:	**15. FINANCE AND FUNDING**
	Formerly read:	This is an investigator led trial. This trial is supported by a project grant from the Association of Anaesthetists of Great Britain and Ireland and the National Institute for Academic Anaaesthesia (UK). Additional funding will be sought from the National Institute for Health Research (UK) and from industry.
	Amended to:	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.
	Section:	**DEFINITIONS APPENDIX**
	Formerly read:	**Other definitions** **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 de-bulking in metastatic disease, partial removal of a tumour or for the purpose of pain or other symptom control. **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. **High flow nasal oxygen** Humidified oxygen therapy delivered via large-bore nasal prongs at flow rates greater than 50 litres per minute. **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 one or more breaths.
	Amended to:	**Aspiration of gastric contents** Inhalation of regurgitated gastric contents directly related to CPAP. **(added to pg 42)** **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 de-bulking 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 (Vt) 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.
13/04/17	Version 1.6 10/04/17	**Section:**	**Title Page (pg 1) and Chief Investigator Agreement (pg 4)**
		Formerly read:	PRISM protocol version 1.5 01 March 2016
		Amended to:	PRISM protocol version 1.6 10 April 2017
		Section:	**6.3 Exclusion criteria (pg 9 and 10)**
		Formerly read:	• Participation in a clinical trial of a treatment with a similar biological mechanism or related primary outcome measure • Clinician refusal
		Amended to:	• 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)
		Section:	**6.4 Study flow diagram (pg 10)**
		Formerly read:	"Randomisation" followed by "surgery as planned"
		Amended to:	"Surgery as planned" followed by "randomisation"
		Section:	**7.1 Recruitment and screening (pg 11)**
		Formerly read:	This is an international randomised controlled trial in several European countries.
		Amended to:	This is an international randomised controlled trial ~~in several European countries.~~
		Section:	**7.3 Randomisation (pg 11)**
		Formerly read:	Randomisation will occur after the participant has provided informed consent and up to four hours after the end of surgery.
		Amended to:	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).
		Section:	**7.4 Trial intervention (pg 12)**
		Formerly read:	The trial intervention will commence immediately after the completion of surgery and continue for at least four hours.
		Amended to:	The trial intervention period will ideally commence immediately after surgery.
		Section:	**7.4 Trial intervention (pg 12)**

	Formerly read:	**Intervention group** The trial intervention is defined as CPAP for at least four hours, with minimal interruption, started immediately after (within four 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. Clinicians may only use commercially available CPAP equipment to deliver the intervention.
	Amended to:	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.
	Section:	**7.7 Data collection**
	Formerly read:	Baseline data • Full name • Gender • Age/DOB • ASA grade • Planned surgical procedure • Diagnosis of chronic lung disease (COPD, Asthma, Interstitial lung disease) • Respiratory infection within the previous month • Diagnosis of ischaemic heart disease • Diagnosis of diabetes • Diagnosis of stroke • Diagnosis of heart failure • Diagnosis of cirrhosis • Diagnosis of active cancer • Preoperative haemoglobin 24 hours postoperative • Patient received CPAP within four hours of surgery? (Y/N)
	Amended to:	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 24 hours postoperative • Patient received CPAP within twelve hours after the end of surgery? (Y/N)
	Section:	**7.8 Predefined protocol deviations**
	Formerly read:	• 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 four hours after the end of surgery • Starting CPAP at a dose other than 5cmH_2O • 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 or 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 prolonged.
	Amended to:	• 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 cmH_2O. • 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.
	Section:	**7.9 Follow-up procedures**
	Formerly read:	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 the HSCIC for UK participants. Prospective consent for ONS/HES data linkage will be sought before enrolment into the trial.
	Amended to:	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.

	Section:	**8.4 Secondary studies**
	Formerly read:	The use of PRISM trial data for further secondary studies is encouraged.
	Amended to:	The use of PRISM trial data for further secondary studies is encouraged. Secondary studies of UK data are detailed in the appendix.
	Section:	**10.3 Archiving**
	Formerly read:	All 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.
	Amended to:	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.
	Section:	**11.1 CPAP delivery**
	Formerly read:	CPAP machines are routinely used in secondary care. Investigators may only use commercially available CPAP equipment in this trial.
	Amended to:	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.
	Section:	**Appendix: National registry linkage (UK only)**
	Formerly read:	
	Amended to:	**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.

Summary of amendments to statistical analysis plan

- The first version of the statistical analysis plan was version 1.2 and the final version was 2.0.
- The previous version of the SAP inadvertently omitted the category 'resection of oesophagus (non-obesity surgery)' as one of the categories of the minimisation variable surgical procedure category. This has been corrected in the randomisation and analysis sections.
- The previous SAP included the outcome 'Mechanical ventilation (invasive or non-invasive) within 30 days of randomisation' – this has been changed to 'Postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation', to clarify that this outcome refers to mechanical ventilation during the postoperative period
- Section 5.1 was updated to clarify that patients who were enrolled in PRISM for a repeat surgery despite previous enrolment would be included in the analysis
- In section 5.2.5 we have separated the category 'Administration of CPAP for less than 4 hours or with significant interruption for a patient in the treatment group (continuous interruption of more than 15 minutes would usually be considered prolonged).' into two separate categories: (i) Administration of CPAP for less than 4 hours duration in the treatment group; and (ii) Administration of CPAP with significant interruption for a patient in the treatment group (continuous interruption of more than 15 minutes would usually be considered prolonged).
- We updated section 5.3 (describing the analysis of the primary outcome) to state that any categories with fewer than 15 patients for the variable planned surgical procedure will be combined with the category 'other intra-peritoneal surgery' for analysis
- We updated section 5.3 (describing the analysis of the primary outcome) to state that missing baseline covariates will be handled using mean imputation or the missing indicator approach for analysis
- We added a per-protocol analysis using inverse-probability weighting for the primary outcome and following secondary outcomes: (a) pneumonia within 30 days of randomisation; (b) endotracheal re-intubation within 30 days of randomisation; (c) all-cause mortality within 30 days of randomisation. Full information is given in section 5.11.
- We added a new appendix (appendix 1) which details how at least 'one' comorbid disease, primary and secondary outcomes will be derived.
- We added a section on summarising CPAP information for the CPAP group (section 5.2.4)
- We added a plan in case of over-stratification when adjusting for covariates in the primary and secondary analysis models (section 5.9)

Protocol version 1.5

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*

The contact person for the above sponsor organisation is:

Dr Sally Burtles
Director of Research Services & Business Development
Joint Research Management Office
5 Walden Street
London
E1 2EF
Phone: 0207 882 7260
Email: sponsorsrep@bartshealth.nhs.uk

REC Reference	15/LO/1595
Chief Investigator	*Professor Rupert Pearse*
UK co-ordinating centre	*Research Office* *Adult Critical Care Unit* *4th Floor* *The Royal London Hospital* *London* *E1 1BB* *Phone: 0203 594 0352* *Email: admin@prismtrial.org.uk*

Contents

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.

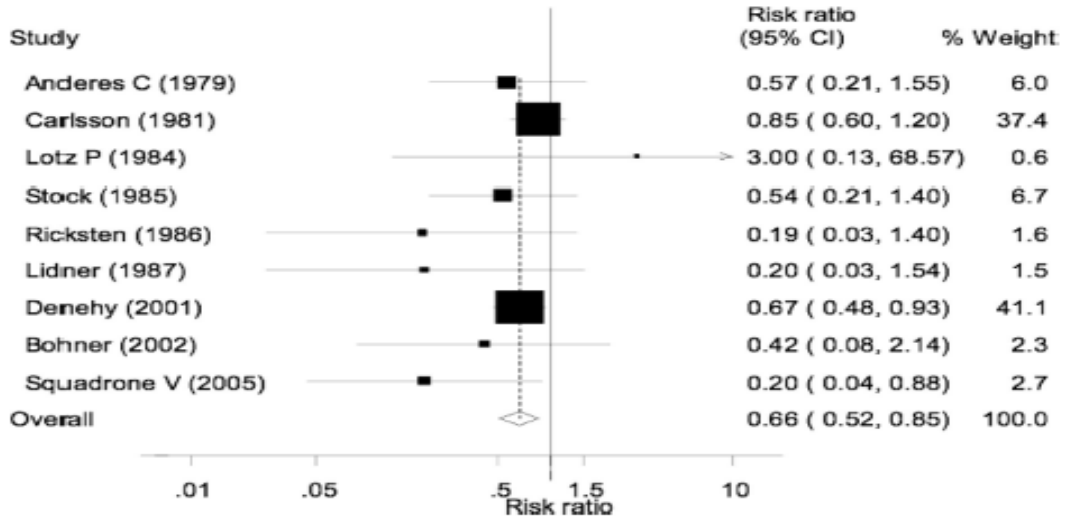


Figure 1. Efficacy of CPAP on a composite endpoint of postoperative pulmonary complications compared to standard treatment.[12]

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

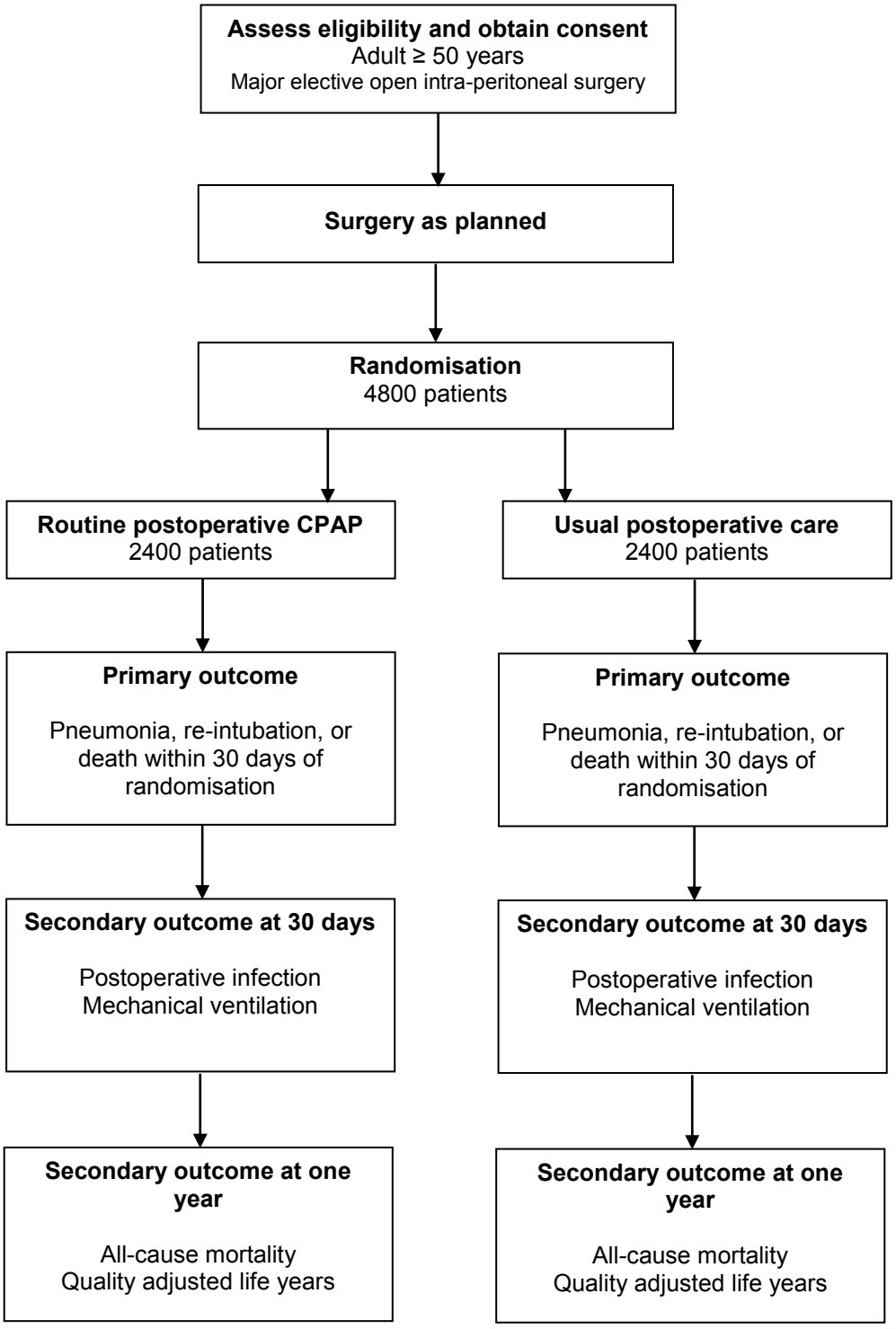
Patients aged 50 years or over undergoing elective major intra-peritoneal surgery using an open surgical technique.

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 cmH_2O and the maximal permissible airway pressure is 10 cmH_2O. 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 cmH_2O 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.

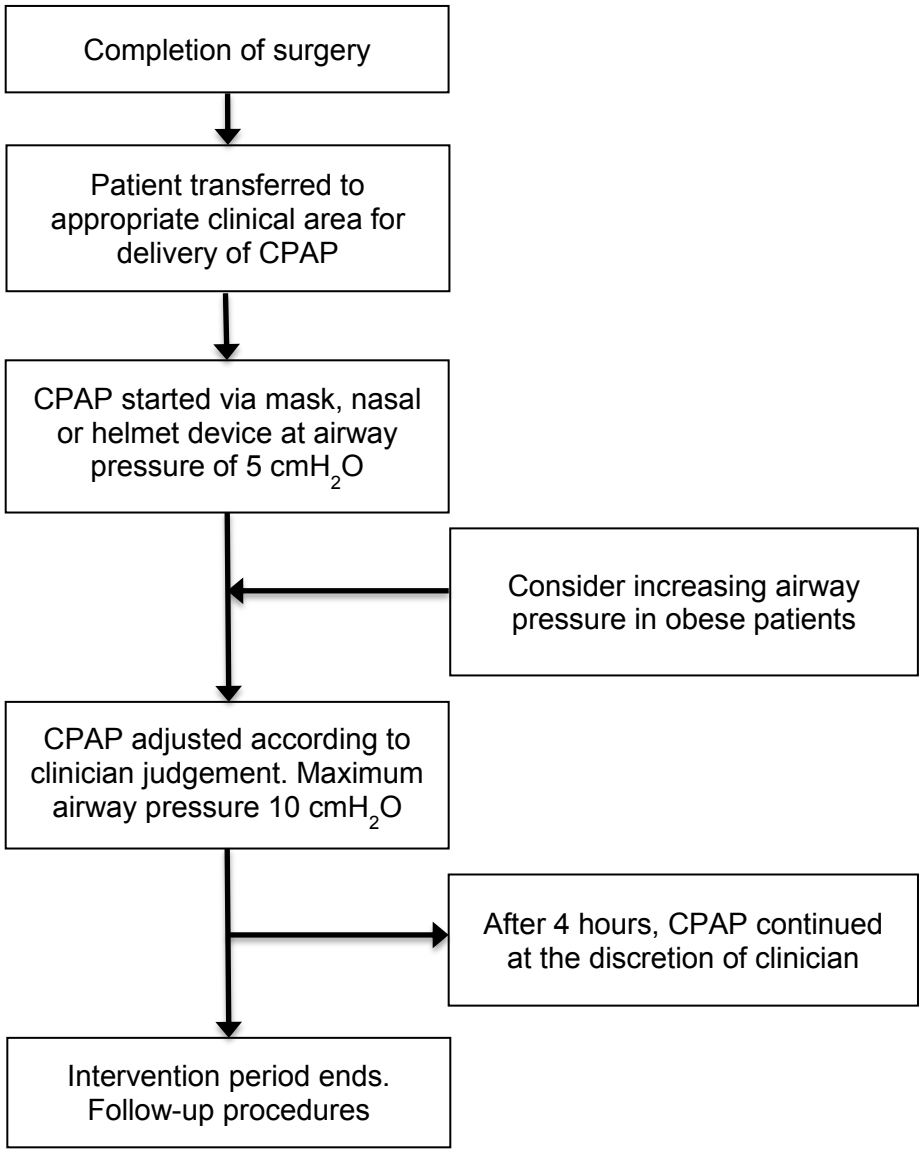
Nasal high flow oxygen is not considered CPAP. It is foreseeable that some patients in the intervention group will not receive CPAP or fail to complete the minimum four hours of CPAP, e.g. due to unplanned invasive or non-invasive ventilation after surgery or because the patient is unable to tolerate 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 FiO_2 (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 $PaCO_2$)
  - 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 cmH_2O.
- 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.

18. REFERENCES

1. Weiser TG, Haynes AB, Molina G, et al. Estimate of the global volume of surgery in 2012: an assessment supporting improved health outcomes. *Lancet* 2015; **385 Suppl 2**: S11.

2. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet* 2008; **372**(9633): 139-44.

3. Pearse RM, Moreno RP, Bauer P, et al. Mortality after surgery in Europe: a 7 day cohort study. *Lancet* 2012; **380**(9847): 1059-65.

4. Pearse RM, Harrison DA, James P, et al. Identification and characterisation of the high-risk surgical population in the United Kingdom. *Critical care* 2006; **10**(3): R81.

5. Head J, Ferrie JE, Alexanderson K, et al. Diagnosis-specific sickness absence as a predictor of mortality: the Whitehall II prospective cohort study. *Bmj* 2008; **337**: a1469.

6. Khuri SF, Henderson WG, DePalma RG, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Annals of surgery* 2005; **242**(3): 326-41; discussion 41-3.

7. Warner DO. Preventing postoperative pulmonary complications: the role of the anesthesiologist. *Anesthesiology* 2000; **92**(5): 1467-72.

8. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Annals of surgery* 2000; **232**(2): 242-53.

9. Ireland CJ, Chapman TM, Mathew SF, Herbison GP, Zacharias M. Continuous positive airway pressure (CPAP) during the postoperative period for prevention of postoperative morbidity and mortality following major abdominal surgery. *The Cochrane database of systematic reviews* 2014; **8**: CD008930.

10. Nunn JF, Payne JP. Hypoxaemia after general anaesthesia. *Lancet* 1962; **2**(7257): 631-2.

11. Cereda M, Neligan PJ, Reed AJ. Noninvasive respiratory support in the perioperative period. *Current opinion in anaesthesiology* 2013; **26**(2): 134-40.

12. Ferreyra GP, Baussano I, Squadrone V, et al. Continuous positive airway pressure for treatment of respiratory complications after abdominal surgery: a systematic review and meta-analysis. *Annals of surgery* 2008; **247**(4): 617-26.

13. Charlesworth M, Lawton T, Fletcher S. Noninvasive positive pressure ventilation for acute respiratory failure following oesophagectomy: Is it safe? A systematic review of the literature. *Journal of the Intensive Care Society* 2015; **16(3)**: 215-21.

14. Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010; **113**(6): 1338-50.

15. Group IS. International Surgical Outcomes Study (ISOS). QMUL; 2014.

16. Waterlow JA. Reliability of the Waterlow score. *Journal of wound care* 1995; **4**(10): 474-5.

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°C) with no other recognised cause
b) leucopaenia (< 4 x 10^9/L) or leucocytosis (>12 x 10^9/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 in 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 ≥354 µmol/L (≥4.0 mg/dL) with an acute rise of > 44 µmol/L (0.5mg/dL)

c) or oliguria of < 0.5 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: PaO_2:FiO_2 26.7-40.0 kPa with PEEP or CPAP ≥ 5cmH_2O
   - Moderate: PaO_2:FiO_2 13.3-26.6 kPa with PEEP ≥ 5cmH_2O
   - Severe: PaO_2:FiO_2 ≤ 13.3 kPa with PEEP ≥ 5cmH_2O

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 or 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°C or >38°C

b) white cell count >12 x 10^9/L or <4 x 10^9/L

c) respiratory rate >20 breaths per minute or $PaCO_2$ < 4.5 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 ≥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°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^{o}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°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 grading[16]:

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 $PaCO_2$ 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 de-bulking 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 (SpO_2)

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 (Vt) 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

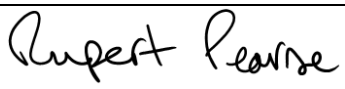
Cost effectiveness is a key determinant of successful implementation of a new intervention. This sub-study aims to assess whether routine postoperative CPAP is likely to be cost-effective on average. The intervention may have effects that impact on quality and duration of life beyond the trial follow-up 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.

Statistical analysis plan version 2.0

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

Statistical Analysis Plan Version 2.0
August 2019

Person(s) contributing to the analysis plan	
Name(s) and position(s)	Akshaykumar Patel (Statistician) Tahania Ahmad (Statistician) Brennan Kahan (Statistician) Tom Abbott (Investigator) Claudia Filippini (Senior statistician) Rupert Pearse (Co-chief Investigator) Marco Ranieri (Co-chief Investigator)
Authorisation	
Position	**Chief investigators**
Name	Professor Rupert Pearse & Professor Marco Ranieri
Signature	
Date	15th August 2019
Position	**Senior trial statistician**
Name	Brennan Kahan
Signature	
Date	15th August 2019

Contents

1. Administrative information

Trial registration number: ISRCTN registry – ISRCTN56012545

This SAP is based on protocol version 1.6 (date: 10/04/2017)

Changes from previous version of SAP

- The previous version of the SAP inadvertently omitted the category '*resection of oesophagus (non-obesity surgery)*' as one of the categories of the minimisation variable *surgical procedure category*. This has been corrected in the randomisation and analysis sections.
- The previous SAP included the outcome 'Mechanical ventilation (invasive or non-invasive) within 30 days of randomisation' – this has been changed to 'Postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation', to clarify that this outcome refers to mechanical ventilation during the postoperative period
- Section 5.1 was updated to clarify that patients who were enrolled in PRISM for a repeat surgery despite previous enrolment would be included in the analysis
- In section 5.2.5 we have separated the category '*Administration of CPAP for less than 4 hours or with significant interruption for a patient in the treatment group (continuous interruption of more than 15 minutes would usually be considered prolonged).*' into two separate categories: (i) *Administration of CPAP for less than 4 hours duration in the treatment group*; and (ii) *Administration of CPAP with significant interruption for a patient in the treatment group (continuous interruption of more than 15 minutes would usually be considered prolonged)*.
- We updated section 5.3 (describing the analysis of the primary outcome) to state that any categories with fewer than 15 patients for the variable *planned surgical procedure* will be combined with the category '*other intra-peritoneal surgery*' for analysis
- We updated section 5.3 (describing the analysis of the primary outcome) to state that missing baseline covariates will be handled using mean imputation or the missing indicator approach for analysis
- We added a per-protocol analysis using inverse-probability weighting for the primary outcome and following secondary outcomes: (a) pneumonia within 30 days of randomisation; (b) endotracheal re-intubation within 30 days of randomisation; (c) all-cause mortality within 30 days of randomisation. Full information is given in section 5.11.
- We added a new appendix (appendix 1) which details how at least 'one' comorbid disease, primary and secondary outcomes will be derived.
- We added a section on summarising CPAP information for the CPAP group (section 5.2.4)
- We added a plan in case of over-stratification when adjusting for covariates in the primary and secondary analysis models (section 5.9)

2. Introduction

2.1 Background

Prevention of Respiratory Insufficiency after Surgical Management (PRISM) is an international, multi-centre, parallel group, randomised controlled trial which aims to evaluate the clinical effectiveness of early post-operative continuous positive airway pressure (CPAP) administered as routine care compared to usual care in patients undergoing major abdominal surgery. The planned sample size is 4800 patients.

2.2 Purpose of statistical analysis plan

This document outlines the statistical analysis planned for the trial. It is important to set these out and to agree them in advance of inspecting the outcome data for the trial, so that data-derived decisions in the analysis are avoided. Any exploratory, post hoc or unplanned analysis will be clearly identified as such in the respective study analysis report. This SAP does not cover the cost and cost-effectiveness analysis, or the quality adjusted life years (QALY) at one-year after randomisation; these analyses will be planned in separate documents.

2.3 Inclusion/Exclusion criteria

Inclusion Criteria

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

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
- Participation in a clinical trial of a treatment with a similar biological mechanism or related primary outcome measure

3. Outcome Measures

3.1 Primary outcome

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

3.2 Secondary outcome

- Pneumonia within 30 days of randomisation
- Endotracheal re-intubation within 30 days of randomisation
- All-cause mortality within 30 days of randomisation
- Postoperative infection within 30 days of randomisation
- Postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation
- All-cause mortality within one year of randomisation

3.3 Process measures

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

- Re-admission to hospital within 30 days of randomisation
- Days in critical care (defined as either level 2 or level 3 critical care)
- Duration of hospital stay (days)

3.4 Safety outcome measures

Safety outcomes will quantify harm associated with CPAP (appendix). Presence or absence of the following pre-defined adverse events will be measured within 24 hours of the end of surgery in patients in the treatment 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

4. Study Methods

4.1 Trial design

PRISM is an international, multi-centre, parallel group, randomised controlled trial with open study group allocation.

4.2 Randomisation

Randomisation will occur after the participant has provided informed consent and up to four hours after the end of surgery. 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 as follows: (a) resection of colon, rectum or small bowel; (b) resection of liver, pancreas or gall bladder; (c) resection of stomach (non-obesity surgery); (d) resection of oesophagus (non-obesity surgery); (e) obesity surgery; (f) vascular procedure; or (g) other intra-peritoneal surgery. 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.

4.3 Sample size

The primary outcome is a composite endpoint of pneumonia, re-intubation, or death within 30 days of 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 treatment 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 [1]. In order to detect a reduction from 11.7% to 8.8% in the primary outcome measure (relative risk reduction of 25%), with 90% power, a 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 80% power and a type I error rate of 5%. The sample size was

calculated, using the '*power two proportions*' function in STATA 14.0 (StataCorp, College Station, USA).

5. Analysis Principles

5.1 General analysis principles

Analyses will follow the intention-to-treat principle: all randomised patients with a recorded outcome will be included in the analysis, and analysed to the treatment to which they were randomised [2, 3]. Patients will be included in the analysis, regardless of whether the treatment they received was compliant with the protocol. Patients with missing outcome data will be excluded from the analysis. Definitions of what constitutes a recorded outcome for each outcome can be found In Appendix 1. Patients who are re-randomised (i.e. enrolled in PRISM for a repeat surgery despite previous enrolment in PRISM) will be included in the analysis for both randomisations, and treated as independent observations [4, 5].

The magnitude of treatment effect estimate will be reported with 95% confidence interval for primary and secondary outcomes. All p-values will be two-sided, and a significance level of 5% will be used. For each outcome, summary statistics (e.g. mean (SD), number (%)) will be presented separately for each treatment arm.

5.2 Initial descriptive analysis

5.2.1 Representativeness of patients

All participating sites have been asked to keep a log of eligible patients not recruited to the trial. Reasons for non-participation will be categorised and summarised. Participation in the trial, treatment allocation and completeness of follow-up will be illustrated by a CONSORT flow diagram.[6]

5.2.2 Comparability of groups

Baseline demographic and clinical data for patients randomised to CPAP (treatment group) and usual care (usual care group) will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The treatment and usual care groups will be compared at entry for the following baseline characteristics:

- Demographic: age (years), gender (male/female)
- Co-morbid disease: (a) COPD; (b) asthma; (c) interstitial lung disease or pulmonary fibrosis; (d) bronchiectasis; (e) ischaemic heart disease; (f) diabetes mellitus; (g) heart failure; (h) liver

cirrhosis; (i) active cancer; (j) previous stoke or TIA; (k) respiratory infections within the previous month; (l) HIV

- Current smoker
- ASA grade: I; II; III; IV
- Body mass index (kg/m^2)
- Minimisation criteria:
    - Planned surgical procedure: (a) resection of colon, rectum or small bowel; (b) resection of liver, pancreas or gall bladder; (c) resection of stomach (non-obesity surgery); (d) resection of oesophagus (non-obesity surgery); (e) obesity surgery; (f) vascular surgery; (g) other intra-peritoneal surgery
    - Country: (a) Italy; (b) Spain; (c) Sweden; (d) United Kingdom; (e) South Africa; (f) Norway
    - Planned use of epidural
- Surgical procedure performed: (a) Resection of colon, rectum or small bowel; (b) resection of liver, pancreas or gall bladder; (c) resection of stomach (non-obesity surgery); (d) resection of oesophagus (non-obesity surgery); (e) obesity surgery; (f) vascular procedure; (g) other intra-peritoneal surgery
- Pre-operative blood tests results: (a) haemoglobin (g/dL); (b) creatinine (µmol/L)
- ARISCAT score: ARISCAT is a risk index based on seven patient factors that evaluates risk for postoperative pulmonary complications in a patient [7, 8]. The seven factors are used to calculate this score are: age, oxygen saturation measured by pulse oximetry (SpO_2, %), pre-operative haemoglobin concentration, respiratory infection in the last month (yes/no), surgical incision category (peripheral/abdominal/thoracic), duration of surgery (hours) and emergency procedure (yes/no). ARISCAT score will be calculated for both groups and presented in the baseline data table. The component variables will be tabulated separately for reference. The ARISCAT Score and its individual components will only be summarised for patients who have all components of the score complete.

5.2.3 Clinical management

Clinical management for the treatment group and usual care group will be summarised but not subjected to statistical testing. Numbers (%) and means (SD) or medians (IQR) will be provided separately for each group. The treatment and usual care groups will be compared for the following clinical management characteristics:

- Surgery: open surgical technique; anaesthetic technique; mechanical ventilation during surgery

- Intravenous fluids during surgery: total intravenous fluid administered excluding blood products; total volume of blood products administered
- Planned and actual level of care on the first night after surgery
- Respiratory support after surgery within four hours of the end of surgery

5.2.4 CPAP after surgery

CPAP information for the CPAP group will be summarised. For each, summary statistics (e.g. mean (SD), median (IQR), number (%)) will be presented. The following CPAP characteristics will be reported:

- Duration of CPAP within 12 hours of the end of the surgery (minutes)
- Maximum airway pressure received within 12 hours after the end of surgery (cmH_2O)
- Primary method of CPAP delivery: face mask, helmet device, nasal mask

5.2.5 Protocol compliance

Numbers and percentages of protocol deviations will be reported. The following protocol deviations will be reported:

- Failure to administer CPAP to a patient in the treatment group
- Starting CPAP at a dose other than $5cmH_2O$ for a patient in the treatment group
- Administration of CPAP for less than 4 hours duration in the treatment group
- Administration of CPAP with significant interruption for a patient in the treatment group (continuous interruption of more than 15 minutes would usually be considered prolonged).
- Administration of CPAP to a patient in usual care group

We will report the number of patients in each treatment group with at least one of the above protocol deviations. In addition, a separate table as described above will be reported by the method which CPAP was delivered.

5.3 Primary outcome

The primary outcome will be analysed using a mixed-effect logistic regression model, with a random intercept for centre [9]. The model will be adjusted for the minimisation variables as fixed factors [10], which are country, planned use of epidural anaesthesia, and planned surgical category as follows: (a) resection of colon, rectum or small bowel; (b) resection of liver, pancreas or gall bladder; (c) resection of stomach (non-obesity surgery); (d) resection of oesophagus (non-obesity surgery); (e) Obesity surgery; or (f) vascular procedure; (g) Other intra-peritoneal surgery. For the

minimisation variable planned surgical procedure, any category from (a)-(f) with fewer than 15 patients will be combined with other intra-peritoneal surgery. The model will also be adjusted for the following pre-specified baseline covariates [11-13]: age, gender (M/F), at least one 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 (current smoker) and ASA score (I & II vs. III & IV). All covariates will be included in the model as fixed factors. Age will be included as a continuous variable, assuming a linear association with the outcome [14]. Categorical covariates with more than two categories (country, planned surgical category, ASA score) will be included using indicator variables. The magnitude of the treatment effect will be reported as an adjusted odds ratio with a 95% confidence interval. Missing data for baseline covariates will be handled using mean imputation for age, and a missing indicator will be added for missing data for categorical variables (gender, co-morbid disease, smoking status, and ASA score) [15].

5.4 Secondary outcomes

Secondary outcomes will be analysed using the same approach as the primary outcome (i.e. a mixed-effect logistic regression model, with a random intercept for centre), except they will adjust only for the minimisation variables apart from country (i.e. the model will be adjusted only for planned use of epidural anaesthesia and planned surgical category). This is to avoid over-stratification, as the expected event rate for these outcomes is low. This analysis strategy will be used for the following secondary outcomes:

1. Pneumonia within 30 days of randomisation
2. Endotracheal re-intubation within 30 days of randomisation
3. All-cause mortality within 30 days of randomisation
4. Post-operative infection within 30 days of randomisation.
5. Postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation.
6. All-cause mortality at one year after randomisation

5.5 Process measures

Summary measures will be presented separately for each treatment group. All patients with recorded data will be included in the summary. Formal statistical analysis will not be performed. Re-admission to hospital within 30 days of randomisation will be summarised by number (%). Days in

critical care will be summarised for the subset of patients admitted to a critical care unit using mean (SD) and median (IQR). Duration of hospital stay will be summarised using mean (SD) and median (IQR).

5.6 Safety outcome measures

Each safety outcome measured will be summarised for patients in the CPAP group by the number (%). All patients with a recorded outcome will be included in the summary. In addition to this, 'other' adverse events will be reported separately if prevalence is more than 1% across all participants in the trial.

5.7 Graphs and other data summaries

- The flow of study participants will be displayed in Consolidated Standards of Reporting Trials (CONSORT) diagram.
- 30-day and one-year survival of patients will be presented for both groups using Kaplan-Meier survival curves.
- Investigator self-assessment of blinding by treatment allocation will be presented as number (%).
- Duration of level 2 and 3 critical care stay within 30 days of randomisation for patients admitted to a critical care unit will be presented as mean (SD) and median (IQR).
- Data describing a predefined list of the most common post-operative complications occurring within 30 days of randomisation will be collected for all patients.

  The number and percentage of patients experiencing each of the following complications will be presented by (a) treatment allocation; (b) treatment allocation and Clavien-Dindo (CD) grade (I-II vs III-V); and (c) treatment allocation and CPAP delivery method for those in the CPAP group only. These summaries will not be subjected to any statistical testing. These complications are:

  Respiratory complications:

  - Pneumonia
  - Pleural effusion
  - Pneumothorax
  - Bronchospasm
  - Aspiration pneumonitis
  - Acute Respiratory Distress Syndrome (ARDS)

Infective complications:

- Surgical site infection (superficial)
- Surgical site infection (deep)
- Surgical site infection (organ space)
- Urinary tract infection
- Infection, source uncertain
- Laboratory confirmed blood stream infection

Cardiac complications:

- Myocardial infraction
- Arrhythmia
- Cardiogenic pulmonary oedema
- Cardiac arrest with successful resuscitation

Other complications:

- Acute kidney injury
- Pulmonary embolism
- Stroke
- Acute psychosis or delirium
- Bowel infarction
- Anastomotic leak
- Perforation of viscus (e.g. bowel, gall bladder etc.)
- Postoperative haemorrhage
- Other postoperative haemorrhage
- Any other complication

5.8 Plan in case of non-convergence of analysis models

If the statistical models for any of the primary or secondary outcomes do not converge, then the following steps will be taken:

1. The model will be fitted without a random intercept for centre
2. As above, but excluding any additional covariates apart from minimisation variables
3. As above, but also excluding minimisation variables.

5.9 Plan in case of over-stratification

When adjusting for covariates in the primary or secondary analysis models, if there is a category within that covariate where no events have occurred in either of the treatment arms, the statistical model will exclude all patients within this category. To overcome this, this category will be merged with another category; this will be decided by the chief investigator who will be blinded to results. This will apply to the following covariates with three or more categories: (a) Country; (b) Planned surgical procedure. However, if all but one category within that covariate have no events recorded in one of the treatment arms then we will exclude this covariate from the model.

Covariates with only two categories will be excluded from the model if there is a category within that covariate where no events occurred in one of the treatment arms. Covariates with only two categories are: (a) planned use of epidural; (b) Gender (M/F); (c) at least one co-morbid disease (chronic respiratory disease, ischaemic heart disease, diabetes mellitus, heart failure, liver cirrhosis, active cancer, and previous stroke or transient ischaemic attack); (d) smoking status (current smoker); (e) ASA score (I & II vs. III & IV).

5.10 Subgroup analyses

A sub-group analysis will be performed for the primary outcome (composite of pneumonia, endotracheal re-intubation or death within 30 days of randomisation). The subgroup of interest will be planned surgical procedure category. This will comprise the following four groups:

- Lower gastrointestinal (resection of colon, rectum, or small bowel)
- Hepatobiliary (resection of liver, pancreas, or gall bladder)
- Upper gastrointestinal (resection of oesophagus, or resection of stomach (non-obesity surgery))
- Other (obesity surgery, vascular procedure, or other intra-peritoneal surgery)

The sub-group analysis will be performed using the same analysis model as for the primary outcome, except planned surgical procedure will be defined as above, instead of as in the minimisation procedure, and the model will include an interaction term between planned surgical procedure category and treatment arm.

The presence of an interaction will be tested using a Wald test assessing the interaction terms. The test will be considered significant at the 5% level. All patients with complete outcome data will be

included in the subgroup analysis. Within each surgical procedure category, we will report summary statistics of the outcome by treatment arm, and a treatment effects and 95% confidence intervals. A p-value for the interaction test will also be reported.

5.11 Per-protocol analysis

A per-protocol analysis using inverse probability-weighting (IPW) [16] will be performed for the primary outcome and the following secondary outcomes: (a) pneumonia within 30 days of randomisation; (b) endotracheal re-intubation within 30 days of randomisation; (c) all-cause mortality within 30 days of randomisation. Participants who are non-adherent will be excluded from the analysis; non-adherence is defined as (a) a participant in the intervention group who does not receive any CPAP; or (b) a participant in the usual care group who does receive CPAP. As post-randomisation exclusions can cause bias, we will use weighting to account for baseline risk factors that we expect to be joint determinants of adherence and the outcome. We will use the following baseline covariates to calculate weights: age, current smoker, ASA grade, COPD, interstitial lung disease, bronchiectasis, heart failure, liver cirrhosis, active cancer, previous stroke, respiratory infection within the previous month, planned surgical procedure, planned use of epidural, and BMI. Missing data for these baseline covariates will be handled using mean imputation for continuous variables and the missing indicator approach for categorical variables. The probability of non-adherence will be estimated from on a logistic regression model with non-adherence as the outcome, and the covariates mentioned above as fixed terms. Age and BMI will be included as linear terms. The weight is calculated as $\frac{1}{1-P(non-adherence)}$; weights will be calculated separately in each treatment group. We will then use the same analysis model as for the main analysis, except we will include the Stata options [pw=weight], and vce(robust).

6. Sensitivity Analysis

We anticipate a very small amount of missing data for the primary outcome. If the level of missing data for the primary outcome exceeds 1% of randomised participants, we will perform a sensitivity analysis to assess the robustness of our analysis of the primary outcome data under the assumption that data is missing-not-at-random (MNAR) [2, 17-19]. For example, this could occur if patients who were discharged home and had no postoperative pneumonia were less likely to respond to their telephone follow-up after 30 days, than patients who did have a postoperative pneumonia.

We will perform a sensitivity analysis assuming the data is MNAR based on the following formula:

$P(Y = 1|X = x) = P(Y = 1|X = x, obs)P(obs|X = x) + P(Y = 1|X, unobs)P(unobs|X = x)$

Where Y denotes the primary outcome (1=yes, 0=no) and X denotes the treatment allocation (1=treatment, 0=usual care), *obs* denotes that the patient's outcome was available, and *unobs* denotes that the patient's outcome was missing.

In this sensitivity analysis, the odds ratio for the treatment effect will be calculated by:

$$\frac{P(Y=1|X=1)/(1-P(Y=1|X=1))}{P(Y=1|X=0)/(1-P(Y=1|X=0))}.$$

$P(Y = 1|X = x, obs)$ will be estimated from the model used in the primary analysis using STATA's 'margins' command. $P(obs|X = x)$ and $P(unobs|X = x)$ will be estimated based on the number of patients with complete and incomplete outcome data in each treatment arm. The probability of an event amongst those with unobserved outcomes in the usual care group, $P(Y = 1|X = usual\ care, unobs)$, will be set at 0.05, 0.10 and 0.15. The probability of an event amongst those with unobserved outcomes in the treatment group, $P(Y = 1|X = treatment, unobs)$, will be set at $P(Y = 1|X = usual\ care, unobs) + \delta$. We will use the following values of δ: -0.02, -0.01, 0, +0.01, +0.02.

Confidence intervals will be calculated on the log scale using the standard errors for the log odds ratio from the complete case analysis then transformed to the odds ratio scale.

References

1. International Surgical Outcomes Study, g., *Global patient outcomes after elective surgery: prospective cohort study in 27 low-, middle- and high-income countries.* Br J Anaesth, 2016. **117**(5): p. 601-609.
2. White, I.R., et al., *Strategy for intention to treat analysis in randomised trials with missing outcome data.* BMJ, 2011. **342**: p. d40.
3. Montori, V.M. and G.H. Guyatt, *Intention-to-treat principle.* CMAJ, 2001. **165**(10): p. 1339-41.
4. Kahan, B.C., et al., *A re-randomisation design for clinical trials.* BMC Med Res Methodol, 2015. **15**: p. 96.
5. Kahan, B.C., et al., *Re-randomization increased recruitment and provided similar treatment estimates as parallel designs in trials of febrile neutropenia.* J Clin Epidemiol, 2018. **97**: p. 14-19.
6. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ, 2010. **340**: p. c332.
7. Canet, J., et al., *Prediction of postoperative pulmonary complications in a population-based surgical cohort.* Anesthesiology, 2010. **113**(6): p. 1338-50.
8. Canet, J., et al., *Development and validation of a score to predict postoperative respiratory failure in a multicentre European cohort: A prospective, observational study.* Eur J Anaesthesiol, 2015. **32**(7): p. 458-70.
9. Kahan, B.C., *Accounting for centre-effects in multicentre trials with a binary outcome - when, why, and how?* BMC Med Res Methodol, 2014. **14**: p. 20.
10. Kahan, B.C. and T.P. Morris, *Improper analysis of trials randomised using stratified blocks or minimisation.* Statistics in Medicine, 2012. **31**(4): p. 328-340.
11. Kahan, B.C., et al., *The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies.* Trials, 2014. **15**: p. 139.
12. Hernandez, A.V., E.W. Steyerberg, and J.D. Habbema, *Covariate adjustment in randomized controlled trials with dichotomous outcomes increases statistical power and reduces sample size requirements.* J Clin Epidemiol, 2004. **57**(5): p. 454-60.
13. Turner, E.L., et al., *Covariate adjustment increased power in randomized controlled trials: an example in traumatic brain injury.* J Clin Epidemiol, 2012. **65**(5): p. 474-81.
14. Kahan, B.C., et al., *A comparison of methods to adjust for continuous covariates in the analysis of randomised trials.* BMC Med Res Methodol, 2016. **16**: p. 42.

15. White, I.R. and S.G. Thompson, *Adjusting for partially missing baseline measurements in randomized trials.* Stat Med, 2005. **24**(7): p. 993-1007.
16. Hernán, M.A. and J.M. Robins, *Per-Protocol Analyses of Pragmatic Trials.* New England Journal of Medicine, 2017. **377**(14): p. 1391-1398.
17. Little, R.J., et al., *The prevention and treatment of missing data in clinical trials.* N Engl J Med, 2012. **367**(14): p. 1355-60.
18. Morris, T.P., B.C. Kahan, and I.R. White, *Choosing sensitivity analyses for randomised trials: principles.* BMC Med Res Methodol, 2014. **14**: p. 11.
19. Wood, A.M., I.R. White, and S.G. Thompson, *Are missing outcome data adequately handled? A review of published randomized controlled trials in major medical journals.* Clin Trials, 2004. **1**(4): p. 368-76.

Appendix 1: Deriving outcomes and variables

Variables

At least 'one' co-morbid disease

- Equal to 1if:
  - At least one of the components of co-morbid disease is marked as 'yes'
- Equal to 0 if all of the components of co-morbid disease are marked as 'no'
- Missing if:
  - All components are missing
  - OR one or more components of co-morbid disease is missing, and all other components are marked as 'no'

Primary Outcome

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

- Equal to 1 if :
  - The patient experienced an event for one or more of the three components of the primary outcome (pneumonia, endotracheal re-intubation, death), even if data is missing for some of the other components (as in this case, the overall outcome is an event, regardless of the values of the missing components)
  - AND date of event is within 30 days of randomisation (for patients who experience an event for more than one of the three components, the primary outcome will be calculated based on the date of the first event)
- Equal to 0 if:
  - Data is available for each of the three components of the primary outcome
  - AND the patient did not experience an event within 30 days of randomisation
- Missing if:
  - Data is missing for all three components of the primary outcome
  - Data is missing for one or more components, and the patient did not experience an event within 30 days of randomisation for any of the observed components
  - One or more components is marked as 'yes' and is missing the date of the event, and the patient did not experience an event within 30 days of randomisation for the other component(s)

Secondary Outcomes

Pneumonia within 30 days of randomisation

- Equal to 1 if:
  - Pneumonia is marked as 'yes'
  - AND date of pneumonia is within 30 days of randomisation
- Equal to 0 if:
  - Pneumonia is marked as 'no'
  - OR pneumonia is marked as 'yes' and date of pneumonia is not within 30 days of randomisation
- Missing if:
  - Data is not available on whether the patient experienced an event or not
  - Pneumonia is marked 'yes' and missing date of pneumonia

Death within 30 days of randomisation

- Equal to 1 if:
  - Patient status at 30-day follow-up is dead
  - AND date of death is within 30 days of randomisation
- Equal to 0 if:
  - Patient status at 30-day follow-up is alive
  - OR patient status at 30-day follow-up is marked as 'dead' and date of death is not within 30 days of randomisation
- Missing if:
  - Patient status at 30-day follow-up is missing
  - Patient status at 30-day follow-up is marked as 'dead' and missing date of death

Endotracheal re-intubation within 30 days of randomisation

- Equal to 1 if:
  - Endotracheal re-intubation is marked as 'yes'
  - AND date of endotracheal re-intubation is within 30 days of randomisation
- Equal to 0 if:
  - Endotracheal re-intubation is marked as 'no'
  - OR endotracheal re-intubation is marked as 'yes' and date of endotracheal re-intubation is not within 30 days of randomisation
- Missing if:
  - Data is not available on whether the patient experienced an event or not
  - Endotracheal re-intubation marked as 'yes' and missing date of endotracheal re-intubation

All-cause mortality at one year after randomisation

- Equal to 1 if:
  - Patient status at one-year follow-up is dead
  - AND date of death is within one year of randomisation
- Equal to 0 if:
  - Patient status at one-year follow-up is alive
  - OR patient status at one-year follow-up is marked as 'yes' and date of death is not within one-year of randomisation
- Missing if:
  - Patient status at one-year follow-up is missing
  - Patient status at one-year follow-up is marked as 'dead' and missing date of death

Postoperative infection within 30 days of randomisation

This is defined as one or more of the following infections (more detail on the definition of each type of infection is available in the PRISM protocol):

1) Superficial surgical site infection
2) Deep surgical site infection
3) Organ space surgical site infection
4) Urinary tract infection
5) Infection, source uncertain
6) Laboratory confirmed blood stream infection
7) Pneumonia

- Equal to 1 if:
  - At least one of the components of postoperative infection is listed as occurring (i.e. listed under Clavien-Dindo grade I-V)
- Equal to 0 if:
  - All of the components of postoperative infection are "None"
- Missing if:
  - All components are missing
  - OR one or more of the components of postoperative infection is missing and all other components are "None"

Postoperative mechanical ventilation (invasive or non-invasive) with 30 days of randomisation

This consists of the following components:

1. Mechanical ventilation (invasive or non-invasive) within four hours of the end of surgery (page 5 of PRISM CRF)
2. Mechanical ventilation (invasive or non-invasive) after leaving the operating room (page 7 of the PRISM CRF)

- Equal to 1 if:
  - At least one of the components of mechanical ventilation is "Yes"
- Equal to 0 if:
  - All of the components of mechanical ventilation are "No"
- Missing if:
  - All of the components are missing
  - One or more components of mechanical ventilation is missing, and all other components are "No"

Appendix 2: Dummy tables

Table 1: Baseline patient characteristics

Baseline Characteristics	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Gender - no. (%)				
Male				
Female				
Age (years)				
Mean (SD)				
Median (IQR)				
Current Smoker - no. (%)				
[a]American Society of Anaesthesiology grade - no. (%)				
I				
II				
III				
IV				
[b]Chronic comorbid disease - no. (%)				
COPD				
Asthma				
Interstitial lung disease or pulmonary fibrosis				
Bronchiectasis				
Ischaemic heart disease				
Diabetes mellitus				
Heart failure				
Liver cirrhosis				
Active cancer				
Previous stroke or TIA				
Respiratory infection within the previous month				
HIV				
Planned surgical procedure - no. (%)				
Resection of colon, rectum or small bowel				
Resection of liver, pancreas or gall bladder				
Resection of stomach (non-obesity surgery)				
Resection of oesophagus (non-obesity surgery)				
Obesity surgery				
Vascular surgery				
Other intra-peritoneal surgery				
Planned use of epidural anaesthesia - no. (%)				
Country - no. (%)				
Italy				
Spain				
Sweden				
United Kingdom				
South Africa				
Norway				
Surgical procedure performed - no (%)				
Resection of colon, rectum or small bowel				
Resection of liver, pancreas or gall bladder				

Resection of stomach (non-obesity surgery)				
Resection of oesophagus (non-obesity surgery)				
Obesity surgery				
Vascular surgery				
Other intra-peritoneal surgery				
Pre-operative blood test results				
Haemoglobin (g/dL)				
Mean (SD)				
Median (IQR)				
Creatinine (µmol/L)				
Mean (SD)				
Median (IQR)				
Body Mass Index (kg/m^2)				
Mean (SD)				
Median (IQR)				
ARISCAT Score				
Mean (SD)				
Median (IQR)				

Abbreviations: SD, standard deviation; IQR, Interquartile range; COPD, chronic obstructive pulmonary disease.

[a] American Society of Anaesthesiology grades are defined as follows (grade 5 patients were not eligible for inclusion): 1, a healthy patient; 2, a patient with mild systemic disease that does not limit physical activity; 3, a patient with severe systemic disease that limits physical activity; and 4, a patient with severe systemic disease that is a constant threat to life.

[b] Patient may have more than one chronic co-morbid disease.

Table 2: Clinical management of study groups

Clinical management	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Open surgical technique used during surgery - no. (%)				
Anaesthetic technique - no. (%)				
General				
Epidural				
Spinal				
Endotracheal tube inserted				
Mechanical ventilation during surgery				
Recruitment manoeuvre - no. (%)				
Mechanical ventilation - no. (%)				
[a]Maximum positive end-expiratory pressure (cmH_2O)				
Mean (SD)				
Median (IQR)				
[a]Maximum set tidal volume (ml)				
Mean (SD)				
Median (IQR)				
[a]Maximum respiratory rate (min^{-1})				
Mean (SD)				
Median (IQR)				
[a]Maximum FiO_2 (%)				
Mean (SD)				
Median (IQR)				
Intravenous fluids during surgery				
Total volume of intravenous fluid administered excluding blood products (mL)				
Mean (SD)				
Median (IQR)				
Total volume of blood products administered (mL)				
Mean (SD)				
Median (IQR)				
Planned level of care on the first night after surgery - no. (%)				
Critical care unit level 3				
Critical care unit level 2				
Post- anaesthesia care unit				
Surgical ward				
Level of care on the first night after surgery - no. (%)				
Critical care unit level 3				
Critical care unit level 2				
Post- anaesthesia care unit				
Surgical ward				
Respiratory support after surgery (within 4 hours of the end of surgery) - no. (%)				
Invasive mechanical ventilation				
Non-invasive mechanical ventilation				
High flow nasal oxygen therapy				

Abbreviation: SD, standard deviation; IQR, Interquartile range

[a] Only summarised for patients who received mechanical ventilation during surgery

Table 3: Adherence and contamination

Adherence and contamination - no. (%)	Usual Care (n=XXXX)	CPAP (n=XXXX)
Patients with ≥ 1 treatment deviation	XX (XX.X %)	XX (XX.X %)
Total number of deviations	XXX	XXX
Number of treatment deviations per patient		
0	XXX (XX.X %)	XXX (XX.X %)
1	XXX (XX.X %)	XXX (XX.X %)
2	N/A	XXX (XX.X %)
3	N/A	XXX (XX.X %)
Types of deviations		
Participant in the intervention group did not receive CPAP	N/A	XXX (XX.X %)
CPAP administered for less than 4 hours duration	N/A	XXX (XX.X %)
CPAP administered with significant interruption	N/A	XXX (XX.X %)
CPAP started at a dose other than 5 cmH_2O	N/A	XXX (XX.X %)
Participant in the usual care group did receive CPAP	XXX (XX.X %)	N/A

Table 4: Adherence and contamination by CPAP delivery method

Adherence and contamination - no. (%)	CPAP[a] (n=XXXX)		
	Face mask (n=XXXX)	Helmet device (n=XXXX)	Nasal mask (n=XXXX)
Patients with ≥ 1 treatment deviation	XX (XX.X %)	XX (XX.X %)	XX (XX.X %)
Total number of deviations	XXX	XXX	XXX
Number of treatment deviations per patient			
0	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
1	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
2	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
3	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Types of deviations			
Participant in the intervention group did not receive CPAP	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
CPAP administered for less than 4 hours duration	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
CPAP administered with significant interruption	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
CPAP started at a dose other than 5 cmH_2O	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)

[a]XXX patients had missing data on CPAP method out of XXXX patients randomised to the CPAP group

Table 5: Primary and secondary outcomes

Outcomes	Number of patients included in analysis - no. (%)		Summary measure		Adjusted odd ratios (95% CI)	P-value
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)						
Pneumonia within 30 days of randomisation						
Endotracheal re-intubation within 30 days of randomisation						
All-cause mortality within 30 days of randomisation						
Postoperative infection within 30 days of randomisation						
Postoperative mechanical ventilation (invasive or non-invasive) within 30 days of randomisation						
All-cause mortality within one year of randomisation						

Table 6: Complications within 30 days of randomisation

Complication	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Respiratory - no. (%)				
Pneumonia				
Pleural effusion				
Pneumothorax				
Bronchospasm				
Aspiration pneumonitis				
Acute respiratory distress syndrome (ARDS)				
Infections - no. (%)				
Surgical site infection (superficial)				
Surgical site infection (deep)				
Surgical site infection (organ space)				
Urinary tract infection				
Infection, source uncertain				
Laboratory confirmed blood stream infection				
Cardiac - no. (%)				
Myocardial infarction				
Arrhythmia				
Cardiogenic pulmonary oedema				
Cardiac arrest with resuscitation				
Other - no. (%)				
Acute kidney injury				
Pulmonary embolism				
Stroke				
Acute psychosis or delirium				
Bowel infarction				
Anastomotic leak				
Perforation of viscus				
Gastro-intestinal bleed				
Other postoperative haemorrhage				
Any other complication				

Table 7: Complications within 30 days of randomisation in the intervention group by CPAP delivery method

Complication	Number of patients included in analysis - no. (%)			Summary measure		
	CPAP[a] (n=XXXX)			CPAP		
	Face mask (n=XXX)	Helmet device (n=XXX)	Nasal mask (n=XXX)	Face mask	Helmet device	Nasal mask
Respiratory - no. (%)						
Pneumonia						
Pleural effusion						
Pneumothorax						
Bronchospasm						
Aspiration pneumonitis						
Acute respiratory distress syndrome						
Infections - no. (%)						
Surgical site infection (superficial)						
Surgical site infection (deep)						
Surgical site infection (organ space)						
Urinary tract infection						
Infection, source uncertain						
Laboratory confirmed blood stream infection						
Cardiac - no. (%)						
Myocardial infarction						
Arrhythmia						
Cardiogenic pulmonary oedema						
Cardiac arrest with resuscitation						
Other - no. (%)						
Acute kidney injury						
Pulmonary embolism						
Stroke						
Acute psychosis or delirium						
Bowel infarction						
Anastomotic leak						
Perforation of viscus						
Gastro-intestinal bleed						
Other postoperative haemorrhage						
Any other complication						

[a]XXX patients had missing data on CPAP method out of XXXX patients randomised to the CPAP group

Table 8: Complications within 30 days of randomisation by treatment allocation and Clavien-Dindo grade

Complication	Number of patients included in analysis - no. (%)		Summary measure					
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care			CPAP		
			I-II	III-V	Total	I-II	III-V	Total
Respiratory - no. (%)								
Pneumonia								
Pleural effusion								
Pneumothorax								
Bronchospasm								
Aspiration pneumonitis								
Acute respiratory distress syndrome (ARDS)								
Infections - no. (%)								
Surgical site infection (superficial)								
Surgical site infection (deep)								
Surgical site infection (organ space)								
Urinary tract infection								
Infection, source uncertain								
Laboratory confirmed blood stream infection								
Cardiac - no. (%)								
Myocardial infarction								
Arrhythmia								
Cardiogenic pulmonary oedema								
Cardiac arrest with resuscitation								
Other - no. (%)								
Acute kidney injury								
Pulmonary embolism								
Stroke								
Acute psychosis or delirium								
Bowel infarction								
Anastomotic leak								
Perforation of viscus								
Gastro-intestinal bleed								
Other postoperative haemorrhage								
Any other complication								

Table 9: Process measures

Process measures	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Re-admission to hospital within 30 days of randomisation - no. (%)				
Duration of primary hospital admission from randomisation (days)				
Mean (SD)				
Median (IQR)				
[a]**Total duration of critical care stay within 30 days of randomisation (days)**				
Number of patients admitted to a critical care unit - no. (%)				
Mean (SD)				
Median (IQR)				

Abbreviation: SD, standard deviation; IQR, interquartile range.

[a]Summarised only for patients admitted to critical care unit

Table 10: Critical care stay within 30 days of randomisation [a]

Critical Care Stay within 30 days of randomisation	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Number of patients admitted to a critical care unit - no. (%)				
Duration of level 2 critical care stay (days)				
Mean (SD)				
Median (IQR)				
Duration of level 3 critical care stay (days)				
Mean (SD)				
Median (IQR)				

Abbreviation: SD, standard deviation; IQR, interquartile range.

[a]Summarised only for patients admitted to critical care unit

Table 11: Summary of CPAP for patients randomised to the CPAP group

CPAP Characteristics	Number of patients included in analysis - no. (%)	Summary measure
	CPAP (n=XXXX)	CPAP
Number of patients who received CPAP - no. (%)		
Total duration of CPAP within 12 hours of the end of surgery (minutes)		
Mean (SD)		
Median (IQR)		
Maximum airway pressure received within 12 hours of the end of surgery (cmH_2O)		
Mean (SD)		
Median (IQR)		
Primary method of CPAP delivery - no. (%)		
Face mask		
Helmet device		
Nasal mask		
Extra research staff present to help deliver CPAP - no. (%)		
Staff administering CPAP used equipment to monitor airway pressures - no. (%)		
Staff administering CPAP used equipment to monitor FiO2 - no. (%)		
Patient had a nasogastric tube in situ during CPAP - no. (%)		

Abbreviation: IQR, interquartile range; SD, standard deviation; CPAP, continuous positive airway pressure

Table 12: Safety outcome measures

Adverse Events - no.(%)	CPAP (n=XXXX)
Patients with ≥ 1 adverse event	XX (XX.X %)
Total number of adverse events	XXX
Number of adverse events per patient	
0	XXX (XX.X %)
1	XXX (XX.X %)
2	XXX (XX.X %)
3	XXX (XX.X %)
4	XXX (XX.X %)
Type of adverse event	
Interface intolerance due to excessive air leak	XXX (XX.X %)
Pain	XXX (XX.X %)
Cutaneous pressure area	XXX (XX.X %)
Claustrophobia	XXX (XX.X %)
Oronasal dryness	XXX (XX.X %)
Hypercapnia	XXX (XX.X %)
Haemodynamic instability	XXX (XX.X %)
Vomiting	XXX (XX.X %)
Aspiration of gastric contents	XXX (XX.X %)
Other	XXX (XX.X%)

Table 13: Summary of 'other' safety outcomes with a prevalence of more than 1%

Other Adverse Events - no.(%)	CPAP (n=XXXX)
Total number of other adverse events	XXX (XX.X %)
Type of adverse event	
Other 1	XXX (XX.X %)
Other 2	XXX (XX.X %)
Other 3	XXX (XX.X %)
Other 4	XXX (XX.X %)
Other 5	XXX (XX.X %)

Table 14: Safety outcomes measures by CPAP delivery method

Adverse Events	CPAP[a] (n=XXXX)		
	Face mask (n=XXXX)	Helmet device (n=XXXX)	Nasal mask (n=XXXX)
Patients with ≥ 1 adverse event	XX (XX.X %)	XX (XX.X %)	XX (XX.X %)
Total number of adverse events	XXX	XXX	XXX
Number of adverse events per patient			
0	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
1	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
2	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
3	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
4	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Type of adverse event			
Interface intolerance due to excessive air leak	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Pain	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Cutaneous pressure area	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Claustrophobia	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Oronasal dryness	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Hypercapnia	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Haemodynamic instability	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Vomiting	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Aspiration of gastric contents	XXX (XX.X %)	XXX (XX.X %)	XXX (XX.X %)
Other	XXX (XX.X%)	XXX (XX.X%)	XXX (XX.X%)

[a]XXX patients had missing data on CPAP method out of XXXX patients randomised to the CPAP group

Table 15: ARISCAT Score

ARISCAT	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
ARISCAT Score				
Mean (SD)				
Median (IQR)				
Components				
Age (years) - no. (%)				
≥50				
51-80				
> 80				
Percentage peripheral oxygen saturation (SpO_2) - no. (%)				
≥ 96%				
91-95%				
≤90%				
Respiratory infection within the last month - no. (%)				
Preoperative anaemia (Hgb ≤10 g/dL) – no. (%)				
Surgical incision - no. (%)				
Upper abdominal				
Intrathoracic				
Peripheral				
Duration of surgery - no. (%)				
< 2 hours				
2-3 hours				
> 3 hours				
[a]Emergency procedure - no. (%)				

Abbreviation: SD, standard deviation; IQR, interquartile range

[a] All patients recruited in the trial were elective

Table 16: Pre-specified subgroup analyses for primary outcome

Planned surgical procedure	Number of patients included in analysis - no. (%)		Pneumonia, endotracheal re-intubation or death within 30 days of randomisation - no. (%)		Adjusted odds ratio (95% CI)	Test for interaction p-value
	Usual care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP		
Lower gastrointestinal (resection of colon, rectum, or small bowel)			XXX/XXXX (XX.X)	XXX/XXXX (XX.X)	X.XX (X.XX-X.XX)	X.XX
Hepatobiliary (resection of liver, pancreas, or gall bladder)			XXX/XXXX (XX.X)	XXX/XXXX (XX.X)	X.XX (X.XX-X.XX)	
Upper gastrointestinal (resection of oesophagus, or resection of stomach (non-obesity surgery))			XXX/XXXX (XX.X)	XXX/XXXX (XX.X)	X.XX (X.XX-X.XX)	
Other (obesity surgery, vascular procedure, or other intra-peritoneal surgery)			XXX/XXXX (XX.X)	XXX/XXXX (XX.X)	X.XX (X.XX-X.XX)	

Table 17: Results of sensitivity analysis for data being missing not at random of primary outcome within 30 days of randomisation

Proportion with missing data in usual care assumed to have an event	Proportion with missing data in intervention group assumed to have an event	Odds ratio (95% CI)
0.05	0.03	
	0.04	
	0.06	
	0.07	
0.10	0.08	
	0.09	
	0.11	
	0.12	
0.15	0.13	
	0.14	
	0.16	
	0.17	

Table 18: Per-protocol analysis using inverse probability weighting

Outcome	Number of patients included in analysis - no. (%)		Summary measure		Adjusted odd ratios (95% CI)	P-value
	Usual Care[a] (n=XXXX)	CPAP[b] (n=XXXX)	Usual Care	CPAP		
Pneumonia, endotracheal re-intubation or death within 30 days of randomisation (primary outcome)						
Pneumonia within 30 days of randomisation						
Endotracheal re-intubation within 30 days of randomisation						
All-cause mortality within 30 days of randomisation						

[a] Excludes XXX/XXXX patients who received CPAP in the usual care group

[b] Excludes XXX/XXXX patients who received no CPAP in the intervention group

Table 19: Summary of investigators' self-assessment of blinding

Investigator self-assessment of blinding - no. (%)	Number of patients included in analysis - no. (%)		Summary measure	
	Usual Care (n=XXXX)	CPAP (n=XXXX)	Usual Care	CPAP
Suitably blinded				
May have known the study group allocation				
Definitely knew the study group allocation				

Figure 1: Information for CONSORT flow diagram

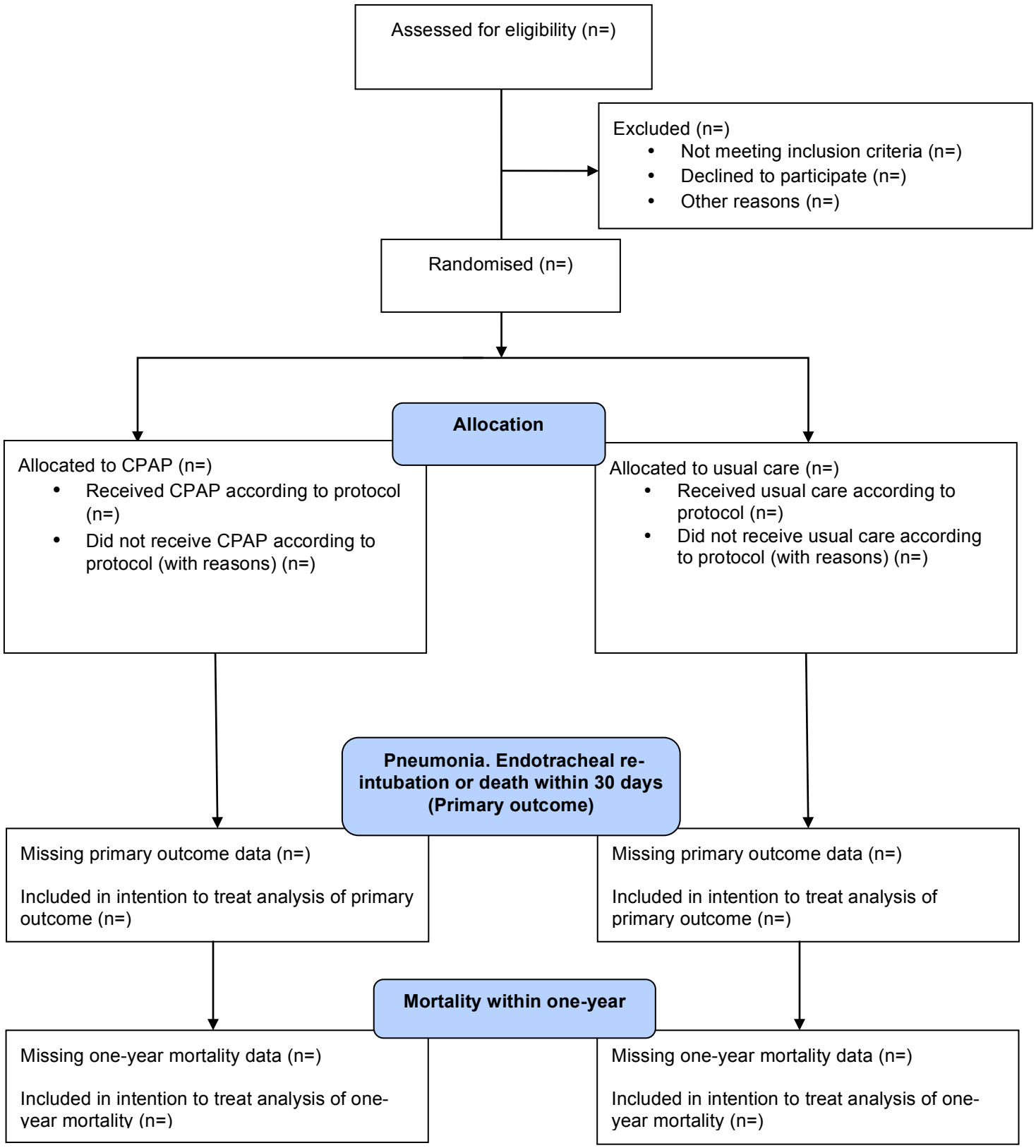


Figure 2: Kaplan-Meier survival curves by treatment allocation for (a) 30 days and (b) one-year following randomisation