Standardised endpoints for pulmonary complications in perioperative medicine research

Running title: Better measures of improved pulmonary outcome

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Summary

Background

There is a need for robust, clearly defined, patient-relevant outcome measures for use in large clinical effectiveness trials in perioperative medicine. Our objective was to establish standard clinical outcome measures for research into the prevention and treatment of perioperative respiratory complications.

Methods

A systematic literature search was conducted using MEDLINE, Web of Science, SciELO and the Korean Journal Database. Definitions were extracted from included manuscripts. We then conducted a three-stage Delphi consensus process to select the optimal outcome measures in terms of methodological quality and overall suitability for perioperative trials.

Results

From 2358 records, the full texts of 81 manuscripts were retrieved, of which 44 met the inclusion criteria. We identified three main categories of outcome measure specific to perioperative pulmonary outcomes: 1) composite outcome measures of multiple pulmonary outcomes (27 definitions); 2) pneumonia (12 definitions); and 3) Respiratory failure (6 definitions). These were rated by the group according to suitability for routine use. The majority of definitions were given a low score, and many were imprecise and/or difficult to apply consistently in large patient populations. A smaller number of highly rated definitions were identified as appropriate for widespread use. The group recommended four outcome measures, some with modifications, for future use.

Conclusions

A wide variety of pulmonary outcome measures have been used in perioperative care research but many are poorly defined. We recommend four outcome measures, which should meet the needs of most clinical effectiveness trials of treatments to improve post-operative pulmonary outcomes.

Introduction

Each year more than 300 million patients undergo surgery worldwide.[1, 2] Estimates of attributable mortality vary from 1 to 4%, however some studies suggest that more than one in five deaths occur in a small group of high-risk patients.[1, 3-6] Even when complications are successfully treated, these are still associated with reduced long term survival.[7] Some of the most common post-operative complications affect the respiratory tract, with incidences ranging from 9 to 40%, depending on the definition used.[8-11] A number of factors may promote pulmonary complications amongst patients undergoing major surgery. Anaesthesia can cause reduced vital capacity, hypoxemia and impaired central respiratory drive, while surgical manipulation can restrict ventilation, damage respiratory muscles and cause atelectasis.[12] When combined with pre-existing respiratory disease and postoperative pain, the risk of pneumonia, respiratory failure and death is increased.[10] There is a need for large, high quality clinical trials to improve the treatment of patients at risk of post-operative pulmonary complications.

The impact of any large clinical trial is critically dependent on the use of well-defined outcome measures, which must be patient-centred and important as well as potentially modifiable by the trial intervention.[13, 14] Inconsistent reporting of outcomes across trials investigating similar clinical problems hinders the interpretation of new research findings in the context of existing research evidence, and prevents the use of pooled data in systematic reviews.[14] Many definitions are similar but not sufficiently so to allow robust comparison. There is a need for a standardised list of clearly defined clinical outcome measures for use in large, pragmatic clinical trials in this field. This would help investigators to improve the design of clinical trials through the use of recognised reference standards. This should lead to a stronger evidence base to inform clinical practice and improve long-term outcomes after surgery.

The Standardized Endpoints for Perioperative Medicine (StEP) collaboration was established to evaluate the literature and create standards for the definition and use of outcome measures in clinical effectiveness research in perioperative medicine, addressing the need for greater precision and consistency in defining outcomes for perioperative clinical trials.[15] As part of this initiative, we performed a systematic literature review of clinical trials and observational studies of pulmonary outcomes in perioperative care.

Methods

Members of the group were recruited to better understand and improve the pulmonary morbidity, which occurs during and after surgery. We performed a systematic literature review to identify studies with relevant clinical outcome measures that should be considered for future use in clinical trials. The group then evaluated these outcomes to decide which should be considered as evidence in a wider evaluation of clinical outcome measures in all areas of perioperative medicine.

Search Strategy

MEDLINE, Web of Science, SciELO and the Korean Journal Database were searched electronically from the year 2005 to present using the Web of Science (Thomson Reuters) platform. The search strategy was: TS=(((Pneumonia[Title/Abstract] OR Respiratory[Title/Abstract] OR Pulmonary[Title/Abstract] OR "Pulmonary Complications"[title/abstract] OR "Respiratory complications"[title/abstract] OR Hypoxia[Title/Abstract] OR "Lower Respiratory Tract"[Title/Abstract] OR Re-Intubation[Title/Abstract] OR "Prolonged Ventilation"[Title/Abstract] OR "Respiratory Failure"[Title/Abstract] OR "Pulmonary Oedema"[Title/Abstract] OR "Respiratory Distress Syndrome"[Title/Abstract] OR "postoperative pulmonary complications"[title/abstract] OR "Acute Lung Injury"[Title/Abstract])) OR ("Lung Injury" OR "Pneumonia" OR "Pulmonary Edema" or "Respiratory Distress Syndrome" OR Pneumothorax OR "Respiratory Aspiration"[MeSH Terms])) AND TS=("Hospital Mortality" OR "Mortality" OR "Morbidity" OR "Prognosis" OR "Perioperative care" OR "Intraoperative Complications" OR "Fatal Outcome" OR "Postoperative Complications" OR "Outcome Assessment Health Care" OR "Outcome and Process Assessment Health Care" OR "Treatment Outcome") AND TS=(Mortality OR Morbidity OR Outcome OR "Postoperative Complications" OR "Prognosis" OR "Perioperative Complications" OR "Intraoperative Complications") AND TS=(("Surgical Procedures" OR "Operative" OR "Surgery" OR "General Surgery" OR "Operation") AND "Postoperative Complications"). Search results were limited to those that were observational trials, randomised controlled trials and meta-analyses conducted in adult subjects. The bibliography of evaluable studies and other selected papers were searched manually for potentially relevant citations.

Study selection criteria

Records were held within a record management system (Mendeley, London, UK*)* and duplicates were removed. The title and abstract of remaining records were then reviewed independently by two researchers. The full text paper of records identified as potentially relevant were downloaded and further assessed. Full texts were selected for inclusion if the study design was that of an observational study with prospective patient recruitment, a randomised controlled trial or a meta-analysis and

reported a respiratory outcome as the primary outcome measure. Articles were excluded if they included paediatric participants (<18 years of age), had a primary outcome unrelated to the respiratory system, or did not provide a primary outcome definition. Differences in opinion were resolved by referral to a third researcher.

Data Extraction

Data were extracted from the selected articles by two researchers acting independently. Data was extracted into a database (Excel 2007, Microsoft, USA) and included lead author name, year of publication, number of participants (and papers for meta-analyses), primary outcome measure and definition of primary outcome measure.

Delphi Process

The results of this systematic review informed a Delphi consensus process to obtain input and consensus from a group of medical and other health researchers with experience in anaesthesia and perioperative medicine trials.[16, 17] The StEP Working Group consisted of experienced perioperative trialists and other investigators from various countries and was overseen by a steering committee (see supplementary online material). Each Delphi round was coordinated by the Health Services Research Centre of the Royal College of Anaesthetists in the UK or the Research Unit of the Department of Anaesthesia and Perioperative Medicine at the Alfred Hospital in Melbourne, Australia. The item scores and number of respondents was recorded for each of the above Delphi rounds in an Excel spreadsheet, and then converted to an SPSS database for calculation of final median and range scores, and consensus rates.

Stage 1: Literature search to develop preliminary list of trial endpoints and definitions

Publications identified in the literature search were used to create a preliminary list of outcome measures and their definitions (Figure 1 and Supplementary table 1).

Stage 2: Formal rating of the recommendations (Delphi round one)

We extracted the outcome measures from manuscripts identified in our literature search, and then created summary tables in different categories, allowing easy comparison of outcome measure definitions. We circulated these tables within the Pulmonary StEP theme group and asked members to submit their ratings via an online form. Manuscripts were first evaluated by using a 'traffic light' scale (green / amber / red) for methodological quality, and overall suitability as endpoints in the context of perioperative trials. This rating encompassed validity, reliability, ease of use, and frequency

of use in the perioperative literature. Where two or more alternative definitions were very similar, we promoted use of the more precise and detailed alternative(s). Definitions that had been superseded or were clearly out of date were categorised as red.

Stage 3: Delphi round two

The second Delphi round included participants from the entire StEP Working Group (n=75). Participants were asked to score each of the items listed using a scale of 1 to 9, with 1 to 3 labelled "Not that important or invalid", 4 to 6 labelled "Important but requires revision", and 7 to 9 labelled "Critical for inclusion".[18, 19] Participants were given the option to select "unsure" if they were unable to offer an opinion as to which category to apply to the item. Participants were invited to suggest any other endpoints, or definitions, or modifications to existing definitions that they believed should be included. A reminder email was sent to ensure prompt completion of the survey. The final numbers of respondents and item completions were recorded. The number of participants who scored the item and the median, and interquartile range of scores were quantified. Members of the Pulmonary StEP theme group were then invited to discuss the results via email. Any items not rated as critical (i.e., 70th centile score <7) but still with a median score of 7 or greater were retained for consideration in the second round. Lower-rated endpoint items identified for removal could be retained if they were considered as critical by any group member for the second round. Items with a median score of ≤3 were not retained.

Stage 4: Delphi round three and final recommendations

Delphi round three included members of the Pulmonary StEP theme group (n=14). The summary results of the above process were provided to these participants, inviting further comments. If responses to this final stage suggested a need for further modification to endpoint definitions, then this was resolved by the authors via email discussion.

Results

Study selection

We identified 2366 records from the electronic search strategy, a further 13 records through other sources. After removal of duplicates, 2358 records remained. The full texts of 81 manuscripts were retrieved, of which 44 met the inclusion criteria. A summary of article selection is shown in Figure 1. A summary of full texts excluded after review, with reason for exclusion, is shown in the supplementary table. The characteristics of included studies are summarised in Table 1. We identified three main categories of outcome measure specific to pulmonary outcomes in perioperative medicine 1) composite outcome measures including a number of pulmonary outcomes (27 definitions); 2) pneumonia (12 definitions); 3) Respiratory failure (five definitions). These are summarised in tables 2, 3 and 4, along with the rating (red / amber /green) given by the group and a summary definition of each outcome measure.

Post-operative pulmonary complications

Despite a large number of candidate definitions, the group was unable to reach a consensus on the best definition of post-operative pulmonary complications. Many definitions employed component definitions, which differed widely in severity and underlying biological mechanism e.g. atelectasis and Acute Respiratory Distress. After a discussion, and having sought advice from the StEP steering committee, we have recommended a new definition which allows lower severity pulmonary events to be captured as part of the overall clinical outcome (Box 1).

Respiratory failure

The group recommended two definitions covering overlapping patient scenarios. The Berlin definition of Acute Respiratory Distress Syndrome was recommended, again because this is a widely used international standard, which has already been carefully developed in a consensus process. The group also recommended a slightly adapted version of a definition reported by Fernandez-Perez,[20] which describes re-institution of mechanical or non-invasive ventilation after extubation (Box 2).

Pneumonia

Only the US Centers for Disease Control definition was recommended.[21] Whilst there are numerous other well-written definitions, there seemed little value in departing from such a widely used international standard (Box 3).

Discussion

We have summarised and evaluated a range of definitions used to describe pulmonary outcomes in perioperative medicine research. Many definitions were imprecise, or difficult to apply consistently in large patient populations because of the requirement from resource intensive diagnostic tests (e.g. bronchoscopy). The composite outcome of post-operative pulmonary complications was widely used, but the group was concerned about the lack of equivalence of component outcomes and the differing biological mechanisms, which may cause these. We therefore propose a new definition for this outcome. The group also recommended one outcome to describe pneumonia and two outcomes to describe respiratory failure.

The adverse events identified do not represent a comprehensive list of all that may occur. Instead, we have focused on those considered most important in a mixed population of surgical patients and relevant to perioperative care as opposed to specific technical complications of surgery or anaesthesia. In some cases, we did not identify existing research which utilised outcomes that would be considered important. An example is pulmonary thromboembolism, which can only be reliably detected through screening of all participating patients in a given trial. Some outcomes may be more appropriate for use in smaller studies or early phase trials e.g. Clinical Pulmonary Infection Score.[22] As previously noted, the physiological changes that follow surgery and anaesthesia, including the systemic inflammatory response, may result in partial compliance with the criteria for a number of outcome measures, in particular atelectasis. We note that reports relating to perioperative medicine are not easily identified through a literature search because there is no standard approach to the use of MeSH terms by authors of perioperative medicine research articles. There is an argument to create a new MeSH heading of 'perioperative medicine' to ensure that trials in this field are more easily identified.

Conclusions

We have summarised and evaluated a wide range of definitions used to describe pulmonary outcomes in perioperative medicine research. This work represents part of an international initiative to improve the definition and use of outcome measures in clinical effectiveness trials in perioperative medicine. These projects include the recent work by the European Society of Anaesthesiology and European Society of Intensive Care Medicine joint taskforce on perioperative outcome measures,[21] and the Core Outcome Measures in Perioperative and Anaesthetic Care (COMPAC) project which is part of the Core Outcome Measures in Effectiveness Trials (COMET) initiative.[23]

Authors Contributions

All authors contributed to protocol design, data acquisition, analysis and preparation of the manuscript.

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Declaration of Interest

RP holds research grants, and has given lectures and/or performed consultancy work for Nestle Health Sciences, BBraun, Medtronic, Glaxo Smithkline, Intersurgical, and Edwards Lifesciences, and is a member of the Associate editorial board of the British Journal of Anaesthesia. All other authors declare no conflicts of interests. MGA has given lectures and/or performed consultancy for Drägerwerk AG, Lübeck, Germany, and Ventinova Ltd, Eindhoven, Netherlands. BCB has undertaken consultancy work for Boehringer Ingelheim and Pfizer. MG is an elected council member of the Royal College of Anaesthetists. All other authors declare they have no conflicts of interest. MM is an elected Council Member of the Royal College of Anaesthetists; Editorial Board Member British Journal of Anaesthesia; his Chair at UCL is endowed by Smiths Medical.

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Figure legends

Figure 1. Selection of papers for consideration in the consensus discussion.

Box 1. Recommended definition of post-operative pulmonary complications.

Post-operative Pulmonary complications

Mechanism

Composite of respiratory diagnoses that share common pathophysiological mechanisms including pulmonary collapse and airway contamination:

- Atelectasis detected on computed tomography or chest radiograph
- Pneumonia using US Centers for Disease Control criteria
- Acute Respiratory Distress Syndrome using Berlin consensus definition
- Pulmonary aspiration

Severity

None: Planned use of supplemental oxygen or mechanical respiratory support as part of routine patient care, but not in response to a complication or deteriorating physiology

Mild: Supplemental oxygen <0.6 FiO_2

Moderate: Supplemental oxygen ≥0.6 FiO_2 and/or requirement for high-flow nasal oxygen

Severe: Unplanned non-invasive mechanical ventilation, Continuous Positive Airways Pressure (CPAP), or invasive mechanical ventilation requiring endotracheal intubation

Exclusions

Other diagnoses that do not share a common biological mechanism are best evaluated separately and only when clearly relevant to the treatment under investigation:

- Pulmonary embolism
- Pleural effusion
- Cardiogenic pulmonary oedema
- Pneumothorax
- Bronchospasm

Box 2. Recommended definition of post-operative pneumonia.

US Centers for Disease Control definition of pneumonia

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

(1) New or progressive and persistent infiltrates (2) consolidation (3) cavitation; AND at least one of the following:

1. fever (>38^{o}C) with no other recognised cause
2. leucopaenia (white cell count <4 x 10^{9} L^{-1}) or leucocytosis (white cell count >12 x10^{9} L^{-1})
3. for adults >70 years old, altered mental status with no other recognised cause;

AND at least two of the following:

1. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
2. new onset or worsening cough, or dyspnoea, or tachypnoea
3. rales or bronchial breath sounds
4. worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)

Box 3. Recommended definition of post-operative respiratory failure.

Berlin definition of Respiratory Distress Syndrome
Timing: Within one week of a known clinical insult or new or worsening respiratory symptoms and…

Chest imaging: Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules and…

Origin of oedema: Respiratory failure not fully explained by cardiac failure or fluid overload (requires objective assessment, e.g. echocardiography, to exclude hydrostatic oedema), and…

Oxygenation: Mild. PaO_2:FiO_2 between 26.7 and 40.0kPa (200–300mmHg) with PEEP or CPAP ≥5 cmH_2O. Moderate. PaO_2:FiO_2 between 13.3 and 26.6 kPa (100–200 mmHg) with PEEP ≥5 cmH_2O. Severe. PaO_2:FiO_2 ≤13.3 kPa (100 mmHg) with PEEP ≥5 cmH_2O.

Mechanical ventilation
The need for mechanical ventilation for more than 24 hours after surgery, or the need for re-institution of mechanical ventilation after extubation. The inclusion of non-invasive ventilation may also be considered.

Table 1. Studies included in the Delphi process

Name of lead author	Year	Type of study	Sample size (n)	Primary outcome measure
Agostini et al[24]	2010	Prospective observational study	234	Postoperative pulmonary complications
Akutsu et al[25]	2010	Prospective observational study	86	Postoperative pneumonia
Bagyi et al[26]	2009	Case-control study	23	Pneumonia
Barrera et al[27]	2005	Prospective observational study	300	Postoperative pulmonary complications
Bellinetti et al[28]	2006	Prospective observational study	70	Postoperative respiratory complications
Bouza et al[29]	2008	Randomised controlled trial	714	Ventilator associated pneumonia
Camp et al[30]	2009	Prospective observational study	2211	Early extubation
Canadian Orthopedic trauma[31]	2006	Randomised controlled trial	315	Acute respiratory distress syndrome
Canet et al[32]	2010	Prospective observational study	2464	Postoperative pulmonary complications
Casado et al[33]	2010	Prospective observational study	45	Respiratory complications
Cassidy et al[34]	2013	Before/After improvement study	1819	Postoperative pneumonia
Dronkers et al[35]	2008	Pilot randomised controlled trial	20	Postoperative pulmonary complications
Fernandez-Perez et al[20]	2009	Case-control study	4420	Respiratory failure
Futier et al[36]	2013	Randomised controlled trial	400	Major pulmonary complications
Galvao Serejo et al[37]	2007	Prospective observational study	266	Postoperative pulmonary complications
Grant et al[38]	2015	Meta-analysis	16 studies (1054 patients)	Postoperative pulmonary complications
Guimaraes et al[39]	2009	Meta-analysis	11 studies (1160 patients)	Pulmonary complications
Haines et al[40]	2013	Prospective observational study	72	Postoperative pulmonary complications
Hemmes et al[41]	2014	Randomised controlled trial	900	Postoperative pulmonary complications
Hodari et al[42]	2013	Prospective observational study	971455	Postoperative respiratory outcomes
Hortal et al[43]	2009	Prospective observational study	1844	Ventilator associated pneumonia
Hulzebos et al[44]	2006	Randomised controlled trial	279	Postoperative pulmonary complications
Ireland et al[11]	2014	Meta-analysis	10 studies (709 patients)	Major respiratory complications
Jammer et al[21]	2015	Systematic review	-	Various pulmonary outcomes
Jiao et al[45]	2015	Prospective observational study	92	Ventilator associated pneumonia
Ladha et al[46]	2015	Prospective observational study	69265	Postoperative respiratory complications
Li et al[47]	2012	Prospective observational study	61	Postoperative pulmonary complications
Lunardi et al[48]	2014	Randomised controlled trial	137	Postoperative pulmonary complications
Mackay et al[49]	2005	Randomised controlled trial	56	Postoperative pulmonary complications

Markar et al[50]	2009	Prospective observational study	202	Postoperative pneumonia
McAlister et al[51]	2005	Prospective observational study	1055	Postoperative pulmonary complications
Muehling et al[52]	2008	Pilot randomised controlled trial	58	Postoperative pulmonary complications
Nascimento Junior et al[53]	2014	Meta-analysis	11 studies (1160 patients)	Pulmonary complications
Nicholos et al[54]	2014	Quasi-experimental study	300	Ventilator associated pneumonia
Paisani et al[55]	2012	Prospective observational study	137	Postoperative pulmonary complications
Perkins et al[56]	2014	Randomised controlled trial	179	Acute lung injury
Scholes et al[57]	2009	Prospective observational study	273	Pulmonary complications
Schussler et al[58]	2006	Prospective observational study	168	Postoperative pneumonia
Schussler et al[59]	2008	Prospective observational study	478	Postoperative pneumonia
Severgnini et al[22]	2013	Randomised controlled trial	56	Clinical pulmonary infection score
Squadrone et al[60]	2005	Randomised controlled trial	209	Endotracheal intubation
Vidotto et al[61]	2011	Prospective observational study	317	Postoperative pulmonary complications
Yang et al[62]	2011	Prospective observational study	122	Postoperative pulmonary complications
Zarbock et al[63]	2009	Randomised controlled trial	500	Postoperative pulmonary Complications

Table 2. Alternative definitions of 'Postoperative pulmonary complications' identified in the literature search.

Includes composite respiratory outcomes recorded as: 'postoperative pulmonary complications', 'major pulmonary complications', 'major respiratory complications', 'postoperative respiratory complications', 'postoperative respiratory outcomes', 'pulmonary complications' or 'respiratory complications'.

Lead author	Outcome measure	Definition	Round 1	Round 2	Round 3
Agostini et al[24]	Postoperative Pulmonary Complications	Four or more of: atelectasis or consolidation on chest x-ray; white cell count >11.2x10^9/L or administration of respiratory antibiotics postoperatively (in addition to prophylactic antibiotics); temperature >38^{o}C; signs of infection on sputum microbiology; purulent sputum differing from preoperative status; oxygen saturations <90% on room air; physician diagnosis of pneumonia; or prolonged HDU stay or readmission to HDU or ITU for respiratory complications	Red	-	-
Barrera et al[27]	Postoperative Pulmonary Complications	Any of: respiratory failure requiring intensive care admission and/or intubation; pneumonia (new pulmonary infiltrate with fever treated with intra-venous antibiotics); atelectasis requiring bronchoscopy (need determined by the surgical team); pulmonary embolism (diagnosed by computed tomography scan and treated); and need for supplemental oxygen at hospital discharge.	Red	-	-
Bellinetti et al[28]	Postoperative Respiratory Complications	Any of: pneumonia (core temperature over 38°C, radiological signs of pulmonary consolidation, and productive cough); atelectasis with evident clinical repercussions; bronchospasm; prolonged mechanical ventilation; pleural effusion or pneumothorax; surgical re-intervention caused by inadequate lung re-expansion; or death related or not to pulmonary disease.	Amber	-	-
Canet et al[32]	Postoperative Pulmonary Complications	Any of: respiratory infection (antibiotics for a suspected respiratory infection and at least one of: new or changed sputum, new or changed lung opacities, fever, leucocyte count >12,000/µ), respiratory failure (postoperative PaO_2 <60 mmHg on room air, a ratio of PaO_2 to inspired oxygen fraction <300, or pulse oximetry <90% and requiring oxygen therapy), pleural effusion (chest x-ray demonstrating blunting of the costo-phrenic angle, loss of the sharp silhouette of the ipsilateral hemi-diaphragm when upright, displacement of adjacent anatomical structures, or a hazy opacity in one hemithorax with preserved vascular shadows when supine), atelectasis (lung opacification with a shift of the mediastinum, hilum or hemi-diaphragm, and compensatory over inflation in the adjacent non-atelectatic lung), pneumothorax (air in the pleural space with no vascular bed surrounding the visceral pleura), bronchospasm (newly detected expiratory wheezing), or aspiration pneumonitis (acute lung injury after the inhalation of regurgitated gastric contents).	Green	Median score 7 44/75 scored ≥7	?

Casado et al[33]	Respiratory Complications	Any of: pneumonia confirmed by a positive culture result (endotracheal aspiration or blood sample) or chest X-ray; acute lung injury (PaO_2/FiO_2 <300), or adult distress respiratory syndrome (ARDS) (PaO_2/FiO_2 <200 regardless of the level of positive end-expiratory pressure, pulmonary capillary wedge pressure <18 mmHg or bilateral infiltrates consistent with pulmonary oedema without clinical evidence of left ventricular failure) according to the American–European Consensus Conference (1994).	Red	-	-
Dronkers et al[35]	Postoperative Pulmonary Complications	Operationalized as atelectasis, which is considered a 'precursor' of more clinically relevant postoperative pulmonary complications. A blinded radiologist evaluated radiographs of the lung base for the presence of atelectasis.	Red	-	-
Futier et al[36]	Major Pulmonary Complications	Pneumonia defined according to standard criteria or the need for invasive or non-invasive ventilation for acute respiratory failure.	Red	-	-
Galvao Serejo et al[37]	Postoperative Pulmonary Complications	Any of: pneumonia (presence of new or progressive pulmonary infiltration on chest x-ray associated with at least two of: purulent trachea-bronchial secretion, elevated temperature >38.3°C or increased blood leucocytes (>25% of base count); atelectasis (pulmonary atelectasis on chest x-ray associated with acute respiratory symptoms without fulfilling the criteria for pneumonia); pleural effusion (excessive fluid in the pleural space, detected by clinical examination and chest radiograph, requiring percutaneous intervention); acute respiratory failure (acute deficiency of gas exchange requiring mechanical ventilation). If patients with pneumonia developed respiratory failure they would be included only in the group ''acute respiratory failure''.	Amber	-	-
Grant et al[38]	Postoperative Pulmonary Complications	Any of: acute lung injury, pulmonary infection or atelectasis, as defined by the individual studies included in the meta-analysis.	Red	-	-
Guimaraes et al[39]	Pulmonary Complications	Any of: i) atelectasis (radiographic, tomographic, or bronchoscopic diagnosis in patients whose clinical signs were acute respiratory symptoms such as dyspnoea, cough, wheeze); ii) respiratory failure (radiographical diagnosis in patients with signs of acute respiratory symptoms such as tracheobronchial purulent secretions, fever (>38°C), or increased white blood cell count (>10,000/mm^3) or; iii) tracheobronchial infection or pneumonia.	Red	-	-

Haines et al[40]	Postoperative Pulmonary Complications	Four or more of: Chest radiograph report of collapse/consolidation; oral temperature >38°C on more than one consecutive postoperative day; pulse-oximetry (SpO_2) <90% on more than one consecutive postoperative day; production of yellow or green sputum different to pre-operative assessment; infection on sputum culture report; unexplained white cell count >11×10^9/L or antibiotic therapy for respiratory infection; new abnormal breath sounds on auscultation different to preoperative assessment; or physician diagnosis of postoperative pulmonary complication.	Red	-	-
Hemmes et al[41]	Postoperative Pulmonary Complications	Any of: hypoxaemia, severe hypoxaemia, bronchospasm, suspected pulmonary infection, pulmonary infiltrate, aspiration pneumonitis, development of acute respiratory distress syndrome, atelectasis, pleural effusion, pulmonary oedema caused by cardiac failure, and pneumothorax.	Green	Median score 6 32/75 scored ≥7	?
Hodari et al[42]	Postoperative Respiratory Outcomes	Respiratory outcomes tracked in NSQIP: re-intubation (placement of an endotracheal tube and mechanical or assisted ventilation due to respiratory or cardiac failure manifested by severe respiratory distress, hypoxia, hypercarbia, or respiratory acidosis within 30 days of surgery); postoperative pneumonia (one of two criteria: Criterion 1: rales or dullness to percussion on physical examination of chest plus: 1) new onset of purulent sputum or change in character of sputum; or 2) organism isolated from blood culture; or 3) isolation of pathogen from specimen obtained by trans-tracheal aspirate, bronchial brushing, or biopsy. Criterion 2: chest x-ray shows new or progressive infiltrate, consolidation, cavitation, or pleural effusion and any of: 1) new onset of purulent sputum or change in character of sputum; or 2) organism isolated from blood culture; or 3) isolation of pathogen from specimen obtained by trans-tracheal aspirate, bronchial brushing, or biopsy; or 4) isolation of virus or detection of viral antigen in respiratory secretions; or 5) diagnostic single antibody titer (immunoglobulin M) or fourfold increase in paired serum samples (immunoglobulin G) for pathogen; or 6) histopathologic evidence of pneumonia); and prolonged ventilation (ventilator-assisted respirations during postoperative hospitalisation >48 hours).	Green	Median score 7 38/75 scored ≥7	?

Hulzebos et al[43]	Postoperative Pulmonary Complications	Grade 1: Cough, or micro-atelectasis (abnormal lung findings and temperature >37.5°C without other cause) or normal/unavailable chest x-ray, or dyspnoea not due to other documented cause. Grade 2: Productive cough, not due to other cause, or bronchospasm (new wheezing or pre-existent wheezing resulting in change therapy), or hypoxemia (alveolar-arterial gradient >29 and symptoms of dyspnoea or wheezing) or atelectasis (radiological confirmation plus either temperature >37.5°C or abnormal lung findings) or hypercarbia (transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation) or adverse reaction to pulmonary medication. Grade 3: Pleural effusion, resulting in thoracentesis, or suspected pneumonia (radiological evidence without bacteriological confirmation) or proven pneumonia (radiological evidence with pathological organism by Gram stain or culture) or pneumothorax or postoperative re-intubation or intubation (period of ventilator dependence not >48 hours). Grade 4: Ventilatory failure (ventilator dependence >48 hours) or re-intubation with ventilator dependence.	Green	Median score 7 37/75 scored ≥7	?
Ireland et al[11]	Major Respiratory Complications	Significant atelectasis, pneumonia, significant hypoxia, tracheal re-intubation, intensive care unit (ICU) admission). Atelectasis was defined by the authors of the individual studies.	Red	-	-
Ladha et al[46]	Postoperative Respiratory Complications	Any of: re-intubation, respiratory failure, pneumonia and pulmonary oedema within three days of the procedure.	Red	-	-
Li et al[47]	Postoperative Pulmonary Complications	Pulmonary infection (fever with positive sputum culture and infiltration on chest X-ray), atelectasis, or hypoxemia (SaO_2<90% for >30 minutes).	Red	-	-
Lunardi et al[48]	Postoperative Pulmonary Complications	Any of: atelectasis with clinical consequences, hypoxemia with oxygen saturation <85% and need of supplemental oxygen, pneumonia, or acute respiratory failure.	Red	-	-
Mackay et al[49]	Postoperative Pulmonary Complications	Three or more of the following signs within the same day, in the first 14 days after surgery: Auscultation changes (decreased breath sounds, crackles, wheezes, bronchial breathing) that were additional to those found prior to surgery. Temperature >38°C. Chest x-ray changes consistent with collapse, consolidation, or atelectasis. Increase in amount and/or changed colour of sputum produced, compared to what the patient reports is usual for them.	Red	-	-
McAlister et al[51]	Postoperative Pulmonary Complications	Any one of: respiratory failure requiring mechanical ventilation, pneumonia, atelectasis requiring bronchoscopic intervention, and pneumothorax or pleural effusion requiring percutaneous intervention.	Red	-	-

Muehling et al[52]	Postoperative Pulmonary Complications	Any one of: atelectasis; pneumonia; or prolonged air leak >7 days. Atelectasis was diagnosed on chest x-ray or computed tomography scan; pneumonia was confirmed if antibiotic medication was required due to clinical and radiological signs of infection combined with elevated white cell count or raised CRP.	Red	-	-
Nascimento et al[53]	Pulmonary Complications	Any one of: atelectasis (radiographic, tomographic, or bronchoscopic diagnosis in patients whose clinical signs were acute respiratory symptoms such as dyspnoea, cough, wheeze); respiratory failure (radiographical diagnosis in patients with signs of acute respiratory symptoms such as tracheobronchial purulent secretions, fever (>38°C), or increased white blood cell count (>10,000/mm^3); tracheobronchial infection or pneumonia.	Red	-	-
Paisani et al[55]	Postoperative Pulmonary Complications	One or more of: pneumonia (presence of radiological evidence of pulmonary infiltration associated with at least two of: purulent sputum, temperature >38.0°C or leucocytosis >25% above baseline value); trachea-bronchitis (marked increase in sputum production or presence of purulent sputum when chest x-ray normal); atelectasis (radiological evidence of atelectasis associated with dyspnoea); acute respiratory failure (acute deficiency of gas exchange with necessity for invasive or non-invasive mechanical ventilation); bronchoconstriction (wheezing associated with dyspnoea, requiring bronchodilators or change in previous dosage of bronchodilator.	Amber	-	-
Scholes et al[57]	Pulmonary Complications	Four or more of: Chest radiograph report of collapse/consolidation; oral temperature >38°C on more than one consecutive postoperative day; pulse-oximetry (SpO_2) <90% on more than one consecutive postoperative day; production of yellow or green sputum different to pre-operative assessment; infection on sputum culture report; unexplained white cell count >11×10^9/L or antibiotic therapy for respiratory infection; new abnormal breath sounds on auscultation different to preoperative assessment; or physician diagnosis of postoperative pulmonary complication.	Red	-	-
Vidotto et al[61]	Postoperative pulmonary complications	Any one of: acute respiratory infection (pneumonia or purulent trachea-bronchitis, where pneumonia was established by the presence of lung infiltration on chest x-ray associated with at least two of: purulent tracheobronchial secretion, temperature >38.3°C or a 25% increase in baseline blood leucocytes; and purulent trachea-bronchitis was diagnosed when tracheobronchial secretions increased in amount or changed in colour or purulence, associated with a normal chest x-ray); atelectasis (acute respiratory symptoms associated with radiological imaging); bronchospasm (wheezing detectable with a stethoscope associated with acute respiratory symptoms and the need for medication therapy).	Amber	-	-
Yang et al[62]	Postoperative pulmonary complications	PaO_2/FiO_2 >300 mmHg and/or the presence of newly developed lung lesions (lung infiltration and atelectasis) within 72 hours of the operation.	Red	-	-

Zarbock et al[63]	Postoperative Pulmonary Complications	Any one of: decreased pulmonary oxygen transfer ratio, nosocomial pneumonia, re-intubation rate, and readmission to the intensive care unit after elective discharge to the general ward.	Red	-	-

Table 3. Definitions of pneumonia outcome measures.

Lead author	Outcome measure	Definition	Round 1	Round 2	Round 3
Akutsu et al[25]	Postoperative pneumonia	All of: increase of sputum, opacity on chest x-ray, consolidation on computed tomography, increased temperature, increased white blood cell count, and CRP value in the serum.	Red	-	
Cassidy et al[34]	Postoperative pneumonia	At least one definitive chest x-ray, and at least one sign (fever, leucocytosis, or altered mental status with no other cause), and at least one microbiologic laboratory finding (positive cultures from blood, broncho-alveolar lavage, or pleural fluid) or at least two symptoms (purulent sputum, worsening cough, dyspnoea or tachypnoea, rales or rhonchi, or worsening gas exchange).	Amber	Median score 5 20/75 scored ≥7	
Markar et al[50]	Postoperative pneumonia	Pyrexia, productive cough, raised white cell count, and localising signs on chest examination or chest radiography.	Red	-	
Schussler et al, 2006[58]	Postoperative pneumonia	Fibreoptic bronchoscopy samples were obtained before antibiotic therapy in every patient with signs of pneumonia: abnormal radiographic findings (new or changing radiographic infiltrates that persisted after physiotherapy or broncho-aspiration), fever >38°C, and one of: a new rise in CRP or WBC count over the last 24 hours (with WBC >12x10^9/L) or increased and modified expectorate, possibly purulent. Patients with positive plugged telescopic catheter sample (>103 cfu/ml), protected specimen brush sample (>103cfu/ml), or positive blood culture represented the "documented POP" group. If the significant cut-off values were not reached, but clinical and radiologic improvement occurred after the administration of antibiotics, patients were considered as having "non-documented POP."	Red	-	
Schussler et al, 2008[59]	Postoperative pneumonia	Quantitative fibreoptic bronchoscopy aspiration, plugged telescopic catheter (PTC), or protected specimen brush (PSB) sampling in case of: abnormal radiographic findings (new or changing radiographic infiltrates that persisted after physiotherapy or fibreoptic bronchial aspiration), fever >38°C and one of: purulent secretions or an increase of >30% of the CRP or white blood cell count during the last 24 hours (with count >12x10^9/L). POP was considered documented if bacteria were identified in blood culture or at the 48-hour culture of the fibreoptic sample with thresholds: PTC or PSB at 103 ≥CFU/mL, or QEBA at ≥106 CFU/mL.	Red	-	

Bagyi et al[26]	Pneumonia	According to American Thoracic Society guidelines by x-ray (new or progressive radiographic infiltrate), new onset of fever >38.0°C, symptoms of coughing with purulent sputum, chest pain and leucocytosis (white blood cell count >10 G/L).	Red	-
Centers for Disease Control definition[21]	Pneumonia	Two or more serial chest radiographs with at least one of the following (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease): New or progressive and persistent infiltrates (2) consolidation (3) cavitation; at least one of the following: 1. fever (>38ºC) with no other recognised cause 2. leucopaenia (white cell count < 4 x 10^9 L^{-1}) or leucocytosis (white cell count >12 x10^9 L^{-1}) 3. for adults >70 years old, altered mental status with no other recognised cause; And at least two of the following: 1. new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements 2. new onset or worsening cough, or dyspnoea, or tachypnoea 3. ales or bronchial breath sounds 4. worsening gas exchange (hypoxaemia, increased oxygen requirement, increased ventilator demand)	Green	Median score 8 56/75 scored ≥7
Bouza et al[29]	Ventilator associated pneumonia	Mechanical ventilation for 48 hours when the presence of new and/or progressive pulmonary infiltrates on a chest x-ray plus two or more of: temperature >38.5°C or <36°C; leucocytosis (>12x10^9 cells/L); purulent tracheobronchial secretions; or a reduction in the PaO_2 fraction of inspired oxygen ratio ~ 15% according to Centers for Disease Control and Prevention definitions. Patients with a clinical pulmonary infection score > 6 were also considered to have pneumonia.	Red	-
Hortal et al[43]	Ventilator associated pneumonia	New and/or progressive pulmonary infiltrates on chest radiograph in a patient ventilated more than 48 h plus two or more of: fever >38.5°C or hypothermia <36°C, leucocytosis >12x10^9/L, purulent tracheobronchial secretions or a reduction of PaO_2/FiO_2 >15% in the last 48 h according to the Centers for Disease Control (CDC) definitions. We also included as pneumonia, those with a clinical pulmonary infection score (CPIS) >6. Early-onset VAP was defined as occurring within the first 4 days of hospitalization and late-onset VAP as occurring in day 5 or later on. The isolation of one or more microorganisms in significant bacterial count was required to confirm the diagnosis.	Red	-

Jiao et al[45]	Ventilator associated pneumonia	Chest x-ray results, with at least two of: Fever >38°C; a white blood cell count of >11,000 or <3,000/µl; or the presence of purulent endotracheal secretions. Microbiological samples were obtained by fibreoptic bronchoalveolar lavage (BAL), and the growth of ≥104 colony-forming units/ml microorganism culture of BAL was considered to be positive.	Red	-
Nicholos et al[54]	Ventilator associated pneumonia	Within 48 hours of intubation or 72 hours after extubation, evidence of a new lung infiltrate on chest x-ray and at least two of: leucocytosis, fever, or purulent tracheobronchial secretion.	Red	-
Severgnini et al[22]	Clinical pulmonary infection score	The modified Clinical Pulmonary Infection Score (mCPIS) was calculated by a modified original score as described by Pelosi *et al*.[64]	Amber	Median score 5 17/75 scored ≥7

Table 4. Definitions of respiratory failure outcome measures.

Lead author	Outcome measure	Definition	Round 1	Round 2	Round 3
Perkins et al[56]	Acute lung injury	American-European Consensus Conference definition: acute onset of bilateral infiltrates on the chest radiograph and hypoxemia (PaO_2/FiO_2 ratio of <300) in the absence of clinical evidence of left atrial hypertension	Red	-	-
Canadian Orthopedic trauma[31]	Acute respiratory distress syndrome	1994 American-European consensus definition: (a) acute onset, (b) bilateral chest infiltrate, (c) pulmonary artery occlusion pressure of 18 mmHg or less and no evidence of left atrial hypertension, (d) impaired oxygenation regardless of the level of positive end-expiratory pressure, and (e) a PaO_2/FiO_2 ratio of < 200.	Red	-	-
ARDS Definition Task Force[65]	Acute respiratory distress syndrome	The Berlin definition of Respiratory Distress Syndrome: Timing. Within one week of a known clinical insult or new or worsening respiratory symptoms and Chest imaging.[a] Bilateral opacities not fully explained by effusions, lobar/lung collapse or nodules and Origin of oedema. Respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic oedema Oxygenation.[b] Mild. $PaO_2:FiO_2$ between 26.7 and 40.0kPa (200–300mmHg) with PEEP or CPAP ≥5 cmH_2O.[c] Moderate. $PaO_2:FiO_2$ between 13.3 and 26.6 kPa (100–200 mmHg) with PEEP ≥5 cmH_2O. Severe. $PaO_2:FiO_2$ 13.3 kPa (100 mmHg) with PEEP ≥5 cmH_2O [a]Chest radiograph or computed tomography scan.[b] If altitude is higher than 1000 m, a correction factor should be calculated ($PaO_2:FiO_2$ x [barometric pressure/101 kPa]). [c]This may be delivered non-invasively in the mild acute respiratory distress syndrome group.	Green	Median score 8 53/75 scored ≥7	?
Camp et al[30]	Early extubation	Removal of breathing tube <6 hours after arrival to cardiovascular intensive care.	Red	-	-

Squadrone et al[60]	Endotracheal intubation	Intubation was performed when patients presented with one of: severe hypoxemia (arterial oxygen saturation <80% despite maximal FiO_2; respiratory acidosis (arterial pH <7.30 with carbon dioxide tension >50 mmHg; signs of patient distress with accessory muscle recruitment and paradoxical abdominal or thoracic motion; hemodynamic instability (80-90 mmHg increase or a 30-40 mmHg decrease in systolic blood pressure relative to the baseline value or need for inotropic drugs for at least two hours to maintain systolic blood pressure higher than 85 mmHg or electrocardiogram evidence of ischemia or significant ventricular arrhythmias); need for sedation for major agitation; decreased alertness defined as a Glasgow Coma Score <9; or cardiac arrest.	Amber	Median score 5 26/75 scored ≥7	?
Fernandez-Perez et al[20]	Respiratory failure	Need for mechanical ventilation for >48 hours postoperatively or need for re-institution of mechanical or non-invasive ventilation after extubation	Amber	Median score 6 25/75 scored ≥7	?

Appendix. Members of the Standardized Endpoints for Perioperative Medicine (StEP) Collaborative*

1. Patient Comfort measures: **Paul Myles**, TJ Gan, Andrea Kurz, Phil Peyton, Dan Sessler, Martin Tramer, Alan Cyna, Gildasio S. De Oliveira Jr., Christopher Wu, Mark Jensen, Oliver Boney.

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3. Delirium, POCD and stroke: **Lis Evered**, David Scott, Brendan Silbert, Diederik van Dijk, Cor Kalkman, Matthew Chan, Hilary Grocott, Guy Haller, Rod Eckenhoff, Lars Rasmussen.

4. Cardiovascular: **PJ Devereaux & Scott Beattie**, Duminda Wijeysundera, Lee Fleisher, Giovanni Landoni, Bruce Biccard, Simon Howell, Hilary Grocott, Toby Richards, Manoj Lalu.

5. Respiratory: **Rupert Pearse**, Monty Mythen, Jaume Canet, Ann Moller, Tony Gin, Marcus Schultz, Paolo Pelosi, Marcelo Gabreu, Emmanuel Futier, Ben Creagh-Brown, Manoj Lalu, Alexander Fowler, Tom Abbott.

6. Inflammation and sepsis: **Mervyn Singer,** Cor Kalkman, Andy Klein, Tomas Corcoran, Monty Mythen, Jamie Cooper, Stefan Dieleman.

7. Acute Kidney Injury: **David McIlroy**, Rinaldo Bellomo, Andy Shaw, John Prowle, Keyvan Karkouti, Josh Billings.

8. Bleeding and Patient blood management: **Duminda Wijeysundera**, Andy Klein, Toby Richards, David Mazer, Paul Myles, Mohindas Jayarajah, Keyvan Karkouti, Michael Murphy, Justyna Bartoszko.

9. Healthcare resource utilisation: **Rob Sneyd**, Scott Beattie, Lee Fleisher, Mike Grocott, Dan Sessler, Steve Morris, Ron George.

10. Patient centred outcomes: **Ramani Moonesinghe**, Matthew Chan, Tim Cook, Paul Myles, Mark Shulman, Mark Neuman, Cor Kalkman, James Bost, Meghan Lane-Fall, Ulrica Nilsson, Nathalie Stevenson.

11. Organ Failure and Survival: **Mike Grocott**, Paul Myles, Rupert Pearse, Andrea Kurz, Ramani Moonesinghe, Jamie Cooper, Wilton van Klei, Luca Cabrini, Tim Miller, Sandy Jackson.

12. Cancer surgery: **Donal Buggy**, Dan Sessler, Kate Leslie, Tim Short, Andrea Kurz, Bernhard Riedel, Vijay Gottumukkala, Mark Johnson.