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Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis

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ABSTRACT

OBJECTIVE

To identify, appraise, and synthesise the best available evidence on the efficacy of perioperative interventions to reduce postoperative pulmonary complications (PPCs) in adult patients undergoing non-cardiac surgery.

DESIGN

Systematic review and meta-analysis of randomised controlled trials.

DATA SOURCES

Medline, Embase, CINHAL, and CENTRAL from January 1990 to December 2017.

ELIGIBILITY CRITERIA

Randomised controlled trials investigating short term, protocolised medical interventions conducted before, during, or after non-cardiac surgery were included. Trials with clinical diagnostic criteria for PPC outcomes were included. Studies of surgical technique or physiological or biochemical outcomes were excluded.

DATA EXTRACTION AND SYNTHESIS

Reviewers independently identified studies, extracted data, and assessed the quality of evidence. Meta-analyses were conducted to calculate risk ratios with 95% confidence intervals. Quality of evidence was summarised in accordance with GRADE methods. The primary outcome was the incidence of PPCs. Secondary outcomes were respiratory infection, atelectasis, length of hospital stay, and mortality. Trial sequential analysis was used to investigate the reliability and conclusiveness of available evidence. Adverse effects of interventions were not measured or compared.

RESULTS

117 trials enrolled 21 940 participants, investigating 11 categories of intervention. 95 randomised controlled trials enrolling 18 062 participants were included in meta-analysis; 22 trials were excluded from meta-analysis because the interventions were not sufficiently similar to be pooled. No high quality evidence was found for interventions to reduce the primary outcome (incidence of PPCs). Seven interventions had low or moderate quality evidence with confidence intervals indicating a probable reduction in PPCs: enhanced recovery pathways (risk ratio 0.35, 95% confidence interval 0.21 to 0.58), prophylactic mucolytics (0.40, 0.23 to 0.67), postoperative continuous positive airway pressure ventilation (0.49, 0.24 to 0.99), lung protective intraoperative ventilation (0.52, 0.30 to 0.88), prophylactic respiratory physiotherapy (0.55, 0.32 to 0.93), epidural analgesia (0.77, 0.65 to 0.92), and goal directed haemodynamic therapy (0.87, 0.77 to 0.98). Moderate quality evidence showed no benefit for incentive spirometry in preventing PPCs. Trial sequential analysis adjustment confidently supported a relative risk reduction of 25% in PPCs for prophylactic respiratory physiotherapy, epidural analgesia, enhanced recovery pathways, and goal directed haemodynamic therapies. Insufficient data were available to support or refute equivalent relative risk reductions for other interventions.

CONCLUSIONS

Predominantly low quality evidence favours multiple perioperative PPC reduction strategies. Clinicians may choose to reassess their perioperative care pathways, but the results indicate that new trials with a low risk of bias are needed to obtain conclusive evidence of efficacy for many of these interventions.

STUDY REGISTRATION

Prospero CRD42016035662.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Postoperative pulmonary complications (PPCs) are common and have an important effect on morbidity and mortality after surgery, with associated resource use and cost implications

Various interventions are available that aim to reduce the risk of PPCs

Evidence shows a mismatch between routine clinical practice to prevent PPCs and outcome data from trials of interventions

WHAT THIS STUDY ADDS

This study provides an overview of the efficacy of different interventions to reduce development of PPCs

No high quality evidence supported the efficacy of any interventions, but moderate quality evidence showed that intraoperative lung protective ventilation and goal directed haemodynamic strategies reduce PPCs

Moderate quality evidence does not support incentive spirometry therapy, and only low quality evidence was available for other treatment interventions

Introduction

Despite advances in perioperative care for patients undergoing major surgery, postoperative pulmonary complications (PPCs) represent a leading cause of morbidity and mortality. The term PPC encompasses a range of conditions affecting the respiratory system, typically within the first week after surgery. Examples range from atelectasis to respiratory failure.[1 2]

PPCs are among the most common post-surgical complications,[3-7] with a prevalence between 1% and 23%, varying considerably depending on patient related and surgical factors. For example, ankle surgery in a healthy, young person may have risk of PPCs of less than 1% and upper gastrointestinal

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surgery in a frail, older patient will have a much higher risk. Proximity of surgical incision to the thorax, where pain disrupts the performance of respiratory muscles after surgery, is a strong predictor of PPCs, as is age, with even healthy older patients being at higher risk of PPCs.[8] PPCs are also predictors of short term and long term health outcomes after surgery and are associated with increased risk of admission to critical care and prolonged length of hospital stay.[9 10] Between 14% and 30% of patients developing a PPC will die within 30 days of major surgery, compared with 0.2-3% of those without a PPC.[9]

The causes of PPCs are multifactorial and relate to both the patient's chronic health and the acute adverse effects of surgery with accompanying anaesthesia.[11] Surgery itself can depress lung function, particularly when surgical pain impairs breathing. Anaesthesia adversely affects lung function intraoperatively, and, to a lesser extent, these effects persist into the postoperative period. Well established chronic risk factors for PPC include poor cardiorespiratory health, increased age, lifestyle factors, and habitus.[12]

Fortunately, multiple opportunities exist to intervene and therefore potentially prevent the development of PPCs. Interventions are diverse, covering pre-emptive strategies (before surgery) to optimise respiratory physiology and intraoperative and postoperative interventions to minimise the adverse effects of surgery and anaesthesia. Table 1 shows examples of interventions used in clinical practice in resourced healthcare systems.

Treatment of PPCs requires multidisciplinary involvement across anaesthesia, surgery, respiratory medicine, physiotherapy, and critical care specialties, with associated economic and health outcome burden.[13] Despite this, consensus guidelines for perioperative management aimed at reducing the risk of PPCs are infrequent or outdated compared with those for cardiovascular complications following surgery.[14 15] This lack of consensus, arising from a broad and diverse evidence base across many interventions, results in much variation in clinical practice.

The aim of this systematic review was to summarise the evidence from randomised controlled trials (RCTs) of perioperative interventions designed to reduce PPCs in adults after non-cardiac surgery. RCTs designed to reduce the incidence of PPC generally consider non-cardiac surgery separately from cardiac surgery. We chose to focus exclusively on non-cardiac surgery because it is more common. We aimed to compare quality, quantity, and risk of bias for evidence of treatment effects for PPC management. Inherent to this approach is a focus on whether benefits are associated with each treatment, rather than comparing their adverse effects. This is because although the benefits of treatments should be similar, the harms vary substantially because the interventions work in very different ways and they may not share common harms. The principal purpose of the review is to inform clinicians wishing to improve their evidence based perioperative care pathways and, by highlighting deficiencies in our evidence base, to facilitate researchers and funders in focusing on areas of greatest need.

Methods

Protocol

Our methods and reporting conform to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Cochrane guidelines.[16 17] This study is registered with the International Prospective Register of Systematic Reviews, number CRD42016035662. The registration includes a pre-specified protocol, which was amended to include length of hospital stay as a replacement secondary outcome measure, alongside a revised categorisation system for types of intervention. We adjusted the search strategy to include an earlier start date for included studies and further secondary search strategies for interventions of relevance. We added trial sequential analysis to the statistical methods. We did not consider network meta-analysis to be suitable, as the studies lack homogeneity in terms of the participants and the definitions of control and intervention.

Search strategy

We searched Medline, Embase, CINHAL, and the Cochrane Central Register of Controlled Trials, using

Table 1 | Current practice for interventions to prevent postoperative pulmonary complications in resourced healthcare settings

What is it?	Is it used commonly?	How burdensome for patients?	How tricky for providers?	Cost
Enhanced recovery pathways	Increasingly commonly used	Minimal	Simple (once established)	Neutral
Prophylactic mucolytics	Not commonly used	Minimal	Simple	£
Postoperative ventilatory support (CPAP, NIV, or HFNC)	Not commonly used*	Moderate	Complex	££
Lung protective ventilation intraoperatively	Not commonly used	None	Simple	Neutral
Respiratory physiotherapy	Not commonly used*	Mild	Complex	££
Epidural analgesia	Commonly used	Mild	Moderate	££
Goal directed fluid therapy	Variably used internationally	None	Moderate	££
Incentive spirometry	Variably used internationally	Mild	Simple	£
Inhaled therapies (in addition to usual drugs)	Not commonly used*	Mild	Simple	£
Smoking cessation	Commonly recommended	Moderate	Simple	Neutral

Costs and degree of burden for patients are generalised and based on empirical estimates.
CPAP=continuous positive airway pressure; HFNC=high flow nasal cannula; NIV=non-invasive ventilation.
*Not commonly used prophylactically, but commonly used in response to deteriorating respiratory function (ie, as treatment).

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a combination of relevant keywords and medical subject heading terms for postoperative pulmonary complications. Search limits were applied to restrict results to RCTs published from 1 January 1990 to 8 December 2017. We chose the start date to overlap with the last systematic review into strategies for prevention of PPCs,[14] as well as to restrict trials to contemporary surgical and anaesthesia practice, including laparoscopic surgery techniques. Subject headings and text terms for intraoperative complications, postoperative complications, perioperative complications, preoperative care, intraoperative care, perioperative care, postoperative care, or anaesthesia were combined with descriptive terms relevant to postoperative respiratory complications based on European Perioperative Clinical Outcome (EPCO) definitions (table 2).[1] Full search terms and search strategy are provided in appendix 1. Secondary searching included manual searching of relevant reference lists for articles not identified in the primary search and review of citation listings in Web of Science. In addition, we did focused searches for perioperative fluid administration and haemodynamic management strategies, intraoperative neuromuscular blockade and monitoring, and airway device and supraglottic suctioning techniques.

Study selection

Population

We included RCTs of adult (age ≥18 years) patients undergoing non-cardiac surgery, excluding organ transplantation surgery (as findings in patients who need immunosuppression may not be generalisable to others).

Intervention

We considered all perioperative care interventions identified by the search if they were protocolised (therapies were systematically provided to patients according to pre-defined algorithm or plan) and were started and completed during the perioperative pathway (that is, during preoperative preparation for surgery, intraoperative care, or inpatient postoperative recovery). Examples of interventions that we did or did not deem perioperative in nature included long term preoperative drug treatment (not included, as not started and completed during the perioperative pathway) and perioperative physiotherapy interventions (included, as both started and completed during the perioperative pathway). We excluded studies in which the intervention was directly related to surgical technique.

Outcomes

To be included, a trial had to use a defined clinical outcome relating to PPC, such as "pneumonia" diagnosed according to the Centers for Disease Control and Prevention's definition. RCTs reporting solely physiological (for example, lung volumes and flow measurements) or biochemical (for example, lung inflammatory markers) outcomes are valuable but neither patient centric nor necessarily clinically relevant, and we therefore excluded them. We applied no language restrictions.

Our primary outcome measure was the incidence of PPCs, with PPCs being defined as the composite of any of respiratory infection, respiratory failure, pleural effusion, atelectasis, or pneumothorax. As the search period pre-dated the most recent consensus definitions of PPC,[1 18] we categorised explicit descriptions of PPCs in each trial according to closeness of match to the EPCO definitions.[1] Where a composite PPC was not reported, we contacted corresponding authors via email to request additional information, including primary data. Secondary outcomes were the incidence of subtypes of PPC (including respiratory infection, respiratory failure, pleural effusion, atelectasis, and pneumothorax), length of hospital stay, and in-hospital mortality. However, our analysis incorporated only the three most commonly reported secondary pulmonary outcome measures.

Data abstraction and risk of bias assessment

Two of three reviewers used pre-piloted abstraction forms to independently extract study characteristics and outcomes for each trial. Risk of bias was assessed using the Cochrane Collaboration tool.[19] Disagreements were resolved by consensus or by consultation with a third reviewer. Where necessary, we contacted authors of relevant studies to obtain additional information. For studies published more than once (duplicates), we included only the report with the most informative and complete data.

Table 2 | Definitions of postoperative respiratory complications from European Perioperative Clinical Outcome consensus statement[1]

Postoperative pulmonary complication	Definition
Respiratory infection	Patient has received antibiotics for suspected respiratory infection and met one or more of the following criteria: new or changed sputum, new or changed lung opacities, fever, white blood cell count >12×10^9/L
Respiratory failure	Postoperative PaO_2 <8 kPa (60 mm Hg) on room air, PaO_2:FiO_2 ratio <40 kPa (300 mm Hg), or arterial oxyhaemoglobin saturation measured with pulse oximetry <90% and needing oxygen therapy
Pleural effusion	Chest radiograph showing blunting of costophrenic angle, loss of sharp silhouette of ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with shift of mediastinum, hilum, or hemidiaphragm towards affected area, and compensatory over-inflation in adjacent non-atelectatic lung
Pneumothorax	Air in pleural space with no vascular bed surrounding visceral pleura

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Data synthesis and statistical methods

For dichotomous data, including binary PPC outcomes, we used risk ratios as the effect measure with 95% confidence intervals calculated using the Mantel-Haenszel method. For continuous data, we presented the results as mean differences with 95% confidence intervals calculated using an inverse variance method. We converted results for length of hospital stay from median and range and/or interquartile range to mean and standard deviation.[20 21] When studies included two or more intervention groups, we merged data into a single group only if the interventions were sufficiently similar. We did meta-analysis when it was reasonable to assume that studies were estimating the same underlying treatment effect on PPC outcomes and two or more studies could be included with measures of clinical, methodological, and statistical heterogeneity indicating that pooling of results was appropriate. We assessed for statistical heterogeneity between studies by using the I^2 statistic. When producing an overall summary estimate, we used random effects models in meta-analysis, as sufficient clinical heterogeneity existed for us to expect that the underlying treatment effects would differ between trials.[22 23] We generated summary forest plots for each intervention by using individual meta-analysis data weighted according to the inverse variance method.

We rated the quality of evidence for each intervention according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group system.[24] Conventional meta-analyses may result in type I errors due to random error from studies with low quality, a small sample size, or publication bias. Likewise, results from smaller trials are often overruled when results from adequately powered larger trials emerge. We used trial sequential analysis for included studies in the meta-analysis to estimate and correct these limitations and determine whether the cumulative evidence was appropriately powered.[23 25] Trial sequential analysis can also guide conduct of new high quality trials or prevent unnecessary trials if intervention effects are found to be large and the required information size has been reached. A network meta-analysis was not suitable owing to trial heterogeneity.

Our assumptions included an a priori determined intervention effect of a 25% risk ratio reduction in PPCs, two sided testing with a type I error of 5%, and a type II error of 20% (power of 80%). We constructed both conventional (with α of 5%) and trial sequential monitoring boundaries for intervention and control group comparisons. The heterogeneity correction in the trial sequential analysis was set to variance based, and the random effects model was applied. We constructed a cumulative, sequential z score curve and used it to evaluate the adequacy of the evidence. We calculated the diversity adjusted required information size, or the number of participants needed in a meta-analysis to detect or reject a certain intervention effect, by using the above modelling. We used Trial Sequential Analysis software 0.9.[26] We compiled a narrative review of trial results and characteristics where trials where unsuitable for meta-analysis.

Patient and public involvement

Patients were not involved in setting this specific research question or the outcome measures. However, our research group is incorporating patient and lay perspectives into future work following this review, including the development of care bundle proposals to reduce PPCs. More specifically, we are considering patient feedback on how prophylactic interventions can be delivered sensitively and comfortably at a time when patients may feel pain, stressed, or fatigued around the time of surgery. For this paper we are expanding our dissemination by writing a BMJ perspective article about our research.

Results

Description of included studies

The literature search retrieved 4525 unique citations. Of these, 117 parallel group RCTs, including 21 940 adult patients, conducted between 1990 to 2017 in 27 countries fulfilled the inclusion criteria (fig 1). Twenty one RCTs were ineligible for meta-analysis, either because the interventions were not sufficiently similar to be pooled with other RCTs or because they were investigating an intervention evaluated in a single trial only. One trial was withheld from meta-analysis because it did not include a standard care control group. The meta-analysis therefore included 95 RCTs, incorporating data from 18 062 participants. Study characteristics, risk of bias assessment, outcomes, and references of all 117 trials are shown in appendix 2. Subgroup analysis according to type of surgery is provided in appendix 3. The total proportion of patients who were diagnosed as having PPCs in the included RCTs (in both control and intervention groups) was 3164/21 940 (14.4%).

All patients received general anaesthesia, with or without a neuraxial block or regional anaesthetic adjunct, except for one trial in the narrative evaluation that compared patients with hip fracture receiving spinal or general anaesthesia. Most patients included in trials underwent laparotomy or open surgical techniques (table 3). The primary outcome measure of PPC was reported or derived for all studies. Reporting of secondary PPC subtypes varied (table 4). We identified 34 different strategies for reducing the risk of PPCs, which we grouped into 11 categories based on mode of intervention (table 5). Analysis of funnel plots showed no obvious evidence of publication bias or that results of smaller trials were systematically different from those of larger trials (appendix 2). We judged most of the studies to have at least some concerns about risk of bias according to the Cochrane instrument (fig 2).

Principal findings

We identified seven perioperative interventions with confidence intervals from conventional meta-analysis

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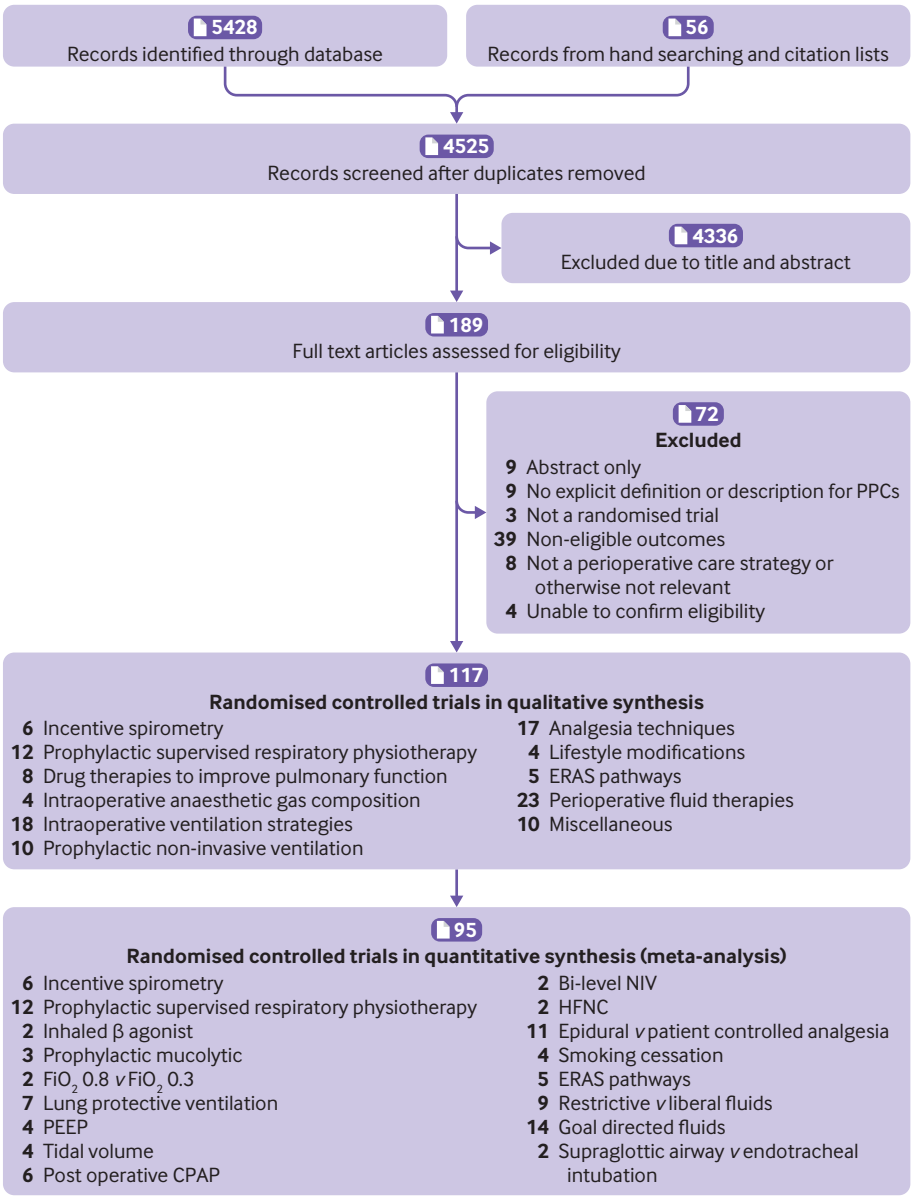

Fig 1 | Screening and selection of studies for systematic review and meta-analysis of postoperative pulmonary complication (PPC) outcomes. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; FiO_2=fractional inspiration oxygen; HFNC=high flow nasal cannula; NIV=non-invasive ventilation; PEEP=positive end expiratory pressure

indicating a probable reduction in PPCs: use of enhanced recovery after surgery pathways, prophylactic mucolytics, postoperative continuous positive airway pressure non-invasive ventilation, lung protective intraoperative ventilation, prophylactic respiratory physiotherapy, epidural analgesia, and goal directed haemodynamic therapy (summarised in table 6). A further seven interventions did not meet statistical limits (all P>0.05) for treatment benefit: restrictive versus liberal fluid administration strategies, postoperative bi-level non-invasive ventilation, postoperative high flow nasal cannula oxygenation, smoking cessation therapy, inhaled β agonists, incentive spirometry, and variation in intraoperative fractional inspiration oxygen concentration (fig 3). Confidence intervals for risk ratios derived from conventional meta-analysis indicate wide imprecision for most estimates of the treatment effects of interventions. Only marginal differences for continuous positive airway pressure, for example, separate the statistical finding for this intervention as beneficial (at P=0.05).

We used trial sequential analysis to evaluate the robustness of our meta-analysis (table 7). Firm evidence of a 25% relative risk reduction is defined by a cumulative z curve crossing the calculated trial sequential monitoring boundary before the calculated diversity adjusted required information size is reached. Alternatively, firm evidence is also reached if the conventional z=−1.96 or z=1.96 monitoring boundary is crossed and the actual information size exceeds the diversity adjusted required information size. If the cumulative z curve crosses the conventional boundary

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Table 3 | Selected trial characteristics, including largest proportion of surgical type received by recruited patients in each trial. Values are numbers (percentages)

Characteristic	Randomised controlled trials (n=112)
Only patients aged ≥65 years	4 (4)
>200 participants	23 (21)
Baseline ARISCAT score ≥26 (intermediate or high predictive risk of PPC)	8 (7)
Type of surgery	
Laparoscopic surgical technique	9 (8)
Laparotomy or otherwise open surgical technique	96 (86)
Lower abdominal surgery (eg, colonic resection)	51 (46)
Upper abdominal surgery (eg, oesophagectomy, sleeve gastrectomy)	16 (14)
Vascular surgery (eg, abdominal aortic aneurysm repair)	12 (11)
Thoracic surgery (eg, lobectomy, video assisted thoracoscopy)	24 (21)
Orthopaedic surgery (eg, spinal surgery, hip fracture repair)	7 (6)
Maxillofacial surgery (major head and neck surgery with tracheostomy)	1 (1)
Urological surgery (eg, robotic assisted radical prostatectomy)	1 (1)
Obstetric surgery (eg, caesarean section)	1 (1)
Neurosurgery (any neurosurgical procedure)	1 (1)

PPC=postoperative pulmonary complication.

but not the trial sequential monitoring boundary, the result may represent random error as a result of repetitive testing on accumulating data (nominal type I error). Trial sequential analysis results are available in full in appendix 4.

Only four of the seven interventions with evidence of benefit in conventional meta-analysis also showed firm evidence of benefit in trial sequential analysis: prophylactic respiratory physiotherapy, epidural analgesia, enhanced recovery after surgery, and goal directed haemodynamic therapies. However, all trials of these interventions were of only low to moderate quality. Despite firm evidence at trial sequential analysis, further randomised trials of these interventions may still be needed to reflect the changing nature of surgical practice and patients' characteristics. The remaining meta-analyses do not provide sufficient data for us to draw definitive conclusions on treatment effects when adjusted for sequential testing on an accumulating number of participants; hence, larger trials of these interventions are still required.

Secondary outcomes

Meta-analysis of respiratory infection and atelectasis outcomes were based on fewer data (fig 4 and fig 5) but indicated treatment effects for postoperative continuous positive airway pressure, mucolytics, respiratory physiotherapy, and enhanced recovery after surgery for both outcomes. Lung protective ventilation reduced the risk of atelectasis and respiratory infection, with similar confidence intervals and point estimates of treatment effects, but significance limits were reached for atelectasis outcomes only. Only RCTs of enhanced recovery after surgery and goal directed haemodynamic therapy showed any reduction in length of hospital stay (fig 6), whereas very limited data suggested no benefits on in-hospital mortality for any intervention (fig 7). Although we found evidence of equivalent outcomes for PPCs with incentive spirometry, the point estimate and confidence interval for developing respiratory infections was large and weighted in favour of control groups, albeit on the basis of two trials only.

Table 4 | Numbers (percentages) of randomised controlled trials (RCTs) reporting individual postoperative pulmonary complication subtypes as discrete outcomes

Type of postoperative pulmonary complication	Reported as discrete outcome in RCTs (n=112)
Respiratory infection	79 (71)
Respiratory failure	35 (31)
Pleural effusion	7 (6)
Atelectasis	37 (33)
Pneumothorax	7 (6)

Interventions with low to moderate supporting evidence of benefit

We found no high quality evidence for any perioperative interventions in the reduction of PPC risk. Only low or moderate quality evidence was available.

Enhanced recovery after surgery pathways

Enhanced recovery pathways involve protocolised implementation of evidence based perioperative care. All studies were at high risk of bias. As a result, the quality of evidence was downgraded to low.

A total of five RCTs with a pooled total of 519 participants included enhanced recovery after surgery style care pathways and included PPCs as an outcome measure.[27-31] None of the studies reported adequately on protocol compliance or prevention of cross contamination of control group patients enrolled at the same sites with intervention care. These confounders may have led to over-estimation or under-estimation of the effect size of enhanced recovery pathways on PPCs. Although we identified no obvious evidence of publication bias, the estimated treatment effect size was disproportionately large (risk ratio 0.35, 95% confidence interval 0.21 to 0.58), especially given that the enhanced recovery protocols generally lacked pulmonary specific treatment components. Content of the enhanced recovery pathways varied from trial to trial, but all patients received a combination of at least three of the following elements: early ambulation, early feeding, protocolised analgesia, early removal of nasogastric tubes, and urinary catheters.

One study included thoracic surgical patients,[32] three included abdominal gastrointestinal tract surgery patients,[27 30 31] and one included older patients with fractured neck of femur.[29] Only one trial included patients receiving laparoscopic abdominal surgery[27]; all other procedures were open, despite the laparoscopic surgical approach being a common feature of enhanced recovery pathways. Protocol compliance was not well reported, and the variability in the application of the principles of enhanced recovery after surgery between trials makes assessing effectiveness difficult. The trial of patients with hip fracture involved randomisation to rapid, expedited medical assessment and corrective surgery, but mobilisation and postoperative care were the same for both groups.[29] This trial was excluded from meta-analysis for methodological heterogeneity. Full details

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Table 5 | Perioperative strategies for reducing postoperative pulmonary complications grouped according to type of intervention

Category of intervention	Included interventions	No of patients	No of RCTs
Incentive spirometry	Incentive spirometry ± deep breathing exercises	1940	6
Prophylactic supervised respiratory physiotherapy	Prophylactic inspiratory muscle training, deep breathing exercise, and mobility programmes, conducted daily under supervision of physiotherapist for ≥3 days, during immediate pre/postoperative period	1345	12
Drug therapies to improve pulmonary function	Inhaled β agonists, inhaled steroid, inhaled mucolytic, prophylactic postoperative antibiotics for respiratory infection, intraoperative magnesium infusion	1032	8
Intraoperative anaesthetic gas composition	High (80%) perioperative fractional inspired concentration of oxygen, nitrous oxide free intraoperative inspired gas mixture	3595	4
Intraoperative ventilation strategies	High PEEP intraoperatively, ventilation strategies targeted to high or low tidal volumes per unit body weight, intraoperative alveolar recruitment strategies, square wave inspiratory flow pattern ventilation	2132	18
Prophylactic non-invasive ventilation	Prophylactic postoperative non-invasive ventilation, continuous positive air pressure, high flow nasal cannula oxygen therapy	1173	10
Analgesia techniques	Thoracic epidural analgesia, patient controlled thoracic epidural analgesia, paravertebral nerve block, preoperative non-steroidal anti-inflammatory drugs, intrapleural local anaesthetic infusion, intrathecal opioid, intraoperative dexmedetomidine infusion	3106	17
Lifestyle modifications	Smoking cessation therapy	571	4
Enhanced recovery after surgery pathways	Protocolised enhanced recovery pathways	519	5
Perioperative fluid administration	Restrictive versus liberal perioperative fluid administration, goal directed haemodynamic therapies	4740	23
Miscellaneous	Spinal *v* general anaesthesia, inhalational *v* intravenous general anaesthesia, breathing system filter, comparison of neuromuscular blocking drugs, perioperative statin use, supraglottic airway *v* endotracheal intubation, perioperative systemic warming, endotracheal tube cuff design	1786	10

PEEP=positive end expiratory pressure; RCT=randomised controlled trial.

of included trials and individual meta-analysis of enhanced recovery after surgery interventions are provided in appendix 2, section 9.

Prophylactic mucolytics

The quality of evidence for prophylactic mucolytics was low. The mucolytic drug ambroxol was investigated in three RCTs including a pooled total of 452 surgical patients.[33-35] Ambroxol reduces the viscosity of bronchial sputum, which may aid clearance. The dose of ambroxol was the same, at 1000 mg, in all studies, varying in duration of daily administration from three to four postoperative days.

Meta-analysis showed a statistically significant benefit from ambroxol in reducing the risk of PPCs (risk ratio 0.40, 0.23 to 0.67), but the pooled sample size was small. Trial sequential analysis showed no firm evidence, indicating a risk of false positive meta-analysis results. Only very limited trial data on drug adverse effects, treatment compliance, pharmacovigilance, and safety were available. Hence, whether ambroxol should be recommended for routine prophylactic use is unclear from these data.

A recent, small study compared intravenous ambroxol, given on the day of surgery and for three postoperative days, against placebo in patients with pulmonary lobectomy.[34] A larger study of 352 patients also found a reduction in PPCs in patients having abdominal surgery, predicated on a difference in atelectasis rather than respiratory infection.[35] A further study, in patients undergoing video assisted thoracic surgery lobectomy or elective colorectal surgery, did not find any significant difference in PPCs between intervention and control groups.[33] Full details of included trials and individual meta-analysis of drug therapies to improve pulmonary function are provided in appendix 2, section 3.

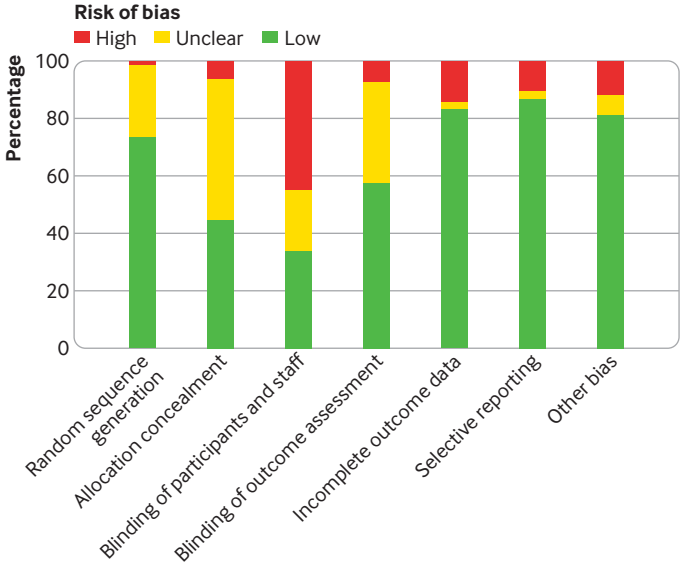

Fig 2 | Risk of bias graph showing each risk of bias item as percentages across all included studies

Prophylactic non-invasive ventilation

The quality of evidence for prophylactic non-invasive ventilation was low. We identified six RCTs investigating single level continuous positive airway pressure[36-41] and two investigating bi-level pressure support ventilation,[42 43] with a pooled total of 437 patients. These modes of ventilatory support use

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Table 6 | Summary of perioperative care strategies with evidence of significant benefit in reducing postoperative pulmonary complications following conventional meta-analysis

Intervention	Relative effect: risk ratio (95% CI)	Quality of evidence
Enhanced recovery pathways	0.35 (0.21 to 0.58; P<0.001; I^2=0%)	Low
Prophylactic mucolytics	0.40 (0.23 to 0.67; P<0.001; I^2=0%)	Low
Postoperative (continuous positive airway pressure) non-invasive ventilation	0.49 (0.24 to 0.99; P=0.05 I^2=48%)	Low
Lung protective intraoperative ventilation	0.52 (0.30 to 0.88; P=0.001; I^2=78%)	Moderate
Prophylactic respiratory physiotherapy	0.55 (0.32 to 0.93; P=0.02; I^2=60%)	Low
Epidural analgesia	0.77 (0.65 to 0.92; P=0.003; I^2=0%)	Low
Goal directed haemodynamic therapy	0.87 (0.77-0.98; P=0.02; I^2=0%)	Moderate

positive pressure to splint open airways and improve work of breathing through improvement in respiratory system compliance and augmentation of inspiratory effort. An additional 330 patients were included in trials of high flow nasal continuous oxygen devices, which were analysed separately.

In the studies of continuous positive airway pressure, a positive end expiratory pressure of at least 8 cm H_2O was applied without interruption for at least eight to 12 hours following extubation or admission to a post-anaesthetic care unit.[36 38] Meta-analysis suggests that starting continuous positive airway pressure prophylactically in the postoperative period for major abdominal and thoracic surgical patients may reduce PPCs (risk ratio 0.49, 0.24 to 0.99); however, included RCTs were small and the cumulative z curve did not cross the calculated trial sequential monitoring boundary. This positive effect on PPC outcomes may therefore may be a false positive, and further trials are likely to change our results. Evidence of a clinical effect was not replicated in trials of bi-level non-invasive ventilation or high flow nasal continuous oxygen, which exerts a similar (but lower magnitude) airway splinting effect to continuous positive airway pressure.[44] The largest trial of bi-level non-invasive ventilation did not show any difference in PPCs between treatment and control groups in thoracic surgical patients.[42]

Four of the studies included only thoracic surgical patients,[37 42 43 45] with two studying patients undergoing thoracoabdominal vascular repairs via a midline laparotomy,[38 41] and two RCTs including elective upper abdominal surgical patients.[39 40] Both trials of high flow nasal cannulas included patients with an intermediate to high predictive risk of PPCs (assessed as an ARISCAT score ≥26[8 46]), with one study recruiting a mixed population of emergency and elective abdominal and thoracic procedures,[28] and one study recruiting only thoracic thoracoscopic lobectomy patients.[45]

All of the included RCTs featured intervention strategies that were started prophylactically on the same day as surgery. Variation was evident in terms of the time between postoperative extubation and start of non-invasive ventilation, the ventilator equipment used, and the intensity and duration of ventilation. Nasal continuous positive airway pressure masks were used in two RCTs[38 41] with face or helmet masks in all other studies. Levels of inspiratory and expiratory

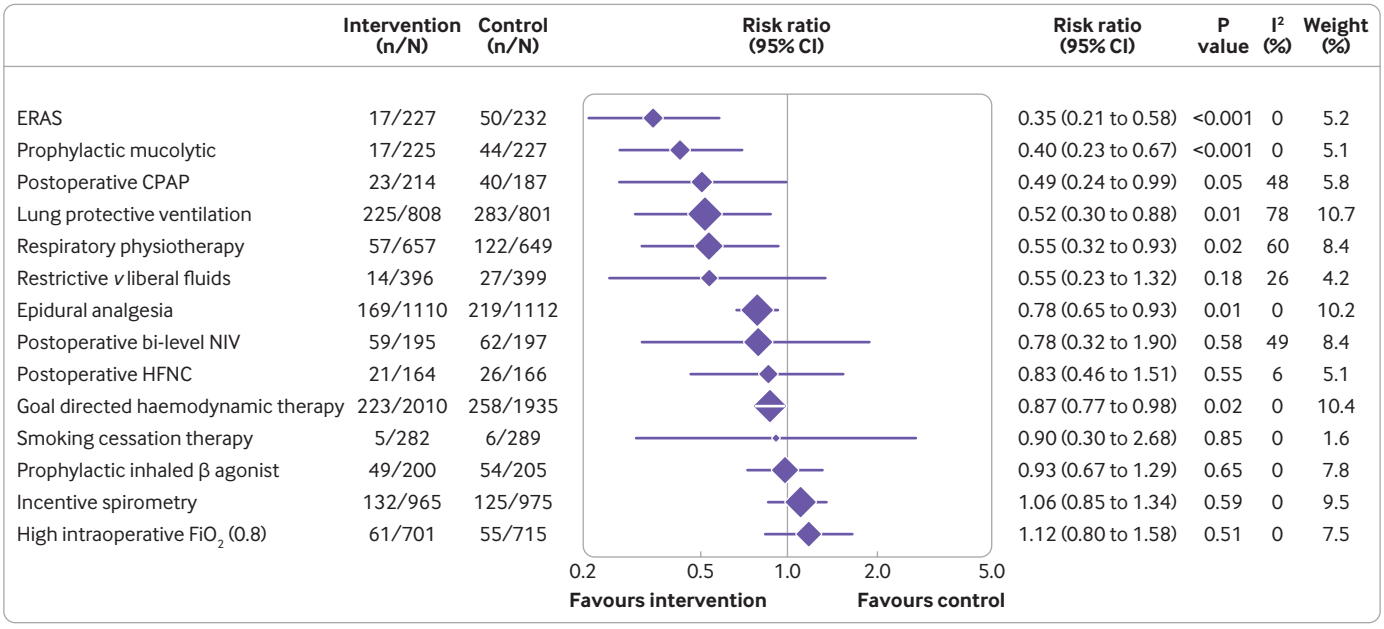

Fig 3 | Forest plot of strategies for efficacy in reducing risk of postoperative pulmonary complications (PPCs). Strategies were tested with standard medical care as control. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; FiO_2=fractional inspiration oxygen; HFNC=high flow nasal cannula; n=number of patients with PPC outcome in each group; N=total number of patients in each group; NIV=non-invasive ventilation

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Table 7 | Results and interpretation of trial sequential analysis, including diversity adjusted relative information size (DARIS), to detect 25% relative risk reduction in postoperative pulmonary complications, with α=5% and power=80%

Category of intervention	Information size in meta-analysis	Trial sequential monitoring boundary crossed	DARIS	Result
Incentive spirometry	1940	No	3055	Inconclusive
Prophylactic supervised respiratory physiotherapy	1345	Yes	6155	Firm evidence
Prophylactic mucolytic	452	No	1888	Inconclusive
FiO_2 0.3 *v* 0.8	1416	No	5346	Inconclusive
Lung protective ventilation	1609	No	6184	Inconclusive
CPAP/BIPAP	437	No	7577	Inconclusive
Epidural	2494	Yes	3058	Firm evidence
Smoking cessation	571	No	20748	Inconclusive
Enhanced recovery after surgery pathways	459	Yes	1653	Firm evidence
Goal directed haemodynamic therapy	3945	Yes	2911	Firm evidence
Restrictive *v* liberal fluids	795	No	9802	Inconclusive

BIPAP=bi-level positive airway pressure; CPAP=continuous positive airway pressure; FiO_2=fractional inspiration oxygen.
Inconclusive results indicate that further trials are likely to influence conventional meta-analysis results or that risk of random error resulting in false positive result exists.

pressure varied, and in the most recent large pragmatic RCT of bi-level positive airway pressure,[42] parameters were defined by responsible physicians, alongside choice of masks, adjustment of ventilator settings, and initial patient set-up. Both trials of high flow nasal cannulas used warmed, humidified circuits provided by the Optiflow system (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand), with oxygen flow rates and fractional inspiration concentration titrated by bedside clinical staff to maintain oxygen saturation at 95% or above.

Duration of ventilatory support ranged from two 120 minute cycles of helmet continuous positive airway pressure on the first postoperative day only to bi-level positive airway pressure provided preoperatively for seven days and then daily during the postoperative inpatient stay.[43] Five of the nine trials involved provision of the intervention for less than 24 hours,[28 36-38 41] and one trial for three days,[40] whereas the remainder continued to provide ventilator support while patients were in hospital.[39 42 43 45] Full details of included trials and individual meta-analysis of prophylactic non-invasive ventilation are provided in appendix 2, section 6.

Lung protective ventilation

Seven RCTs including a pooled total of 1609 participants investigated the effect of lung protective intraoperative ventilation strategies on PPCs.[47-53] The definition of lung protective ventilation varied between trials, but for the purposes of analysis we used a single definition of reduced tidal volumes (≤8 mL/kg) and at least 5 cm H_2O positive end expiratory pressure together with intermittent recruitment manoeuvres. Statistical heterogeneity was high (I^2=78%), and the quality of evidence for this intervention was moderate. Meta-analysis showed a significant treatment effect of lung protective ventilation on PPC outcomes (risk ratio 0.52, 0.30 to 0.88). Although the cumulative z curve crossed the conventional monitoring boundaries, the trial sequential monitoring boundaries were not crossed. Hence, no firm evidence suggested that lung protective ventilation could effect a 25% relative risk reduction in PPCs and further trials are still needed.

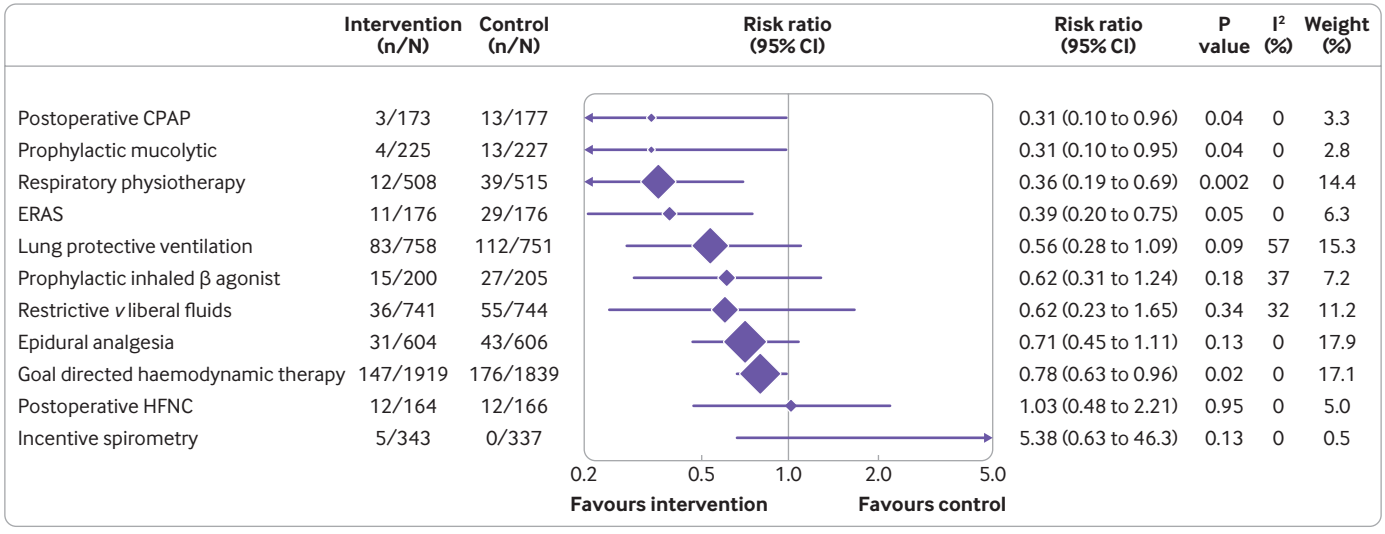

Fig 4 | Forest plot of strategies for efficacy in reducing risk of respiratory infection. Strategies were tested with standard medical care as control. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; HFNC=high flow nasal cannula; n=number of patients with respiratory infection outcome in each group; N=total number of patients in each group

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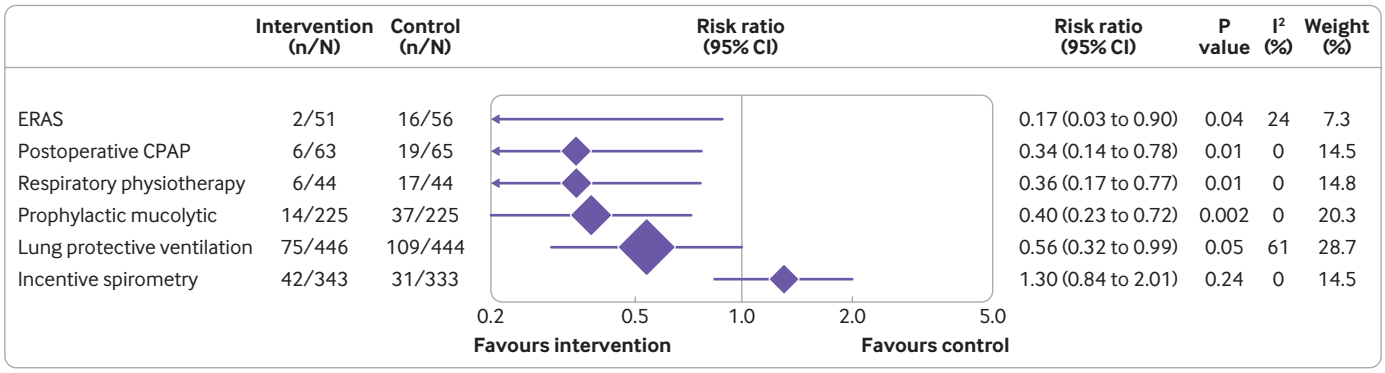

Fig 5 | Forest plot of strategies for efficacy of reducing risk of atelectasis. Strategies were tested with standard medical care as control. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; n=number of patients with atelectasis outcome in each group; N=total number of patients in each group

In total, 18 RCTs investigating different aspects of intraoperative ventilation were identified in this review,[47-64] including a pool of 2171 patients. Seven studies were of patients having open abdominal surgery,[47 49-51 54 56 64] five were of exclusively minimally invasive surgery (laparoscopic or robotic),[52 55 58-60] three were of lung cancer resection surgery (open or thoracoscopic),[48 57 61] one was of neurosurgery,[62] one was obstetric,[53] and one recruited patients from a range of specialties united in having prolonged surgery.[63]

Four studies primarily investigated the role of different levels of positive end expiratory pressure, recruiting a total of 1073 patients. Four studies explored the use of different target tidal volumes, recruiting 244 patients. A single centre study recruited 44 patients having open lung resection, and one lung (the non-dependent one) was either ventilated with high frequency percussive ventilation or received continuous positive airway pressure.[61] Although some mechanistic variables were improved, we saw no reduction in PPC for any of these interventions.

The largest trial was the PROVHILO study,[51] which recruited 894 patients from 30 international hospitals and compared high positive end expiratory pressure (12 cm H_2O) with recruitment manoeuvre versus low positive end expiratory pressure (≤2 cm H_2O) in patients having major abdominal surgery and at increased risk of PPCs. No beneficial treatment effect was found in PROVHILO, but the smaller IMPROVE study randomised 400 patients at increased risk of PPCs and showed a significant reduction in PPCs with lung protective ventilation.[50]

In contrast to the benefit found when protective ventilatory strategies were combined, only one small study of 5 mL/kg versus an 8 mL/kg tidal volume control group during single lung ventilation of patients undergoing minimally invasive oesophagectomy found a reduction in PPCs in the intervention group.[58] Full details of included trials and individual meta-analysis of intraoperative ventilation strategies are provided in appendix 2, section 5.

Respiratory physiotherapy

Respiratory physiotherapists train and supervise patients in sputum clearance, developing inspiratory muscle strength, and deep breathing exercises. Prophylactic application of these techniques may improve respiratory endurance and expel pulmonary secretions, thereby reducing the risk of PPCs. A total of 12 RCTs including a pooled total of 1345 patients undergoing abdominal and thoracic surgical procedures investigated the application of prophylactic supervised respiratory physiotherapy.[65-76] The quality of the evidence was low. Physiotherapy regimens varied between trials and included both preoperative and postoperative interventions. Meta-analysis

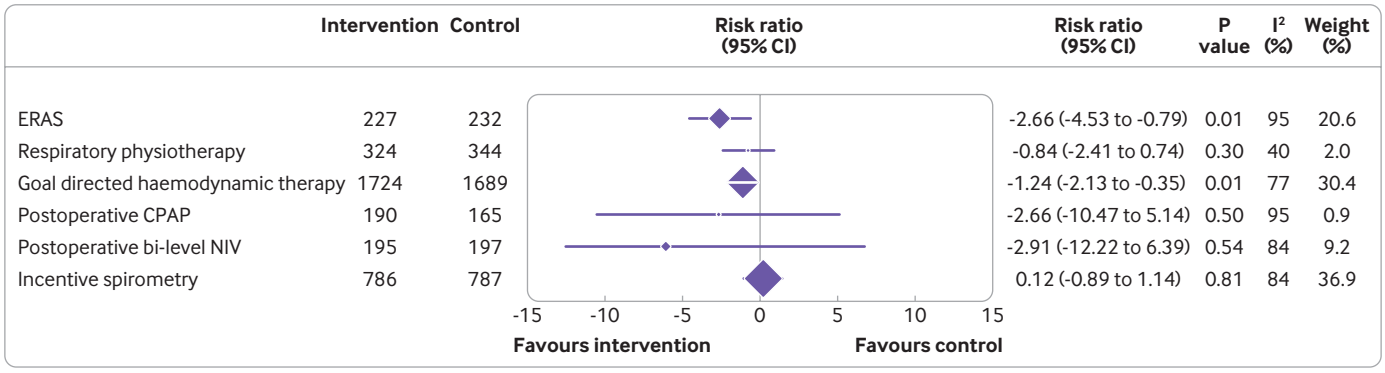

Fig 6 | Forest plot of hospital length of stay for strategies investigated to reduce postoperative pulmonary complications. Strategies were tested with standard medical care as a control. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; NIV=non-invasive ventilation

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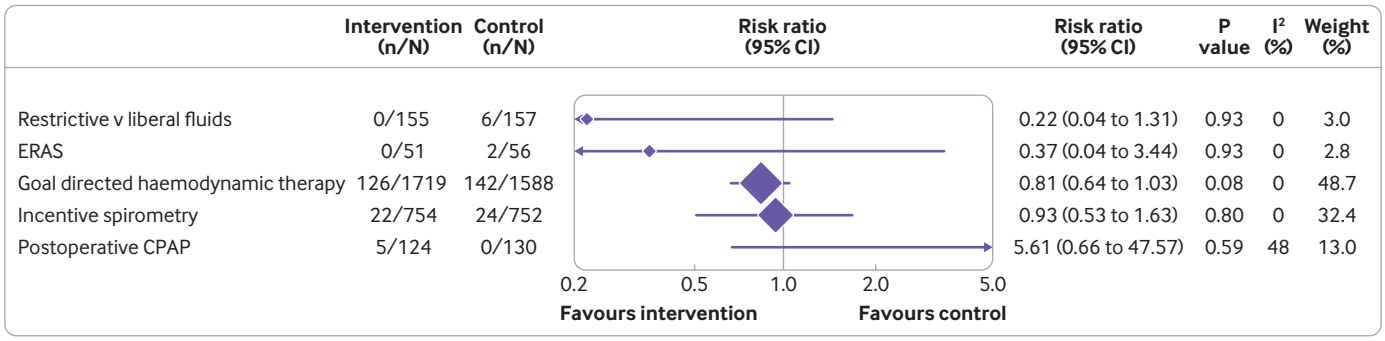

Fig 7 | Forest plot of mortality for strategies investigated to reduce postoperative pulmonary complications. Strategies were tested with standard medical care as control. CPAP=continuous positive airway pressure; ERAS=enhanced recovery after surgery; n=number of patients with mortality outcome in each group; N=total number of patients in each group; NIV=non-invasive ventilation

of pooled results from 11 RCTs showed an overall benefit (risk ratio 0.55, 0.32 to 0.93) of prophylactic physiotherapy in reducing the development of PPCs. Trial sequential analysis supported the meta-analysis findings, indicating that the information size was sufficient to find firm evidence of a 25% relative risk reduction in PPCs.

Risk of bias was high; in particular, overall study quality was reduced by the lack of blinding of patients to intervention allocation, crossover between group allocations (with control group patients receiving physiotherapy ad hoc), and a high loss to follow-up in several of the studies. Furthermore, study sample sizes were small, with only three RCTs featuring intervention or control group sizes of more than 50 patients each.[66 68 71]

Patients undergoing a variety of surgical procedures were studied, including elective thoracic surgery,[71 73 76] elective open abdominal aortic aneurysm repairs,[67] unselected elective open abdominal surgery,[66 70 72] and upper abdominal surgery.[65 68 69 74 75] Only one study included laparoscopic surgical patients (with a corresponding lower reported proportion of PPCs in both intervention and control groups than for other studies),[69] and the remainder were open procedures.

A large variety of physiotherapy regimens were tested in the included studies, although all incorporated instruction and supervision of patients by a trained physiotherapist for at least three preoperative or postoperative days. Three studies included preoperative inspiratory muscle training.[67 70 75] Eight studies including postoperative supervision across a range of deep breathing exercises, coughing exercises, assistance with ambulation, and inspiratory muscle training.[65 66 69 71-74 76] Only one study included patients receiving both preoperative and postoperative exercises supervised by physiotherapists.[68] Comparator groups were standard care only, in which physiotherapy was withheld unless requested by a clinician or unless a PPC developed, with the exception of one study in which low intensity preoperative physiotherapy training was compared with high intensity physiotherapy.[75]

Most (11/12) trials reported no benefit of prophylactic physiotherapy for PPC outcomes. However, the largest and highest quality RCT,[68] which included preoperative and postoperative physiotherapy exercises, showed a significant difference in the proportion of patients developing PPCs after elective major abdominal surgery (10/172 (6%) in the intervention group and 52/192 (27%) in the control group; P<0.001). Full details of included trials and individual meta-analysis of supervised respiratory physiotherapy are provided in appendix 2, section 2.

Epidural analgesia

Eleven studies investigated epidural analgesia against patient controlled analgesia with morphine, with a pooled total of 2494 patients.[77-87] The quality of the evidence was low. Meta-analysis showed a benefit in PPC outcomes with use of epidural analgesia (risk ratio 0.78, 0.65 to 0.93), and the information size was sufficient in trial sequential analysis to draw firm conclusions of a 25% relative risk reduction. Most trials were for abdominal procedures, although two studies included thoracic procedures.[81 83] Variability existed in the time point for starting epidural analgesia, regimens, and constituents of infusion, although epidurals routinely remained in situ for 72 hours postoperatively. The MASTER trial,[81] which focused on surgical patients at high risk, had significant weighting in the meta-analysis (63.5%); if this was removed, the risk reduction with epidurals would not be apparent. Full details of included trials and individual meta-analysis of all analgesic strategies (including epidural analgesia) are provided in appendix 2, section 7.

Goal directed haemodynamic therapy

Goal directed haemodynamic therapy was investigated in 14 studies, with a pooled total of 3945 patients.[88-101] Goal directed haemodynamic therapy involves individualised perioperative fluid, inotrope, or vasopressor administration to achieve pre-defined biological targets (such as calculated oxygen delivery, pulmonary capillary wedge pressure, or cardiac stroke volume variation). Moderate quality evidence showed a small treatment effect (risk ratio 0.87, 0.77 to 0.98); however, the limited data available did not suggest superiority of any specific haemodynamic goal. We found firm evidence of superiority for the goal directed haemodynamic therapies (based on a 25% relative risk

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reduction) in trial sequential analysis. Conversely, we found no significant benefit in our meta-analysis of nine trials of 795 patients for restrictive versus liberal fluid volume based administration strategies.[102-110]

Subgroup analysis of five studies in which goal directed haemodynamic therapy consisted solely for trials of fluid administration interventions (that is, without the additional use of vasoactive drugs) included a pooled total of 557 patients.[91 92 96 97 99] Moderate quality evidence showed a more pronounced treatment effect of goal directed fluid therapy compared with studies in which fluids were used in combination with vasoactive drugs. Full details of included trials and individual meta-analysis of perioperative fluid administration and goal directed haemodynamic therapies are provided in appendix 2, section 10.

Narrative review of miscellaneous interventions

A total of 22 RCTs were identified by the review but were unsuitable for pooling of data with data from other trials either because the interventions were dissimilar or because interventions were evaluated in a single trial only. Full details of all trials are included in appendix 2.

Several interventions were included in the miscellaneous category, including a trial showing a reduction of PPCs (but not respiratory infections) in patients receiving maintenance inhalational anaesthesia (with sevoflurane) compared with those receiving propofol total intravenous anaesthesia for lung cancer surgery.[111] One randomised pilot study measured postoperative complications in older patients having general anaesthesia versus spinal anaesthesia for hip fracture surgery in a single centre in the UK.[112] The study showed no difference in the risk of PPCs between the groups.

The role of neuromuscular blockade during surgery was evaluated in two studies. One RCT investigated the effect of different neuromuscular blocking drugs on residual muscular weakness at the end of surgery and PPCs.[113] A second trial investigated whether sugammadex (at a dose of 2-4 mg/kg) reduced the incidence of PPCs compared with conventional reversal of intraoperative neuromuscular blockade (neostigmine and glycopyrrolate).[114] In the first trial, significantly more patients in the pancuronium group than in the atracurium or vecuronium groups showed residual neuromuscular block. The incidence of PPCs was higher in patients with residual neuromuscular block who received pancuronium, but no significant difference in PPCs was seen in patients with or without residual block for the atracurium or vecuronium groups. The second trial of sugammadex showed no significant difference in PPCs between reversal groups (risk ratio 0.26, 0.03 to 2.27; P=0.22).

Perioperative systemic warming was investigated in more than 60 randomised trials, but only one reported discrete PPC outcomes.[115] This single trial identified no significant difference in PPCs between an intervention group receiving extended perioperative warming and a group receiving intraoperative warming only. Likewise, a trial of different endotracheal tube cuff designs (spherical or taped) in surgical patients did not show any significant difference in PPC outcomes,[116] and nor did a trial on the presence or absence of a breathing system filter during intraoperative ventilation.[117] Two trials investigated whether a supraglottic airway device or endotracheal tube was superior for reducing PPCs in patients undergoing laparoscopic surgery.[118 119] No difference was seen in meta-analysis (risk ratio 3.08, 0.13 to 74.41). Finally, four studies reported on non-epidural analgesic techniques consisting of nerve blocks, intrathecal opiates, and intravenous dexmedetomidine.[120-123] None of the non-epidural analgesic studies reported any difference in PPCs between control and intervention groups. Most of the above trials reported PPCs as a secondary outcome measure only and were underpowered for PPC outcomes.

Discussion

Our study identified 11 categories of perioperative care interventions that have been tested in randomised trials with the aim of reducing PPCs. Our main finding is that despite a huge literature and the clinical prevalence and importance of the outcome, the existing evidence is of generally poor quality and does not give definitive answers. None of the interventions we evaluated was supported by high quality evidence. Only one—goal directed fluid therapy—was supported both by moderate quality evidence and trial sequential analysis. One further intervention—lung protective intraoperative ventilation—was supported by moderate quality evidence, but trial sequential analysis indicated that further data would be needed for us to be confident of this. A further five interventions had low quality evidence of treatment benefit: enhanced recovery pathways, prophylactic mucolytics, postoperative continuous positive airway pressure ventilation, prophylactic respiratory physiotherapy, and epidural analgesia. Trial sequential analysis indicated a risk of false positive results for continuous positive airway pressure and mucolytics for a relative risk reduction of 25%.

Intervention effect sizes

Effect sizes of relative risk reduction for interventions were generally small to moderate (table 8), with the exception of enhanced recovery pathways, for which it was disproportionately large but based on trials with a high risk of bias. Interventions investigated in higher risk cohorts, with a higher baseline proportion of PPCs in controls groups, were more likely to show significant benefit, but the findings may not be generalisable to lower risk cohorts. Given the relatively high prevalence of PPCs (14.4% of all patients included in this review) and their associations with longer term outcomes,[9] the potential effect that effective treatments may offer in improving perioperative healthcare provision is large. PPCs have implications for healthcare costs, primarily as a result of increased length of hospital stay.[124] A retrospective study found that surgical

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patients in a Canadian tertiary hospital who developed postoperative pneumonia had 55% higher costs and 89% longer hospital stays.[125] PPCs therefore represent a major opportunity for improved outcomes for patients and financial savings, with evidence of beneficial preventive measures reducing mortality, morbidity, and the cost of a surgical procedure.

Lung protective ventilation

Lung protective ventilation describes strategies to adjust the ventilator intraoperatively to minimise lung injury. We found a significant treatment effect on PPCs, and despite inclusion of different trials, our effect was consistent with those of other meta-analyses and systematic reviews of lung protective ventilation.[126-130] However, our trial sequential analysis did not find that the accumulated information size was sufficient to draw firm conclusions on a 25% relative risk reduction, so further trials are still needed. Our definition of lung protective ventilation covered a range of interventions that were sufficiently similar to be grouped together: all trials included use of positive end expiratory pressure of at least 5 cm H_2O and tidal volume of no more than 8 mL/kg predicted body weight, and all but one included some form of recruitment manoeuvre (a short period of high pressure applied to the lungs to inflate them more fully).[48] Although recruitment manoeuvres have good physiological rationale for optimising pulmonary compliance, they may cause harm through their effects on the circulation.[131] In the high quality and relatively recent PROVHILO trial (which showed no benefit of lung protective ventilation on the primary outcome of PPCs),[51] any beneficial effects of the recruitment manoeuvres on the lungs were probably outweighed by the adverse effects on the circulation. A disadvantage of comparing two extreme values of positive end expiratory pressure (low versus high) is that each patient may have an optimal positive end expiratory pressure that is neither of these. Aiming to identify optimal positive end expiratory pressure for an individual patient has been evaluated in a proof of concept study,[132] which was followed by a large multicentre RCT (iPROVE, published subsequently to our search dates). iPROVE studied 1012 patients receiving abdominal surgery and at moderate to high risk of PPCs, and no benefit was seen in those receiving individually optimised ventilation.[133] All patients in this study received many of the elements of lung protective ventilation, and, in this context, the additive benefit of optimising positive end expiratory pressure may not be apparent. Although lung protective ventilation is a particularly attractive intervention, as it has no associated financial cost, the fidelity of its implementation in routine practice (as described in large scale audit data from the US and the UK[134-136]) is often disappointing.

Table 8 | Point estimates of number needed to treat (NNT) for interventions with evidence of benefit in reducing postoperative pulmonary complications

Category of intervention	NNT (95% CI)	GRADE quality of evidence
Enhanced recovery after surgery pathways	8 (4.9 to 12.9)	Low
Prophylactic mucolytic	9 (5.5 to 17.8)	Low
Postoperative CPAP	10 (5.6 to 29)	Low
Lung protective ventilation	14 (8.3 to 33.8)	Moderate
Respiratory physiotherapy	10 (7.2 to 15.6)	Low
Epidural analgesia	22 (13.4 to 59.7)	Low
Goal directed haemodynamic therapy	45 (23.3 to 514.1)	Moderate

CPAP=continuous positive airway pressure; GRADE=Grades of Recommendation, Assessment, Development, and Evaluation.

Goal directed haemodynamic therapy

Goal directed haemodynamic therapy aims to improve oxygen delivery to the tissues through the optimisation of end organ perfusion and has moderate quality evidence of a reduction in PPCs. Goal directed haemodynamic therapy can be achieved by the use of vasoactive drugs, fluids, or both, dosed according to the response of specific physiological parameters in individual patients, towards a pre-defined goal. Trials of goal directed haemodynamic therapy have shown a reduction in several postoperative complications, and our meta-analysis confirms this specifically for pulmonary complications. In this study, a subgroup meta-analysis of trials that relied solely on the administration of fluids (goal directed fluid therapy) for haemodynamic optimisation without the use of vasoactive drugs shows a reduction in the risk of PPCs (risk ratio 0.47, 0.32 to 0.71; P=0.001). This finding suggests that goal directed fluid alone, without the addition of vasoactive drugs, also has a protective effect on the lungs.

Trials comparing restrictive and liberal fluid management strategies have shown that restrictive fluid regimens have been associated with an increased risk of acute kidney injury,[137] whereas liberal regimens have been associated with fluid overload and pulmonary congestion, poor wound healing, and paralytic ileus.[91 94 105] Neither liberal nor restrictive fluid strategies are protective against PPCs. Our meta-analysis showed a reduction in length of hospital stay with restrictive fluid regimens, but with a small effect size. Arguably, in many of the included studies, the volumes of fluid administered, even to patients in the restrictive groups, is excessive compared with the volumes administered in the goal directed haemodynamic therapy trials.

A recently published multicentre RCT from Spain (FEDORA,[138] published subsequently to our search dates and therefore not included in the meta-analysis) of goal directed haemodynamic therapy versus standard care in patients at lower risk undergoing major surgery showed a statistically significant reduction in PPCs (and other complications) and reduced length of hospital stay. The benefits were exclusively seen in patients having abdominal surgery, and this is relevant as the ongoing OPTIMISE-II study is exclusively recruiting patients undergoing major gastrointestinal surgery.[139]

Role for care bundles?

Substantial changes in the perioperative care of patients have occurred in the past decade. An

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increasingly popular and evidence based approach to minimise the risk of complications in surgical and medical patients is the adoption of care bundles. Care bundles are collections of evidence based practices (ideally no more than five interventions in one bundle), which when performed together result in better outcomes than when applied individually. Recent research from our group has clarified important principles for care bundles[140]: interventions within a care bundle should reflect best practice, bundles with a small number of simple elements have better compliance rates, bundles should also be used to guide teamwork in achieving care delivery, and measurement of success is binary—all of the individual interventions need to be implemented together in a single patient for delivery of the bundle to be considered compliant. Such bundles have already been shown to reduce some postoperative complications,[141] particularly surgical site infection.[142 143]

Despite care bundles being strongly endorsed for prevention of ventilator associated pneumonia in intensive care,[144 145] evidence for equivalent non-ventilator bundles in perioperative patient care to prevent PPCs is still uncertain.[146] An international Delphi consensus process considered which interventions might best be combined to reduce PPCs,[147] and a UK based, patient centred quality improvement project (ERAS+) used a PPC reduction care bundle with notable success.[148] To date, these care bundles have predominantly included relatively simple and inexpensive interventions, often with imperfect evidence of efficacy. Ideally, the interventions within a care bundle would have robust supportive evidence and interact with each other synergistically. We propose that the evidence from this review be used to guide development of care bundles for prevention of PPCs, although we acknowledge that further research is needed to determine the ideal components of PPC bundles and establish evidence of effectiveness.

Implications for research

The most common reason for RCTs to be excluded from the analysis phase of this review was a lack of reported clinical PPC outcomes, with many trials using more easily measured surrogate recordings such as lung spirometry tests instead. We suggest that clinically detectable pathology, such as PPCs, is more meaningful to patients and should be used to design relevant future research. Trials should use standardised definitions for PPCs, such as the EPCO criteria or the recently published standardised endpoints in perioperative medicine (StEP) initiative PPC definitions.[118]

Likewise, although this review evaluates the best available RCT evidence for PPCs, other forms of evidence are available. For example, the adverse influence of neuromuscular blocking drugs is now well established,[149-153] especially when they are associated with inadequate reversal (a train of four ratio of <0.9). Furthermore, active intraoperative warming, airway suctioning, and choice of airway device are all relevant interventions with an effect on PPCs. However, most of the above interventions have been predominantly studied in observational, rather than randomised, trial designs or with evidence translated from critical care, rather than surgical, patient cohorts. Hence, the pool of randomised studies of adult surgical patients with clinical outcomes for several of the interventions was surprisingly small. The results from this review therefore need to be interpreted in the context of other forms of relevant evidence and clearly indicate a role for large, well designed propensity score studies in best understanding the role of intraoperative interventions that are challenging to study in RCTs.

Strengths and limitations of review

Using robust and standardised methods including GRADE methods and pre-specified analyses, we comprehensive reviewed a vast literature spanning anaesthesia, surgery, and respiratory and intensive care medicine. This included meta-analysis of treatment effects and trial sequential analysis. We used trial sequential analysis to explore the risk of random error as a result of sparse data and repetitive testing in order to increase the robustness of the meta-analyses and distinguish the current information size from the required information size.

However, in our study, and in general, the literature evaluating interventions to reduce PPCs is limited by several factors. The quality of trials was mixed, with only a minority being large, multicentre studies with a low risk of bias. Heterogeneity of trial design and outcome measures used, and variation in surveillance fidelity and diagnostic classifications for PPC outcomes, pose a problem for evidence synthesis. We anticipated heterogeneity and used random effect model analysis and trial sequential analysis to provide conservative estimates of treatment effects and reduce false positives.

As a composite measure, PPCs do not convey the precise nature of complications that are experienced by patients. One intervention may have a relatively larger effect on atelectasis than on respiratory infection, for example. For this reason, we specifically evaluated the individual outcomes of respiratory infection, atelectasis, mortality, and length of hospital stay in our meta-analyses.

The quality of the literature we evaluated was also limited by imprecise and varying descriptions of the interventions. We identified significant heterogeneity in several aspects of the included trials, such as precise terms, timings and limits of tested interventions, characteristics of participants in trials, surgery type, outcome measurement timings and definitions, and other factors that might influence PPCs such as fluid therapy, analgesia types, and smoking status. This information was also not universally available for the patients included in the trials we analysed.

We have focused on the evidence of efficacy in reducing PPCs and not taken into consideration other factors that would be necessary to evaluate effectiveness or whether these interventions would be suitable to introduce, either in isolation or within a "care bundle." The breadth of this review, in terms

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of number of trials and range of interventions studied, necessarily meant that we were unable to compare individual adverse effects. Adverse effects were often intervention specific and lacked a common outcome framework between trials. We have also not considered the costs of the interventions, nor their tolerance, concordance, or acceptability for patients.

Conclusions

We have shown that the best quality evidence is in favour of lung protective ventilation and perioperative goal directed haemodynamic therapy in reducing PPCs. Some interventions that are commonly used, sometimes within care bundles, lack supportive evidence. Despite a large number of patients enrolled in many studies in this area, the evidence base is often of low quality and is both diverse and conflicting.

Several large trials that are in progress, or soon to start, will add to our understanding of the role of perioperative goal directed haemodynamic therapy, continuous positive airway pressure, and inspiratory muscle training.[139 154 155] Although it is challenging, trialists should attempt to use standardised endpoints (for both efficacy and adverse effects) and consider aspects relating to the cost and acceptability of interventions. These data are needed to enable the best synthesis of the evidence for making recommendations and informing clinical practice.

Contributors: SRM, PMO, and SB had the idea for the study. PMO and SB designed the search strategy. PMO, SB, and DG screened abstracts and full texts, acquired data, and assessed risk of bias in studies. PMO did the data analysis. SRM and BCB helped to coordinate the review and critically reviewed the manuscript. All authors interpreted the data analysis. PMO wrote the manuscript, with revisions from all authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PMO is the guarantor.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination: We plan to disseminate the results of the published study widely through traditional media and social media, using the communications offices of our respective hospitals and universities. Other dissemination includes presentation at scientific meetings. We have no way of directly contacting the original trial participants. No plans exist to involve members of the public in dissemination. However, for this paper we are expanding our dissemination by writing a *BMJ* perspective article with a patient about our research

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