# PCRC PROPOSAL COVER SHEET

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|---|---|
| Title of Study or Project: | **Association Between Driving Pressure and Postoperative Outcomes in Non-Cardiac Surgery Patients** |
| Primary Institution: | Memorial Sloan Kettering Cancer Center, New York, NY |
| Principal Investigator: | Todd Liu, MD |
| Co-Investigators: | Patrick McCormick, MD<br>Kay See Tan, PhD<br>Gregory Fischer, MD |
| Type of Study: | ☐ Exploratory<br>x Retrospective Observational<br>☐ Prospective Randomized |
| IRB Number/Status: | Approved, IRB Exempt Protocol X18-028 |
| Hypothesis: | Increased driving pressure during nonspontaneous mechanical ventilation will correlate with increased 30-day in-hospital mortality in a noncardiac surgery population |
| Number of Patients/Participants: | Estimated 85,000.<br>(DataDirect query found 128,489 patients with 144,876 cases, and we estimate 1/3 loss of cases due to insufficient data.) |
| Power Analysis: | The primary hypothesis of interest is the effect of driving pressure in the presence of other covariates using multivariable logistic regression. We assume squared multiple correlation coefficient ($R^2$) of 0.3 to generate the variance inflation factor. Assuming an alpha of 0.05 and 10% event rate, an anticipated sample size of 85,000 will provide 95% power to detect an effect size of 0.049. |
| Proposed statistical test/analysis: | Multivariate logistic regression will be performed using the postoperative outcome of 30-day in-hospital mortality and driving pressure as the exposure to determine if an association exists. Secondary outcome analysis will focus on pulmonary complications defined by ICD 9/10 Codes. Variables including but not limited to age, gender, intubation time length, pulmonary disease, BMI, and ASA score will be analyzed. |
| Resources (Brief summary of resources for data collection, personnel, financial): | The MPOG database will be queried for the specified concept IDs with programmatic support from the MPOG Coordinating Center. Statistical analyses will be performed by biostatisticians from the MSKCC Department of Epidemiology & Biostatistics led by Dr Tan. |

# Introduction

## What is the significance of the clinical problem being addressed?

Low tidal volume ventilation strategies based on ideal body weight gained prominence with the ARDSNet trial as a lung protective strategy and became widely adopted in critical care.[1] Over the last decade this strategy has also found acceptance in anesthesiology. However, it is important to remember that these results were from intensive care unit patients with acute respiratory distress syndrome (ARDS) who have far different lung mechanics than the surgical patient population. It is unclear that we can generalize the survival benefit of a tidal volume of 6 mL/kg of ideal body weight (IBW) versus 12 mL/kg IBW. There is data to suggest that by extrapolating this low tidal volume strategy to patients presenting to the operating room with healthy lungs, an increase in mortality in the setting of minimal positive end-expiratory pressure (PEEP) can be seen.[2] It is thought that this may be due to variations in lung compliance and that PEEP may be recruiting functional lung when properly titrated. Too much PEEP can cause barotrauma as well.[3] Ideal body weight-based tidal volume ventilation strategies do not take respiratory compliance and the volume of aerated functional lung volumes into consideration.

Driving pressure (ΔP) is defined as the tidal volume ($V_T$) divided by respiratory-system compliance ($C_{RS}$), so $\Delta P = V_T/C_{RS}$. Driving pressure has been proposed as a possible solution to this problem since it is more reflective of compliance for each individual patient and has been shown to improve survival in a meta-analysis.[4] A recent randomized controlled trial of driving pressure during thoracic surgery found that patients in the driving pressure group had fewer postoperative pulmonary complications.[5]

We hope to demonstrate that increased driving pressure will correlate with risk of increased mortality in the immediate perioperative time period for non-cardiac surgery patients. This may suggest that driving pressure may be a non-inferior/superior measure to monitor patients' intraoperative ventilatory status rather than low tidal volumes. Our primary outcome will be 30-day in-hospital mortality and its correlation to driving pressure with nonspontaneous mechanical ventilation. Cox and logistical regression analysis will be utilized to investigate this association. It will be important to take into consideration covariates that may confound conclusions and outcomes.

A secondary outcome will be the incidence of postoperative pulmonary complications (PPCs.) PPCs will be defined by a tiered categorization of ICD 9/10 codes for pulmonary complications as proposed by Douville *et al* (see appendix). PPCs include pneumonia, pulmonary edema, respiratory failure, and other complications. Length of stay will also be a secondary outcome.

30-day mortality was chosen as primary outcome instead of PPCs because it is more clearly defined and universally equivalent amongst institutions. Reporting of PPCs are more likely to be variable amongst institutions. The clinical significance of some PPCs on long-term outcome for patients is arguably less than 30-day mortality. Furthermore, the authors believe that if the null hypothesis were rejected for 30-day mortality that this would help advance the understanding of ventilatory strategies.

## What current gaps exist in the understanding of this problem?

The theorized mechanism for low driving pressure being association with mortality is due to the belief that driving pressure corresponds to recruited lung size and therefore modulated by PEEP and tidal volume. Hyperinflation can lead to increased inflammatory markers and worse outcomes in ARDS.[6] But under-recruited lung can be associated with increased mortality as well.[2] Similar to "euvolemia" in intravascular volume status management, optimized lung recruitment is difficult to define for each

individual patient but the definition and concept is clearer when talking in general terms. Current practice using tidal volumes of 6-8 mL/kg IBW may work for the population as a whole, but the nuance of individualized care for each patient may be lost. Does it make sense to ventilate the same tidal volume to a 60 kg otherwise healthy patient, a 60 kg end-stage emphysema patient, and a 60 kg patient with an obstructive bronchial tumor? Driving pressure presumably will be different for these different patients' lung compliances and better reflect functional lung volumes.

## How will this project address this gap and advance clinical care and/or research knowledge?

The Multicenter Perioperative Outcomes Group (MPOG) database will allow us to conduct a multicenter retrospective look at the effect of driving pressure in surgical patients.

The specific goals of the project are as follows:

1) Investigate the association of driving pressure and 30-day in-hospital mortality in nonspontaneous mechanically ventilated non-cardiac surgical patients undergoing two lung ventilation.
2) Investigate the association of tidal volume in mL per kg IBW with 30 day in-hospital mortality and how this relationship is modified by driving pressure
3) Subgroup analysis: There are several patient subgroups that may play a role in modifying the association between driving pressure and mortality:
    - Pulmonary pressure using supraglottic airway devices (i.e. LMA's) may not be identical to endotracheal tubes given that the physiology is slightly different. We will analyze these two groups to determine if how the association to outcomes are modified.
    - Laparoscopic cases have increased extra-thoracic pressures on the lung due to insufflation which may not be analogous to increased pulmonary pressures due to ventilatory strategies.
    - Craniotomy cases sometimes are managed with hyperventilatory strategies to decrease intracranial pressures through hypocapnia. These hyperventilatory strategies may cause increased pulmonary pressure that is different from other types of cases and should be examined separately.

2) Secondary objective: Investigate the association of driving pressure and postoperative pulmonary complications within 30 days (presence of class 1, 2, or 3), and also length of stay.

# Methods

## Study Database and Population

MPOG is a non-profit academic consortium analyzing perioperative outcomes from hospitals in 18 states and 2 countries. Using electronic records including over 8.2 million anesthetic cases, MPOG facilitates analysis of the critical factors we are investigating regarding intraoperative respiratory variables and postoperative outcomes.

## IRB statement

The project has been approved by the Memorial Sloan Kettering Cancer Center IRB under protocol X18-028.

## Exposure Variables

- **Case Start:**
  1. Anesthesia Induction End (Concept 50005). If not available, then
  2. Anesthesia Induction Begin (Concept 50004). If not available, then
  3. Procedure Start (Concept 50006). If not available, then
  4. Patient in Room (Concept 50003). If not available, then
  5. Anesthesia Start (Concept 50002).
- **Case End:**
  1. Patient Extubated (Concept 50202). If not available, then
  2. Procedure End (Concept 50007). If not available, then
  3. Patient Out of Room (Concept 50008). If not available, then
  4. Anesthesia End (Concept 50009).
- **Peak Inspiratory Pressure:** Use PIP (Concept 3185).
- **PEEP:** Use Measured PEEP (Concept 3210); if not documented use Set PEEP (Concept 3212).
- **Plateau Pressure:** Use Plateau Inspiratory Pressure (Concept 3186)
- **Ventilator minutes** included are only those where positive pressure ventilation occurred, defined by PIP existing, PEEP existing, and PIP - PEEP ≤ 6. (Similar to ASPIRE PUL 02).
- **Driving pressure** will be calculated from plateau pressure and PEEP. For each case we will calculate the median driving pressure for each patient
- **Tidal volume:** For each case, we will calculate the median tidal volume per kg-IBW during ventilation.

## Primary outcome

The primary outcome will be 30 day in-hospital mortality following first surgical intervention a patient encounters during the time range being investigated. Since there is variability in how hospitals collect and report mortality data, we will only use in-hospital mortality data.

## Secondary outcomes

Secondary outcomes will be post-operative pulmonary complications (PPCs) and length of stay. See appendix for definitions of pulmonary complications based on ICD 9/10 codes. Definitions were arranged by Douville *et al* to categorize PPCs based on likelihood of anesthesia etiology from ventilator management.

## Patient inclusion criteria

- Adult patients (greater than 18 years of page) who underwent a non-cardiac operation with nonspontaneous mechanical ventilation as a same-day admission or inpatient procedure.
  - Outpatients are excluded because they are unlikely to have ICD-9/10 codes recorded for postoperative pulmonary complications after they are discharged.
- Patients with a positive peak inspiratory pressure of at least 5 $cmH_2O$ for a minimum of two hours.

    - This criterion will eliminate cases without controlled ventilation (i.e. spontaneous ventilation cases). The two hour duration was chosen to allow patients significant exposure to the driving pressure as to have an impact on the primary outcome.
- Anesthesia record must have at least one plateau pressure recorded every five minutes.

## Patient exclusion criteria

- Patients with ASA score 5 or greater will be removed since they represent such a high-risk population
- Patients who do not have height and weight available.
- Patient undergoing multiple surgeries within the same admission will have cases after the index case excluded to avoid bias.
- Patients with a tracheostomy (in-situ or new) or in-situ endotracheal tube (Concept 50671). Supraglottic airways will be included in the study but examined more closely with secondary statistical analysis as described below.
- Patients with single-lung ventilation will be excluded
- Patients with presence of a double-lumen endotracheal tube or presence of bronchial blocker will be excluded
- Cardiac operations will be excluded
    - Anesthesia CPTs 00560, 00561, 00562, 00563, 00566, 00567, 00580
- All cases with cardiopulmonary bypass will be excluded
    - 50399 Cardiopulmonary bypass - aortic clamp on/off note
    - 50409 Cardiopulmonary bypass terminated
    - 50410 Cardiopulmonary bypass initiated (full)
    - 50416 Cardiopulmonary bypass - crossclamp and circulatory arrest time totals
    - 50417 Cardiopulmonary bypass - Access cannula removed note
    - 50714 Cardiopulmonary bypass - Bypass start / stop event
- Cases performed by cardiac surgical service (Concept 80005)
- Lung and liver transplant surgery will be excluded since they have unique pathophysiology to influence pulmonary complications:
    - Anesthesia CPT 00796 (liver), 00580 (lung)
- Highest base unit value of Anesthesia CPT is 3 or less.

## Data source

An MPOG DataDirect query for cases meeting recording plateau pressure found 128,489 patients with 144,876 cases. We estimate 1/3 loss of cases due to insufficient data, so we expect approximately 85,000 patients with measured plateau pressure.

# Statistical analysis

All patient demographic and clinical factors will be summarized using Number (%) and median ($25^{th}$, $75^{th}$ percentile) or mean (standard deviation) where appropriate. Summaries may be stratified by quantiles of driving pressure.

In the primary analyses, driving pressure will be recorded as the median of patient trajectory. The correlation between driving pressure and other ventilatory parameters (tidal volume, PEEP, plateau pressure etc.) will be quantified by the Spearman correlation coefficients.

The primary outcome is 30-day in-hospital mortality from the date of surgery, recorded as a binary outcome. Since MPOG data does not reliably have out of hospital mortality, we will assume mortality is only recorded in-hospital.

The primary exposure is driving pressure, recorded as the median of patient trajectory (continuous variable). The relationship between driving pressure and 30-day in-hospital mortality will be assessed with a multivariable logistic regression model, adjusting for preoperative and intraoperative factors. Confounders include but are not limited to age at surgery, gender, intubation time, ventilatory mode, airway device (i.e. endotracheal tube, LMA), pulmonary disease, BMI, ASA score. Potential non-linear relationship between driving pressure and the outcome will be examined using restricted cubic spline analysis. If a significant non-linear relationship between driving pressure and the outcome is detected, all subsequent analyses will include non-linear version of driving pressure. The non-linearity assumption will also apply to all other continuous variables across all analyses where appropriate.

If time to mortality is available, we will summarize the time to death (overall survival) as a survival endpoint using survival analysis approach: Kaplan-Meier curves to depict the pattern of survival over time and Cox proportional hazards model to assess the association between driving pressure and death adjusting for all relevant variables as done in the multivariable logistic model described above.

To address the second objective, the multivariable logistic regression model for 30-day mortality will include tidal volume in mL per kg of ideal body weight as well as its interaction with driving pressure, along with potential confounders. A significant interaction term will indicate that the relationship between tidal volume and 30-day mortality is moderated by driving pressure. The varying impact of the interaction between tidal volume and driving pressure on the probability of the primary outcome may be described graphically using quantiles of driving pressure.

Similarly, we will assess the interaction between driving pressure and 3 specific factors on the primary outcome: (1) supraglottic air way devices (i.e., LMAs) vs endotracheal tubes, (2) laparoscopic cases vs non-laparoscopic, and (3) craniotomy vs non-craniotomy cases. A significant interaction term will indicate that the relationship between driving pressure and the outcome is modified by these specific factors. Subsequent subgroup analyses will be performed in each subgroup to identify the impact of driving pressure specifically within each subgroup (i.e., driving pressure has a much larger impact on 30-day mortality among craniotomy cases than those observed among non-craniotomy cases). As a sensitivity analysis, we will also perform the primary analysis after exclusion of emergency surgery cases.

Secondary outcomes include postoperative pulmonary complications (PPCs) within 30 days (presence of class 1, 2, or 3) and length of stay. PPCs will be analyzed using multivariable logistic regression, while length of stay will utilize Poisson regression. All models will include driving pressure as the variable of interest, adjusting for the same factors as in the primary analyses. As above, we will assess the interaction between driving pressure and tidal volume to investigate the presence of modification of the relationship between tidal volume and the outcome by the driving pressure.

The primary exposure variable (driving pressure) is defined as the median of patient driving pressure values collected intraoperatively. In an exploratory manner, we plan to investigate other methods to quantify driving pressure that is informative of the outcome and can provide clinical relevance. One alternative is to utilize the cumulative number of minutes with a driving pressure over 15 $cmH_2O$, based

on findings in acute respiratory distress syndrome patients.[4] Another alternative is to consider the area under the curve (of the continuously measured driving pressure) for each patient.

## Power analysis

We estimate that 85,000 cases may be available for analysis. For the binary outcome of 30-day mortality, we present a power analysis based on a multivariable logistic regression following the procedure by Hsieh et al.[7] The primary hypothesis of interest is the effect of driving pressure in the presence of other covariates (see statistical analysis for a list of potential confounders). In the following power analysis, we assume squared multiple correlation coefficient ($R^2$) of 0.3 to generate the variance inflation factor. Assuming an alpha of 0.05 and 10% event rate, this sample size will have 95% power to detect an effect size of 0.049.

We present a few scenarios for reference: If the number of cases available was reduced to 40,000 cases, we will have 95% power to detect an effect size of 0.072. With the same sample size but higher $R^2$, we will have 95% power to detect an effect size of 0.085. If instead, the event rate was lowered to 5% and $R^2$ is reduced to 0.1, the anticipated sample size of 85,000 cases will provide 95% power to detect an effect side of 0.060.

# Variables to be collected

| Variable | Description | Data Type | Location |
|---|---|---|---|
| Age | Age in years | Integer | View [Case_Demographics] |
| Gender | Gender | String | View [Case_Demographics] |
| ASA Physical Status | ASA Physical Status | Integer | Concept 70233 |
| Emergent | Emergent status | Boolean | Concept 70233 |
| Weight | Weight (kg) | Number | View [Case_Anthropometrics] |
| Height | Height (cm) | Number | View [Case_Anthropometrics] |
| Smoking Status | | | |
| Surgical Admission Type | Surgical Admission Type | String | Column AIMS_Admission_Type |
| Year of service | Year of surgical date of service | Integer | Column AIMS_Scheduled_DT |
| Length of Stay | Length of stay in days | Number | Billing data |
| Chronic pulmonary disease? | Presence of chronic pulmonary disease (Elixhauser) in diagnosis codes | Boolean | Billing data |
| Inhaled steroid? | Presence of inhaled steroid in home medication list | Boolean | Home medication list |
| Laparoscopic procedure? | Is procedure laparoscopic, based on CPT code | Boolean | |
| Procedural service | | String | Column AIMS_Primary_Procedural_Service |
| Procedure name | | String | |
| Craniotomy procedure? | Is procedure a craniotomy, based on CPT code | Boolean | |
| Prone Position? | Whether position is prone | | Unclear source – 50136 Positioning? or 50692 – categorized note positioning |
| Surgery Duration | First procedure start to last procedure finish, in minutes | Integer | View Case_Times |
| ETT Type | Endotracheal tube type | String | Concept 50123 ETT Type |
| LMA Type | LMA type | String | Concept 50141 LMA Type |
| Ventilation Mode | Ventilation mode | String | Concept 3182 Ventilator Mode (most common for case) |
| Intubation Time | First Intubation time (as minutes | Integer | Concept 50695 Categorized note Intubation |

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| | from anesthesia start) | | |
| Extubation Time | Last Extubation Time | Integer | Concept 50202 – Emergence Patient Extubated |
| Reversal Time | Time of administration of NMB reversal | Integer | Concept 10739 – Sugammadex<br>Concept 10315 – Neostigmine<br>Concept 10383 – Pyridostigmine |
| Median tidal volume | Median TV | Integer | Concept 3190 – Tidal Volume Actual |
| Median respiratory rate | Median respiratory rate | Integer | Concept 3580 – RR |
| Median peak inspiratory pressure | Median peak inspiratory pressure | Integer | Concept 3185 – PIP |
| Median plateau inspiratory pressure | Median plateau inspiratory pressure | Integer | Concept 3186 – Plateau IP |
| Median PEEP | Median Positive End Expiratory Pressure | Integer | Concept 3210 – PEEP Measured |
| Median $EtCO_2$ | Median end tidal carbon dioxide | Integer | Concept 3235 – EtCO2 (mmHg) |
| Median $FiO_2$ | Median Fraction of Inspired Oxygen | Integer | Concept 3200 – Ventilator FiO2 Measured |
| Mortality (days) | Days from Date of Surgery to Date of Death | Integer | Mortality Table |
| Pulmonary Complications | See Appendix for ICD Diagnosis codes associated with Pulmonary Complications | | |

# Appendix: ICD Diagnosis Codes Associated with Pulmonary Complications

Based on Douville study under review for publication.

| ***Class 1 Pulmonary Complications*** | |
|---|---|
| 514 | Pulmonary congestion and hypostasis |
| 518.7 | Transfusion related lung injury (TRALI) |
| 997.3 | Respiratory complications not elsewhere classified |
| 997.31 | Ventilator associated pneumonia |
| 997.32 | Postprocedural aspiration pneumonia |
| 997.39 | Other respiratory complications |
| J95.84 | Transfusion related lung injury (TRALI) |
| J95.851 | Ventilator associated pneumonia |
| J98.9 | Respiratory disorder, unspecified |
| J95.859 | Other complication of respirator |
| J95.88 | Other intraoperative complications of respiratory system, not elsewhere classified |
| J95.89 | Other postprocedural complications and disorders of respiratory system, not elsewhere classified |

| ***Class 2 Pulmonary Complications*** | |
|---|---|
| 480* | Viral pneumonia |
| 481* | Pneumococcal pneumonia |
| 482* | Other bacterial pneumonia |
| 483* | Pneumonia due to other specified organisms |
| 484* | Pneumonia in infectious diseases classified elsewhere |
| 485* | Bronchopneumonia, organism unspecified |
| 486* | Pneumonia, organism unspecified |
| 506 | Respiratory conditions due to chemical fumes and vapors |
| 506.1 | Acute pulmonary edema due to fumes and vapors |
| 506.2 | Upper respiratory inflammation due to fumes and vapors |
| 506.3 | Other acute and subacute respiratory conditions due to fumes and vapors |
| 507* | Pneumonitis due to solids and liquids |
| 512* | Pneumothorax and air leak |
| 518.1 | Nontraumatic subcutaneous emphysema |
| 518.4 | Acute edema of the lung, unspecified |
| 518.5 | Pulmonary insufficiency following trauma and surgery |
| 518.51 | Acute respiratory failure following trauma and surgery |
| 518.52 | Other pulmonary insufficiency, not elsewhere classified, following trauma and surgery |
| 518.53 | Acute and chronic respiratory failure following trauma and surgery |
| 518.81 | Acute respiratory failure |
| 518.82 | Other pulmonary insufficiency, not elsewhere classified |
| 786.09 | Respiratory Insufficiency |
| 799.1 | Respiratory arrest |
| J12* | Viral pneumonia, not elsewhere classified |
| J13* | Pneumonia due to Streptococcus pneumoniae |
| J14* | Pneumonia due to Hemophilus influenzae |

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|---|---|
| J15* | Bacteria pneumonia, not elsewhere classified |
| J16* | Pneumonia due to other infectious organisms, not elsewhere classified |
| J17 | Pneumoniae in diseases classified elsewhere |
| J18* | Pneumonia, unspecified organism |
| J68.0 | Bronchitis and pneumonitis due to chemicals, gases, fumes and vapors |
| J68.1 | Pulmonary edema due to chemicals, gases, fumes, and vapors |
| J68.2 | Upper respiratory inflammation due to chemicals, gases, fumes, and vapors, not elsewhere classified |
| J68.3 | Other acute and subacute respiratory conditions due to chemicals, gases, fumes, and vapors |
| J68.4 | Chronic respiratory conditions due to chemicals, gases, fumes, and vapors |
| J68.8 | Other respiratory conditions due to chemicals, gases, fumes, and vapors |
| J68.9 | Unspecified respiratory conditions due to chemicals, gases, fumes, and vapors |
| J85.1 | Abscess of lung with pneumonia |
| J69.0 | Pneumonitis due to inhalation of food and vomit |
| J80 | Acute respiratory distress syndrome |
| J81.0 | Acute pulmonary edema |
| J93* | Pneumothorax and air leak |
| J95.811 | Postprocedural pneumothorax |
| J95.812 | Postprocedural air leak |
| J95.821 | Acute postprocedural respiratory failure |
| J95.822 | Acute and chronic postprocedural respiratory failure |
| J96.0 | Acute respiratory failure |
| J96.00 | Acute respiratory failure, unspecified whether with hypoxia or hypercapnia |
| J96.01 | Acute respiratory failure with hypoxia |
| J96.02 | Acute respiratory failure with hypercapnia |
| J96.1 | Chronic respiratory failure |
| J96.10 | Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia |
| J96.11 | Chronic respiratory failure, with hypoxia |
| J96.12 | Chronic respiratory failure, with hypercapnia |
| J96.2 | Acute and chronic respiratory failure following trauma and surgery |
| J96.20 | Acute and chronic respiratory failure unspecified whether with hypoxia or hypercapnia |
| J96.21 | Acute and chronic respiratory failure with hypoxia |
| J96.22 | Acute and chronic respiratory failure with hypercapnia |
| J96.9 | Respiratory failure, unspecified |
| J96.90 | Respiratory failure, unspecified whether with hypoxia or hypercapnia |
| J96.91 | Respiratory failure, unspecified with hypoxia |
| J96.92 | Respiratory failure, unspecified with hypercapnia |
| R09.0 | Asphyxia and hypoxemia |
| R09.01 | Asphyxia |
| R09.02 | Hypoxemia |
| R09.2 | Respiratory arrest |
| S27.0 | Traumatic pneumothorax |

***Class 3 Pulmonary Complications***

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|---|---|
| 415.1 | Pulmonary embolism and infarction |
| 415.11 | Iatrogenic pulmonary embolism and infarction |
| 415.12 | Septic pulmonary embolism |

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| 415.19 | Other pulmonary embolism and infarction |
| 415.3 | Pulmonary embolism and infarction, episode of care unspecified |
| 487* | Influenza |
| 488* | Influenza due to certain identified influenza viruses |
| 799* | Cerebral asphyxia/suffocation/asphyxia/hypoxia |
| 998.81 | Surgical subcutaneous emphysema |
| 958.7 | Traumatic subcutaneous emphysema |
| I26.0 | Pulmonary embolism with acute cor pulmonale |
| I26.01 | Septic pulmonary embolism with acute cor pulmonale |
| I26.02 | Saddle embolus of pulmonary artery with acute cor pulmonale |
| I26.09 | Other pulmonary embolism with acute cor pulmonale |
| I26.9 | Pulmonary embolism without acute cor pulmonale |
| I26.90 | Septic pulmonary embolism without acute cor pulmonale |
| J09* | Influenza due to certain identified influenza viruses |
| J10* | Influenza due to other identified influenza virus |
| J11* | Influenza due to unidentified influenza virus |
| R06.4 | Hyperventilation |
| R09.1 | Pleurisy |
| R09.3 | Abnormal sputum |
| R09.8 | Other specified symptoms and signs involving the circulatory and respiratory systems |
| T79.7 | Traumatic subcutaneous emphysema |

# Appendix: Inhaled Steroids and Tradenames

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|---|---|
| Beclomethasone | QVAR, Beconase Aq, Becotide, Beclocort |
| Flunisolide | Aerospan |
| Fluticasone | Flovent, Advair Diskus, Arnuity Ellipta |
| Budesonide | Pulmicort |
| Fluticasone-salmeterol | Advair HFA |
| Budesonide-formoterol | Symbicort |
| Mometasone | Asmanex |
| Ciclesonide | Alvesco, Zetonna |
| Formoterol-mometasone | Dulera |
| Fluticasone-vilanterol | Breo Ellipta, Relvar Ellipta |
| fluticasone/umeclidinium/vilanterol | Trelegy Ellipta |

## Handling of missing data and artifacts

Patterns of missingness will be summarized. We expect low proportion of missing data in the primary endpoint as it is one that is clearly defined and conventionally reported. Similarly, we expect low missingness in intraoperative measures. We will investigate whether the missingness is missing completely at random or missing at random. In the absence of informative missingness, we will proceed with complete-case analyses. Otherwise, multiple imputation will be performed.

Medians will be used to summarize tidal volume and pressure data. Zero value artifacts will be removed. For tidal volumes we will remove values less than 2 mL/kg and more than 20 mL/kg. Only values between intubation and extubation will be used in these medians.

## Areas for discussion/known limitations

- Alternative methods for selecting a patient's index case are:
    - First surgery for patient (current proposal)
    - Remove all patients with repeat surgeries
    - Surgery with longest ventilator duration (maximum exposure)
    - First surgery during admission or 30-day period (possibly multiple cases per patient, if multiple admissions)
    - Surgery with highest anesthesia CPT base unit value
- There will be selection bias since not all locations report all the included data.
- We will exclude one-lung ventilation patient group since they may represent a significantly different patient population and pulmonary physiology. Why not focus on sicker patients?
    - Our study focuses on the noncardiac surgery patient population in general and assumes ventilatory management can have impact on patients 30-day mortality. While the broadness of our study is a strength, it also introduces a possibility that a signal may be drowned in the noise of its large, heterogenous patient population. Focusing on only high-risk groups opens the criticism that finding a correlation will only show that “sick patients are more likely to be sicker.”
- Peak pressure and plateau pressures are often similar. Is there utility in using a modified driving pressure calculation that uses PIP instead of plateau? Using the modified driving pressure will greatly increase the n of the study, but will not represent true driving pressure as well.

# References


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7. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med*. 1998;17(14):1623-1634.

# STROBE Statement

Checklist of items that should be included in reports of observational studies

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection |
| Participants | 6 | (*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>*Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls<br>*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants |
| | | (*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed<br>*Case-control study*—For matched studies, give matching criteria and the number of controls per case |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at |

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| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding |
| | | (*b*) Describe any methods used to examine subgroups and interactions |
| | | (*c*) Explain how missing data were addressed |
| | | (*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed<br>*Case-control study*—If applicable, explain how matching of cases and controls was addressed<br>*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy |
| | | (*e*) Describe any sensitivity analyses |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed |
| | | (b) Give reasons for non-participation at each stage |
| | | (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders |
| | | (b) Indicate number of participants with missing data for each variable of interest |
| | | (c) *Cohort study*—Summarise follow-up time (eg, average and total amount) |
| Outcome data | 15* | *Cohort study*—Report numbers of outcome events or summary measures over time |
| | | *Case-control study*—Report numbers in each exposure category, or summary measures of exposure |
| | | *Cross-sectional study*—Report numbers of outcome events or summary measures |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included |
| | | (*b*) Report category boundaries when continuous variables were categorized |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |

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| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based |

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.