RESEARCH PROTOCOL

Manag**E**m**E**n**T** of mechanical **VEN**tilation d**U**ring **S**urgery (**MEET VENUS**): an international, multicenter, and observational data registry

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Title

Management of mechanical ventilation during surgery: an international, multicenter, and observational data registry

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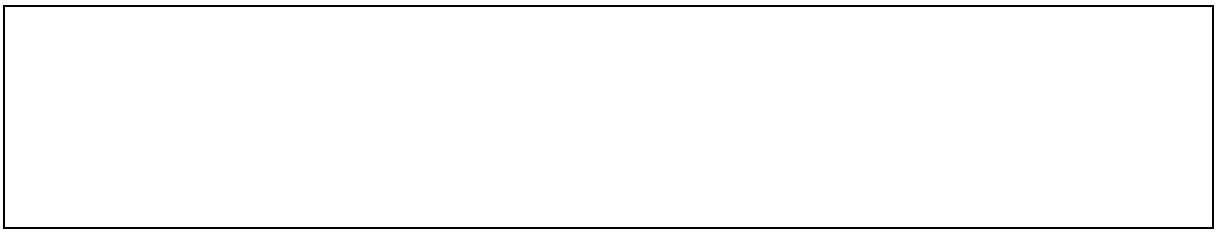

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Sommario

SUMMARY

Rationale

Intraoperative ventilation poses risks for patients under general anesthesia for surgery, leading to postoperative pulmonary complications (PPCs), especially in high–risk patients. Recent randomized clinical trials have deepened our understanding of how PPCs can be prevented by using certain 'lung–protective' ventilator settings. Meanwhile, ventilation practices are rapidly changing due to an increased use of minimally invasive interventions and robotic surgical procedures that usually require extreme body positions during surgery.

Main objectives

The here proposed study, conducted in patients undergoing surgery, aims to 1) describe the incidence and types of postoperative pulmonary complications (PPCs), 2) describe patient demographics, baseline characteristics, and intraoperative ventilation management, 3) describe the occurrence of intraoperative adverse events (IAEs), and 4) their associations with PPCs, and 5) assess the practice of intraoperative mechanical ventilation.

Study design

This is an observational investigator–initiated, international, multicenter, prospective, cross–sectional study.

Local investigators will capture data in an electronic CRF (eCRF), including patient demographics and baseline characteristics, intraoperative ventilator settings and ventilation parameters, and outcomes.

Study population

Patients are eligible for participation if: 1) adult and 2) receiving intraoperative ventilation during general anesthesia for surgery. We will exclude patients receiving ventilation outside of an operating room as well as patients receiving intraoperative ventilation during extracorporeal life support.

Main study endpoints

The primary endpoint is to report the number of patients with PPCs occurring in the first 5 postoperative days. As secondary endpoint, the practice of mechanical ventilation in patients undergoing general anesthesia for surgery will be ascertained including key intraoperative ventilator characteristics and respiratory system mechanics. Other secondary endpoints will include: incidence and type of IAEs; postoperative complications other than PPCs in the first 5 postoperative days; impact of intraoperative hemodynamic management on the occurrence of

PPCs, intensive care unit (ICU) admission and length of stay, hospital length of stay, and hospital mortality on day 28.

Study duration

The overall duration of the study is 18 months, with 9 months allocated for enrollment and data collection, and 9 months dedicated to statistical analysis.

Participating hospitals have to prospectively collect data in a consecutive manner within a predefined period of 1 week (7 days). Also, participating hospitals can decide on which period they choose to collect data, but data collection must take place during a predetermined time window of 8 weeks, following the ethical committee/internal review board approval.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Prospective collection of demographic data, ventilation settings and ventilation parameters, and outcomes means the risks are negligible and the burden is minimal.

Data collection

- Informed consent and data of admission
- Demographic and clinical characteristics
- Characteristics of the surgical procedure (elective vs non-elective, cardiac vs non-cardiac, open vs minimally invasive)
- The type of anesthesia (involving volatile anesthetic medications or intravenous agents)
- Mechanical ventilation settings and respiratory system mechanics variables
- Monitored parameters (peripheral oxygen saturation, end-tidal carbon dioxide tension, arterial blood gases if available, mean blood pressure, systolic and diastolic blood pressure, and heart rate)
- Extubation procedure
- Peri- and postoperative variables and outcomes
- Follow up to the fifth postoperative day
- In-hospital death and hospital length of stay on 28^{th} day after surgery.

Sample size

Considering a PPCs incidence around 10% as found in previous research, at least 10000 patients are needed to achieve a confidence interval width of 0.0119.

Statistical analysis

Variables will be reported as mean and standard deviation or median and interquartile

range according to the normal or non-normal distribution. Also, the comparisons among variables will be carried out through student T-test or Mann- Whitney U test according to data distribution. As regards as categorical variables, proportions will be reported and comparisons will be performed by the Chi-square or Fisher exact test as appropriate. The following planned secondary analyses will be carried out:

- Cardiac vs non-cardiac surgery
- Elective vs non-elective procedures
- Practice of weaning from invasive mechanical ventilation
- Open vs minimally invasive/robotic surgery
- Comparison among the different obesity classes
- Obese vs non obese patients
- Impact of geo-economical difference

1. RATIONALE

1.1. Practice of intraoperative mechanical ventilation

Ventilation during surgery carries potential risks for patients receiving general anesthesia (1). Postoperative pulmonary complications (PPCs) have been described to occur in up to 4% of general surgical cases (2). Nevertheless, patients at an elevated risk for PPCs have reported significantly higher incidence rates (3-7). PPCs are intricately tied to heightened degrees of both morbidity and mortality, even when PPCs are mild (8). In general surgery population (4) and surgical patients undergoing minimally invasive procedures (9), it has been demonstrated that specific ventilator settings impact the onset of PPCs. Since these two studies (4,8), numerous randomized clinical trials focused on the intraoperative ventilation regulation have investigated the impact of ventilator settings on PPCs in patients undergoing major surgery (9-10), abdominal surgery (6,11-13), or thoracic surgery (14-15). In addition, several systematic reviews and meta-analysis have been performed and published (2,16-19). The findings from these studies and meta-analyses may have significantly influenced ventilator management in these patient groups. Concurrently, evolving surgical practices favor minimally invasive procedures over open surgery, particularly in abdominal surgeries where deep Trendelenburg positioning can substantially affect ventilatory characteristics (20). As experience and knowledge about intraoperative ventilation in these challenging scenarios proliferate within medical communities, this evolving understanding is even translating into updated guidelines (21-23).

1.2. Need for a study

A new worldwide study is needed with the aim of ascertaining how patients are ventilated during general anesthesia for surgery. This study will help us understand how intraoperative ventilation is currently managed in general patients population and specific patients groups. It will also shed the light on risk factors that currently have associations with PPCs and, finally, with poor clinical outcomes. This information can help in deciding which ventilation strategies should be tested in future randomized clinical trials of intraoperative ventilation, and will inform trialists on sample size calculations of such studies.

2. HYPOTHESYS AND OBJECTIVES

2.1. Study hypothesis

PPCs incidence is high and related to patient and surgery characteristics. The key mechanical ventilator regulations during general anesthesia for surgery are independently associated with PPCs incidence. Finally, postoperative outcomes is strongly conditioned by PPCs occurrence.

2.2. Study objectives

- To describe the incidence and type of PPCs in the first 5 postoperative days;
- To describe associations of patient, surgery, and intraoperative ventilation characteristics with the occurrence of PPCs;
- To describe the impact of intraoperative hemodynamic management on the occurrence of PPCs;
- To describe the occurrence of intraoperative adverse events (IAEs); and
- To describe geo–economic differences in intraoperative ventilation management.

3. STUDY DESIGN

This is an observational investigator–initiated, international, multicenter, prospective, cross–sectional study recruiting academic and non-academic centers.

3.1. Center Recruitment

Participation is voluntary and without financial incentive. The study will be promoted through web and social media channels to share study protocol and information to potentially interested investigators. The project will be presented during national and international anesthesiology conferences and symposia.

3.2. Study duration

The overall duration of the study is 18 months, with 9 months allocated for enrollment and data collection, and 9 months dedicated to statistical analysis. Participating hospitals have to prospectively collect data in a consecutive manner within a predefined period of 1 week. Participating hospitals can decide on which period they choose to collect data, but data collection must take place during a predetermined time window of 8 weeks.

4. STUDY POPULATION

4.1. Population (base)

Patients subjected to invasive mechanical ventilation (IMV) during general anesthesia for surgery will be included in a consecutive manner.

4.2. Inclusion criteria

Patients are eligible if:

- adults;
- receiving intraoperative IMV (via tracheal intubation, or supraglottic device) during general anesthesia for surgery.

4.3. Exclusion criteria

The following patients will be excluded:

- subjected to IMV outside of an operating room; and
- subjected to IMV during extracorporeal life support.

4.4. Sample size calculation

The sample size estimation for the multicenter data-registry was carried out focusing on the main outcome, the PPCs rate of incidence among patients subjected to IMV during general anesthesia for surgery. Initial results presented in existing research highlighted an event rate around 10% (4); Figure 1 was used to determine the size of the study through a method focused on optimizing the precision of the estimates in terms of Confidence Interval (CI) width. The calculation indicates that a sample size of 10,000 subjects will achieve a confidence interval width of 0.0119, as shown in Figure 1. The Clopper-Pearson method was employed for this estimation process, as a more conservative solution.

5. METHODS

5.1. Study Outcome

5.1.1. Primary outcome

The primary endpoint is to report the number of patients with PPCs, considered as a composite incidence of predefined postoperative pulmonary complications occurring in the first 5 postoperative days or hospital discharge whichever comes first, examining also individual PPCs incidence and type (for the definitions of PPCs see ‘11’).

5.1.2. Secondary outcomes

Secondary endpoints include: 1) ascertaining the practice of mechanical ventilation in patients undergoing general anesthesia for surgery including key intraoperative ventilator characteristics and respiratory system mechanics; 2) describing the incidence and type of IAEs; 3) describing postoperative complications other than PPCs in the first 5 postoperative days or hospital discharge whichever comes first; 4) describing the impact of intraoperative hemodynamic management on the occurrence of PPCs; 5) reporting intensive care unit (ICU) admission and length of stay, hospital length of stay, and hospital mortality on day 28.

5.2. Data collection

Hospitals participating in the study will proactively gather data from all surgical procedures involving patients in a consecutive manner, under the supervision of the local investigator. All data collected are integral to standard clinical care. A visual representation of the trial's design can be found in Figure 2.

Patient characteristics: information such as baseline characteristics and preoperative risk factors essential for identifying patients prone to PPCs. This includes details like age, gender, height, weight, predicted body weight, smoking status, comorbidities, preoperative biochemical exams, peripheral oxygen saturation (SpO2), frailty scale, and American Society of Anesthesiologists (ASA) score. Additionally, data on the type and indication for surgery will be gathered for computing the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) and Revised Cardiac Risk Index (RCRI).

Surgical characteristics: urgency degree of surgery (emergent vs urgent vs elective procedure), planned duration of surgery, type of surgical procedure, and surgical technique.

Operator characteristics: gender, years of anesthesiologist practice, and experience in critical care.

Center characteristics: academic vs non-academic, grade of workload.

Data collection on day 0: type of anesthesia (volatile anesthetic medications or intravenous agents); IMV settings and monitored parameters will be intra-operatively collected at induction and hourly including ventilatory mode, peak inspiratory pressure (cmH_2O), plateau pressure (cmH_2O) (if available), inspiratory to expiratory ratio (I/E), and plateau time (seconds or %), mean airway pressure (cmH_2O), actual inspired tidal volume (Vt) (ml), applied positive end-expiratory pressure (PEEP) and total PEEP with any intrinsic PEEP (cmH_2O) (if present), respiratory rate (breaths/min), dynamic and static respiratory system compliance (cmH_2O/ml) (if clinically available); airway

resistance (Raw) ($cmH_2O/(l/sec)$) (if clinically available), inspired oxygen fraction (FiO_2), use of recruitment maneuvers (number and type), peripheral oxygen saturation (SpO_2) (%), end-tidal carbon dioxide tension ($EtCO_2$) (mmHg or kPa), mean, systolic, and diastolic arterial pressure (either invasive or non-invasive) (mmHg), heart rate (beats per minute), body temperature (°C) (if assessed), and arterial blood gases analysis (if present).

Weaning phase: at beginning and at the end of weaning phase, the following variables will be acquired: ventilatory mode, Vt (ml), PEEP (cmH_2O), pressure support over PEEP (if any) (cmH_2O), inspiratory trigger regulations, FiO_2, respiratory rate (breaths/min), SpO2 (%), $EtCO_2$(mmHg or kPa), mean, systolic, and diastolic arterial pressure (either invasive or non-invasive), mmHg, heart rate (beats per minute).

It will also be recorded if aspiration is performed prior to tube removal.The number and type of IAEs will be acquired throughout the whole duration of surgical and anesthesiologic procedures (see “11” for definitions).

Peri–operative variables: duration of anesthesia procedure, duration of surgical procedure, tube type and size, type of anesthesia, type of analgesia (total endo-venous, antibiotic prophylaxis, details on neuromuscular function monitoring and about the use of reversal agents (if any), total intra–operative fluid and total transfusion of blood products, temperature and hemoglobin at end of surgery (if clinically available).

The possible admission to post-anesthesia care unit (PACU) and the eventual administration of non-invasive respiratory support (NIRS), namely, high flow oxygen therapy, continuous positive airway pressure, and non-invasive bilevel positive airway pressure ventilation, and the settings will be recorded.

Post-operative variables: vital signs involving SpO_2, heart rate, systolic, diastolic, and mean arterial pressure, body temperature if assessed, eventual arrythmias occurrence, and the blood gas analysis parameters (optional assessment) will be hourly collected in the immediate post-operative period or PACU stay, and at the discharge to surgical ward or ICU.

Follow up (day 0 to 5): PPCs are recorded from the medical chart on day 0 (end of surgery to 23:59h) and on days 1,2,3,4 and 5 post-operative (each day runs from 00:00 AM to 23:59 PM). Follow–up is completed on the day of discharge or on day 5 if the patient is still admitted.

On day 0 the following variables are collected: IMV after discharge from the operation room, admission to ICU/PACU after surgery, PPCs (see “11”).

On day 1,2,3,4 and 5 the following variables will be collected: any new admission to ICU; any new or prolonged IMV; PPCs (see “11”).

The data mentioned above are considered essential to defined as “complete” each patient's medical record.

ICU or PACU admission: recording of data during the critical care submission can be left out by the participating centers if this workload exceeds their possibilities. However, it is requested to collect the ICU/PACU data. In case of IMV and/or admission to the ICU/PACU during the follow–up period (day 0, 1, 2, 3, 4 or 5), the following variables will be collected on a different CRF: reason for ICU/PACU admission, reason for IMV or NIRS, APACHE II score (24), on (first) admission to and within the first 24 hours in ICU (i.e., the APACHE II score to be collected and reported for patients who were in the ICU before surgery, and were referred to the ICU after surgery, starts direct after the first admission to the ICU; the APACHE II score to be collected and reported for patients who were not in the ICU before surgery, but were referred to the ICU after surgery, starts direct after surgery, in the ICU). At the first hour of ICU/PACU admission and in case of continued admission each day (during morning rounds) the following variables are collected: SOFA score, IMV regulations, arterial blood gas values (pH, $PaCO_2$, PaO_2 if available), closest to 08:00 AM, PPCs (number and type, see “p 11”), extra–pulmonary organ failure (number and type), and risk factors for respiratory failure (number and type).

If a patient is transferred back to the ward, the non–ICU/PACU follow–up CRF will be used to record the variables of the remaining follow–up days.

Follow up (day 28): On day 28 ICU and hospital length of stay as well as in hospital death are assessed.

5.3. Study procedure

Upon the obtainment of local Institutional Review Board/Ethical Committee (IRB/EC) approval, each center will choose a start date and the screening process will take place. The local investigator will supervise and coordinate the screening and enrollment procedures in the local center.

5.4. Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

5.5. Replacement of individual subjects after withdrawal

There will be no replacement of an individual subject after withdrawal.

5.6. Follow-up of subjects withdrawn from treatment

There will be no follow-up of a subject after withdrawal.

5.7. Premature termination of the study

There will be no reason for premature termination as no research related interventions will take place.

6. STATISTICAL ANALYSIS

The demographic and baseline characteristics of the study population will be reported. Continuous variables will be summarized using median and interquartile range (IQR), and categorical variables will be summarized using frequencies and percentages. The comparison among groups for categorical variables will be performed by considering the Chi-square test or Fisher's exact test whatever is appropriate; for continuous variables, the Wilcoxon -Rank Sum test will be used.

The primary endpoint, namely, the PPCs rate, will be calculated together with the 95% confidence interval (CI). Moreover, the impact of the patient's characteristics on the risk of PPCs will be handled by using appropriate statistical models, such as Logistic Regression. These analyses will be adjusted for potential confounders identified at the study's outset, providing insights into factors that may influence PPCs rates among the patients population subjected to surgery. The 95% CIs on the model OR (Odds Ratios) and predicted probability of PPCs, according to the patient's profile, will be estimated. Handling of missing data will be addressed through robust methods like multiple imputation or complete case analysis, depending on the nature and extent of the missingness. Sensitivity analyses will further assess the robustness of the findings, examining how different assumptions about the missing data and analytical methods influence the results.

The significance of differences will be defined by the *p*-values, with a value of less than 0.05 considered statistically significant.

The following planned secondary analyses will be performed:

- Cardiac vs non-cardiac surgery
- Elective vs non-elective procedures
- Obese vs non-obese patients
- Open vs minimally invasive/robotic surgery

- Comparison among the different obesity classes
- Practice of weaning from invasive mechanical ventilation
- Impact of geo-economical difference

The analyses will be performed by using R 3.4.2.

7. ETHICAL CONSIDERATIONS

7.1. Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki.

7.2. Ethical and Regulatory authorities' approval

All participating centers must submit the study to the local IRB/EC for ethical judgment and obtain document of proof that the trial has been subject to IRB/EC review and given approval/favorable opinion. Considering that all study data is recorded from medical charts and no additional data collection or patient assessment is performed, ethical approval may not be required in some centers. However, where ethical approval is required, this approval must be obtained before the start of inclusion. If authorization/approval/notification by the regulatory authorities is applicable locally, this document should be obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).

7.3. Recruitment and consent

The investigator will enroll patients in the study. All adult patients admitted to the operating room and receiving IMV will be included. If needed, informed consent by the patient will be obtained by the investigator.

7.4. Benefits and risks assessment, group relatedness

This study does not result in any risk or burdens to patients.

7.5. Compensation for injury

Since the study only collects data and no research related interventions will take place, participating in the study is without risk.

7.6. Incentives

There is no financial incentive for subjects to participate in this study.

8. ADMINISTRATIVE ASPECTS, MONITORING, AND PUBLICATION

8.1. Handling and storage of data and documents

Local investigators are expected to collect data in an electronic Case Report Form (eCRF), Research electronic data capture – REDCAP). Each local investigator will be trained on the use of eCRF and will receive a personalized account with

username and password. The passwords will only be given to directly involved investigators.

The eCRF will generate a code for patient identification and no patient's name and birth date will be reported in paper and electronic CRF. Any handling of personal data will comply with the General Data Protection Regulation.

Data will be confidentially managed and paper CRFs will be securely stored at each local site. Any information allowing to link a record to a specific patient will be destroyed at the end of the monitoring stage.

8.2. Monitoring and Quality Assurance

In order to minimize the number of errors and missing data we will use standard operating procedures. Accuracy and consistency checks will be carried out through an ad hoc checking by investigation coordinators.

8.3. Public disclosure and publication policy

The study protocol will be registered on www.clinicaltrials.gov before the start of the investigation. The results of the study will be published in international scientific peer-reviewed journals. The project leader will have final responsibility for the decision to submit for publication.

9. PUBLICATION AND AUTHORSHIP POLICY

The main results of the study will be submitted for peer–review and publication to international medical journal. The first report that comes will be written by the Writing Committee, a subgroup of the Steering Commitee; The primary manuscript reporting the study results will have the intention to be published as a paper by the MEET VENUS study group – this may mean that there are no names of individual researchers in the author's byline. The Principal Investigator will be mentioned as the contact person, whereas the members of the Steering Committee, Writing Committee, and ALL national and local investigators of participating centers are summarized at the end of a manuscript or in the appendix depending on the journal policy.

10. PROPOSAL OF SUB-STUDY/ANALYSIS

On request, the dataset will be available for investigators for secondary analyses, after submission of a sub-study/analysis proposal which will be evaluated for approval by the steering committee.

Before submission, the final version of all manuscripts related to the MEET VENUS study dataset must be approved by the Steering Committee. All the publications derived from the MEET VENUS study dataset will be submitted with the investigators

having their names in the authors' byline, but always using 'on behalf of the MEET VENUS study group investigators'.

11. DEFINITIONS

11.1. PPCs definition

For PPCs (within a time window ranging from day of surgery to 5 days after surgery) we intend unplanned supplementary oxygen administration for hypoxemia, i.e., as oxygen saturation less than 90% in room air, but excluding oxygen supplementation given as standard care, e.g. directly after arrival in the post-anesthesia care unit, respiratory failure defined as oxygen saturation less than 90% despite oxygen therapy or need for non-invasive respiratory support (NIRS), unplanned new or prolonged IMV (after discharge from the operating room), acute respiratory distress syndrome (ARDS) (25), pneumonia (presence of a new or progressive radiographic infiltrate and at least two of three clinical features; fever >38°C, leucocytosis, or leukopenia (white blood cells count >12000 cells*µl-3 or <4000 cells*µl-3 and purulent secretions), pneumothorax, pneumomediastinum, and atelectasis (all confirmed through chest radiograph, computed tomography and/or thoracic ultrasonography).For NIRS we intend high flow oxygen therapy, continuous positive airway pressure, and non-invasive bilevel positive airway pressure ventilation.

11.2. IAEs definition

IAEs include episodes of hypoxia (SpO2<92%), use of unplanned lung recruitment maneuvers (ventilation strategies aimed to restore aeration of the lungs); airway pressure reduction (ventilation strategies aimed to lower peak and plateau pressure), presence of expiratory flow limitation (expiratory flow higher than zero at end-expiration as suggested by visual analysis of the expiratory gas flow curve), use of vasoactive drugs (any given to correct hypotension), and new arrhythmias (atrial fibrillation, sustained ventricular tachycardia, supraventricular tachycardia, or ventricular fibrillation).

11.3. Definition of other postoperative complications

Other postoperative complications that will be assessed include: sepsis of non-pulmonary genesis, defined as a life-threatening organ dysfunction following non-pulmonary infection, deep venous thrombosis more or less associated to pulmonary embolism as assessed through ultrasound more or less accompanied by CT scanning, myocardial infarction, acute pulmonary edema, cardiac arrest, acute kidney injury

defined as an increase in serum creatinine by ≥50% within 7days or increase in serum creatinine ≥0.3mg/dl (26.5μmol/l) within 2 days or oliguria for ≥ 6hours, and cerebrovascular accident/stroke.

12. REFERENCES

1) Ball L, et al. Clinical Anaesthesiology 2015; Sep;29(3):285-99;

2) PROVE network Investigators. Lancet Respir Med. 2016 Apr;4(4):272-80.

3) Canet J et al. Anesthesiology. 2010 Dec;113(6):1338-50.

4) LAS VEGAS Eur J Anaesth 2017; 34:492;

5) Neto AS et al, Eur J Anaesthesiol. 2018 Sep;35(9):691-701.

6) Piccioni F et al. Minerva Anestesiol 2023 Nov;89(11):964-976.

7) Perioperative Research Network investigators. JAMA Surgery 2017; 152:157

8) AVATaR investigators. Br J Anaesth 2021 126 (2): 533e543

9) Karalapillai D et al. Eur J Anaesthesiol. 2022 Jan 1;39(1):67-74.

10) The Writing Committee for the PROBESE Collaborative Group. JAMA 2019 Jun 18;321(23):2292-2305.

11) PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology. Lancet. 2014 Aug 9;384(9942):495-503.

12) Individualized PeRioperative Open-lung VEntilation (iPROVE) Network. Lancet Respir Med. 2018 Mar;6(3):193-203.

13) Khaled L. BMJ Open. 2022 May 6;12(5):e054823.

14) PROTHOR investigators; Trials. 2019 Apr 11;20(1):213.

15) Liu K et al. Ann Transl Med. 2019 Dec;7(23):757.

16) Campos NS et al. Br J Anaesth. 2022 Jun;128(6):1040-1051.

17)Mazzinari G et al. F1000Res. 2023 Jun 23;11:1090. doi: 10.12688/f1000research.125861.1.

18) Guldner A et al. Anesthesiology. 2015 Sep;123(3):692-713.

19) Neto AS et al., Anesthesiology. 2015 Jul;123(1):66-78.

20) Kim YJ, Br J Anaesth. 2023 Nov;131(5):955-965.

21) Young CC et al. Br J Anaesth. 2019 Dec;123(6):898-913.

22) Gao S et al. Thorac Dis. 2017 Sep;9(9):3246-3254.

23) Blaine KP et al. Curr Anesthesiol Rep 12, 183–191 (2022).

24) Knaus WA, Draper EA, Wagner DP, Zimmerman JE: APACHE II: a severity of disease classification system. Crit Care Med 1985,13(10):818-29

25) Acute respiratory distress syndrome: The Berlin definition. JAMA: The Journal of the American Medical Association. 2012;307(23):2526-2533

13. FIGURES

Figure 1. 95% confidence interval width according to sample size

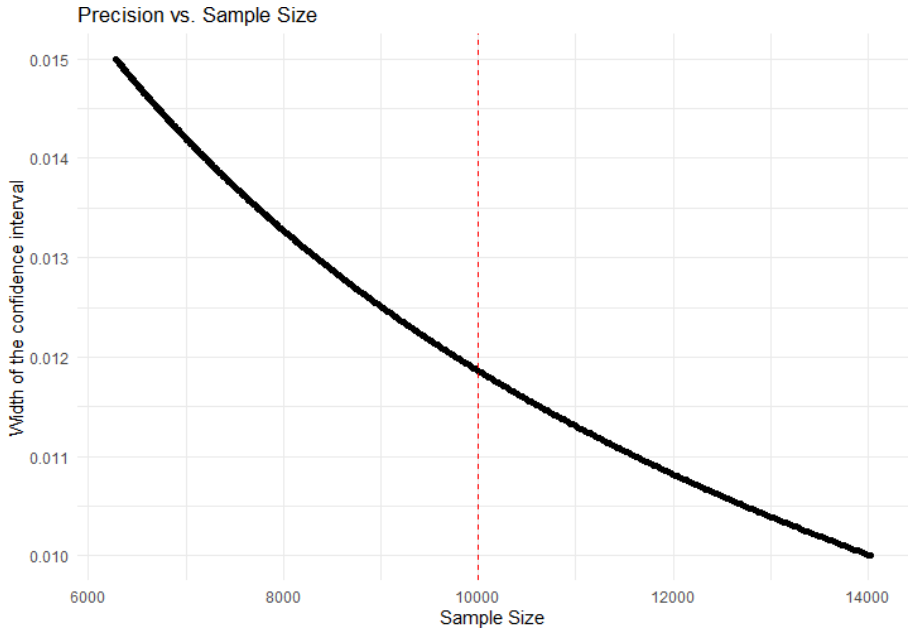
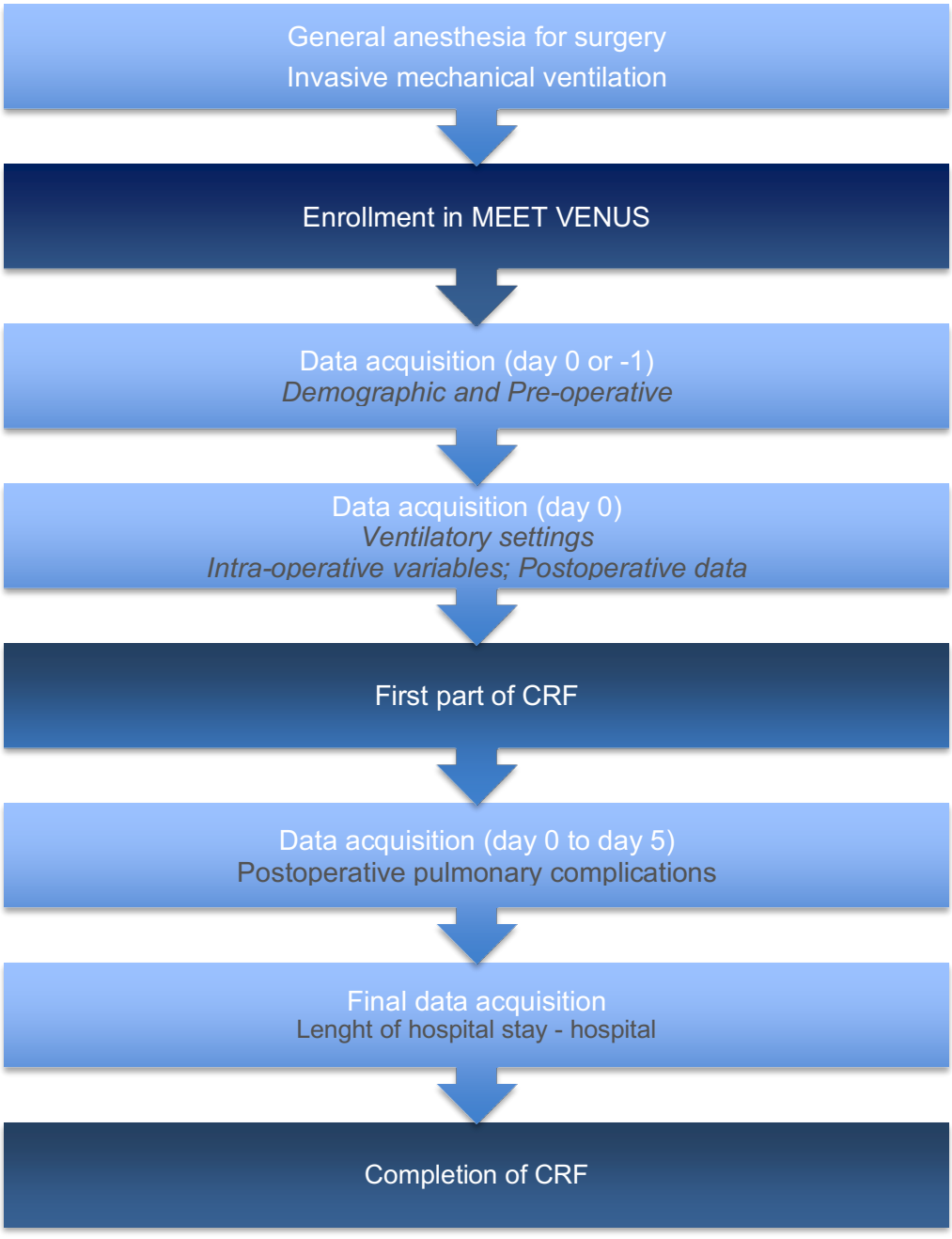


Figure 2. Schematic diagram of trial design: procedures and stages



CRF, case report form