Supplementary Appendix:
Study Protocol and Statistical Analysis Plan

Trial: Pragmatic Trial Examining Oxygenation Prior to Intubation (PREOXI)

Manuscript: Noninvasive Ventilation for Preoxygenation during Emergency Intubation

ClinicalTrials.gov: NCT05267652

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This Supplementary Appendix contains the following items:

1) Initial Trial Protocol -Version 1.0 [dated 2/21/2022]
2) Final Trial Protocol -Version 1.1 [dated 7/7/2023]
3) Summary of changes to Trial Protocol
4) Original Statistical Analysis Plan [posted 3/24/2023]
5) Final Statistical Analysis Plan [published 9/1/2023]
6) Summary of changes to Statistical Analysis Plan

PRagmatic Trial Examining OXygenation prior to Intubation (PREOXI)

Title	Pragmatic trial examining oxygenation prior to intubation
Acronym	PREOXI
Version	Version 1.0
Date	February 21, 2022
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1. TRIAL SUMMARY

Title	Pragmatic Trial Examining Oxygenation prior to Intubation (PREOXI)
Background	Clinicians perform rapid sequence induction, laryngoscopy, and tracheal intubation for more than 5 million critically ill adults as a part of clinical care each year in the United States. One-in-ten emergency tracheal intubations is complicated by life-threatening hypoxemia. Administering supplemental oxygen prior to induction and intubation ("preoxygenation") decreases the risk of life-threatening hypoxemia. In current clinical practice, the most common methods for preoxygenation are non-invasive positive pressure ventilation and facemask oxygen. Prior trials comparing non-invasive positive pressure ventilation and facemask oxygen for preoxygenation have been small and have yielded conflicting results. A better understanding of the comparative effectiveness of these two common, standard-of-care approaches to preoxygenation could improve the care clinicians deliver and patient outcomes.
Study Design	Multicenter, pragmatic, non-blinded, parallel-group, randomized trial
Treatment Groups	• Non-invasive positive pressure ventilation group: Patients will receive preoxygenation with non-invasive mechanical ventilation via a tight-fitting mask. • Facemask oxygen group: Patients will receive preoxygenation via either a non-rebreather mask or a compressed bag-mask device without manual ventilation.
Sample Size	1,300 patients
Inclusion Criteria	1. Patient is located in a participating unit 2. Planned procedure is tracheal intubation using a laryngoscope and sedation 3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.
Exclusion Criteria	1. Patient is receiving positive pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway 2. Patient is known to be less than 18 years old 3. Patient is known to be pregnant 4. Patient is known to be a prisoner 5. Immediate need for tracheal intubation precludes safe performance of study procedures 6. Patient is apneic, hypopneic, or has another condition requiring positive pressure ventilation between enrollment and induction 7. Operator has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen is required or contraindicated for optimal care of the patient
Risks	Participation in this study involves minimal incremental risk because: • All patients eligible for the study are already undergoing tracheal intubation with preoxygenation as part of their clinical care

	• Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are the most common approaches to preoxygenation of critically ill adults in clinical care • No benefits or risks are currently known to differ between the two approaches • If clinicians determine either approach to be required or contraindicated for the optimal care of an individual patient, the patient is excluded from the study
Benefits	The benefits of the PREOXI trial are largely the indirect benefits to future patients that will result by a better understanding of whether preoxygenation with non-invasive positive pressure ventilation or pre-oxygenation with facemask oxygen prevents complications during tracheal intubation of critically ill adults.
Consent	The trial will be conducted with waiver of informed consent because: • Participation in the study involves minimal incremental risk • Obtaining informed consent prior to emergency tracheal intubation of critically ill adults is impracticable
Randomization	Eligible patients will be randomized 1:1 to preoxygenation with non-invasive positive pressure ventilation or pre-oxygenation with facemask oxygen. Randomization will be completed in permuted blocks of variable size and stratified by site.
Blinding	Study group assignment will remain concealed to study personnel and clinicians until after the decision has been made to enroll the patient in the study. Following enrollment, the trial will not blind patients or clinicians to study group assignment.
Primary Outcome	Hypoxemia: Oxygen saturation <85% from induction to 2 minutes after tracheal intubation
Secondary Outcome	Lowest oxygen saturation from induction to 2 minutes after tracheal intubation
Safety Outcomes	• Operator-reported aspiration • Fraction of inspired oxygen at 24 hours after induction • Oxygen saturation at 24 hours after induction • Radiology report of new pneumothorax on chest x-ray in the 24 hours after induction
Exploratory Outcomes	• Procedural characteristics & complications o Severe hypoxemia (lowest oxygen saturation of <80%) between induction and two minutes after tracheal intubation o Very severe hypoxemia (lowest oxygen saturation of <70%) between induction and two minutes after tracheal intubation o Oxygen saturation at induction o Systolic blood pressure at induction o Duration from induction to successful intubation o Cormack-Lehane grade of glottic view on first attempt o Number of laryngoscopy attempts

	○ Number of attempts at passing bougie ○ Number of attempts at passing endotracheal tube ○ Cardiovascular collapse, defined as a composite of one or more of the following between induction and 2 minutes after intubation: 1. Systolic blood pressure < 65 mmHg 2. New or increased vasopressor 3. Cardiac arrest not resulting in death 4. Cardiac arrest resulting in death • Clinical Outcomes ○ 28-day in-hospital mortality ○ Ventilator-free days to 28 days ○ ICU-free days to 28 days
Analysis	The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to preoxygenation with non-invasive positive pressure ventilation versus patients randomized to preoxygenation with facemask oxygen with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.
Sample Size	We will plan to enroll 1300 patients, which we estimate will provide 85% power at a two-sided alpha level of 0.05 to detect a 6% absolute difference in the incidence of the primary outcome, assuming an incidence of hypoxemia of 17% in the facemask group and missing data on the primary outcome for up to 3% of patients.
Expected Duration	18 months

2. TRIAL DESCRIPTION

2.1 Background

Clinicians frequently perform tracheal intubation of critically ill patients in the emergency department (ED) or intensive care unit (ICU). Complications of intubation, including hypoxemia and cardiovascular instability, occur in nearly half of intubations performed in these settings (1, 2, 4, 5). Preventing complications during tracheal intubation is a key focus of clinical care and airway management research (4, 6, 7).

2.1.1 Hypoxemia during Intubation of Critically Ill Patients

Life-threatening hypoxemia occurs in 1-in-10 cases of emergency tracheal intubation.(8) Severe hypoxemia during intubation is associated with increased risk of cardiac arrest and death.(9, 10) Severe hypoxemia may be associated with worse outcomes in survivors. For example, neurologic recovery from traumatic brain injury may be worse after hypoxemia due to secondary ischemic insult.(11)

2.1.2 Role of Preoxygenation in Preventing Hypoxemia during Intubation

In current clinical practice, emergency tracheal intubation involves the nearly simultaneous administration of a sedative agent and a neuromuscular blocking agent to optimize the anatomic conditions for intubation. Following medication administration, patients rapidly become hypopneic and then apneic until invasive mechanical ventilation is initiated through the newly-placed endotracheal tube. The oxygen contained in the lungs at the time of neuromuscular blockade (i.e., the patient's functional residual capacity) is the reservoir of oxygen available to the patient's body to prevent hypoxemia and tissue hypoxia during the intubation procedure. For a patient breathing ambient air (i.e., room air), only 21% of the gas in the functional residual capacity is oxygen; 78% is nitrogen. Administering 100% oxygen to a patient prior to induction of anesthesia and tracheal intubation, referred to as "preoxygenation," can replace the nitrogen in the lung with oxygen, increasing up to five-fold the reservoir of oxygen available to the body during the procedure and prolonging the period during which intubation can be performed safely without encountering hypoxemia. In current clinical practice, the two most common methods of providing preoxygenation are:

1. **Non-invasive positive pressure ventilation** - a tight-fitting mask connected to either an invasive ventilator or non-invasive mechanical ventilator.
2. **Facemask oxygen** - with either a non-rebreather mask or a bag-mask device.

2.1.3 Preoxygenation with Non-Invasive Positive Pressure Ventilation

Preoxygenation with non-invasive positive pressure ventilation is common during emergency tracheal intubation of critically ill adults in current clinical practice. During preoxygenation with non-invasive positive pressure ventilation, a tight-fitting mask is connected to a machine capable of providing positive pressure ventilation. Non-invasive positive pressure ventilation delivers up to 95-100% oxygen and can be provided by either a conventional invasive mechanical ventilator or a dedicated non-invasive ventilation machine, commonly referred to as a Bilevel Positive Airway Pressure (BiPAP) machine. In addition to providing high concentrations of oxygen, non-invasive positive pressure ventilation increases mean airway pressure and delivers breaths at a set rate during the period of hyponea/apnea after induction. Because a mechanical ventilator is always required following intubation of a critically ill adult, no specialized equipment is required

to use non-invasive positive pressure ventilation for preoxygenation of critically ill adults undergoing tracheal intubation.

2.1.4 Preoxygenation with Facemask Oxygen

In current clinical practice, preoxygenation with facemask oxygen is commonly performed using one of the following two types of facemask: [1] a non-rebreather mask or [2] a bag-mask device (8, 12). Both a types of facemask (a non-rebreather and a compressed bag-mask device) deliver supplemental oxygen without increasing airway pressures or providing assistance with ventilation.

- A non-rebreather mask is a type of facemask with a loose-fitting mask that sits over a patient's nose and mouth and is connected to an oxygen reservoir. It delivers at least 15 liters per minute of 100% oxygen, but it may not reliably deliver flows of oxygen greater than 15 liters per minute and may allow entrainment of ambient air. Studies show that the while the oxygen content for healthy and calm volunteers may approach 100%, the oxygen content received by critically ill patients with tachypnea may be as low as 50%.(14) It does not provide positive pressure.
- A bag mask device is a type of facemask with a mask that forms a tight seal over the mouth and nose when held in place by the operator, an exhalation port, and a self-inflating bag that serves as a reservoir for oxygen and can be compressed to provide positive pressure ventilation.(13) If the bag of this device is compressed, this device delivers oxygen without providing positive pressure ventilation and can deliver more than 90% oxygen with an ideal mask seal. However, in the setting of emergency intubation leaks may result in the entrainment of ambient air and reduced oxygen delivery.

2.1.5 Potential Advantages of Preoxygenation with Non-Invasive Positive Pressure Ventilation or Preoxygenation with Facemask Oxygen

Preoxygenation with non-invasive positive pressure ventilation has been proposed to offer the following potential advantages compared to preoxygenation with facemask oxygen:

- *Entrainment of ambient air*: The tight-fitting mask used to deliver non-invasive ventilation entrains less ambient air than a non-rebreather or bag-mask device. The higher flow rates of oxygen gas with non-invasive ventilation may also help prevent entrainment of ambient air and increase the fraction of inspired oxygen. (15)
- *Atelectasis and alveolar recruitment*: Preoxygenation and induction of anesthesia rapidly results in the development of atelectasis in both healthy patients and critically ill patients.(16) This atelectasis increases shunt fraction and increases the risk of peri-procedural hypoxia. By delivering positive pressure during both inspiration and expiration, non-invasive ventilation raises mean airway pressure, recruiting alveoli and preventing the development of atelectasis.
- *Hypopnea and Apnea.* Administration of sedation and neuromuscular blocking agents reduces or eliminates spontaneous respiratory effort. This hypoventilation leads to accumulation of alveolar carbon dioxide and reductions in alveolar oxygen, contributing to hypoxemia. Use of non-invasive ventilation before induction and between induction and laryngoscopy provides continuous oxygen to the alveoli, increases the size of breaths taken in the setting of hypopnea, and delivers controlled breaths when patients are apneic.

Preoxygenation with facemask oxygen (via a non-rebreather or compressed bag-mask device) has been proposed to offer the following potential advantages compared with preoxygenation with non-invasive positive pressure ventilation:

Simplicity of use: Preoxygenation with facemask oxygen (using either a non-rebreather or compressed bag-mask device) is simpler to set up than non-invasive positive pressure ventilation.

Low risk of gastric insufflation: Although no clinical evidence exist to suggest that preoxygenation with non-invasive positive pressure ventilation increases the risk of gastric insufflation or aspiration of gastric contents,(19) use of facemask oxygen (without any positive pressure) avoids this hypothetical concern.

2.1.6 Prior Evidence from Clinical Trials.

Two small clinical trials have compared preoxygenation with non-invasive ventilation to preoxygenation with facemask oxygen during the tracheal intubation of critically ill adults.(20, 21) The first trial compared non-invasive ventilation to a facemask among 53 critically ill ICU patients in two hospitals and found that non-invasive ventilation increased the lowest oxygen saturation (93% vs. 81%, $p<0.001$) with no difference in incidence of aspiration (6% vs. 8%). The second trial compared non-invasive ventilation to a facemask oyxgen with regard to severity of illness in the 7 days after intubation among 201 critically ill ICU patients. This trial found no significant difference in the severity of illness between groups and no significant difference in the rate of severe hypoxemia (18.4% vs 27.7%, $p=0.10$). This trial did not have adequate statistical power to detect clinically important differences between groups in the risk of hypoxemia. No large, multicenter trials have compared preoxygenation with non-invasive positive pressure ventilation to preoxygenation with facemask oxygen for critically ill adults undergoing tracheal intubation. Based on the available data from these small randomized clinical trials, preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen both represent acceptable approaches to emergency tracheal intubation. Both approaches are considered standard-of-care and are used commonly in current clinical practice.

2.1.7 Rationale for a Large Multicenter Trial of Preoxygenation

Because of the imperative to optimize emergency tracheal intubation in clinical care, the common use of both preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen in current clinical practice, and the lack of existing data from randomized trials to definitively inform whether preoxygenation strategy effects the rate of hypoxemia, examining the approach to preoxygenation during emergency tracheal intubation represents an urgent research priority. To address this knowledge gap, we propose to conduct a large, multicenter, randomized clinical trial comparing preoxygenation with non-invasive positive pressure ventilation versus preoxygenation with facemask oxygen with regard to hypoxemic during tracheal intubation of critically ill adults in the ED or ICU.

2.2. Primary Aim and Hypothesis

2.2.1 Study Aim:
To compare the effect of preoxygenation with non-invasive positive pressure ventilation versus preoxygenation with facemask oxygen on hypoxemia during tracheal intubation of critically ill adults.

2.2.2 Study Hypothesis:
Among critically ill adults undergoing tracheal intubation, preoxygenation with non-invasive positive pressure ventilation will reduce the incidence of hypoxemia between induction to 2 minutes after tracheal intubation, compared to preoxygenation with facemask oxygen.

2.3 Study Description
We will conduct an investigator-initiated, non-blinded, pragmatic, parallel-group, randomized trial evaluating the effect of preoxygenation with non-invasive ventilation versus preoxygenation with a facemask on the incidence of hypoxemia among critically ill adults undergoing tracheal intubation in the ED and ICU.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria:
1. Patient is located in a participating unit
2. Planned procedure is tracheal intubation using a laryngoscope and sedation
3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.

3.2 Exclusion Criteria:
1. Patient is receiving positive pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway
2. Patient is known to be less than 18 years old
3. Patient is known to be pregnant
4. Patient is known to be a prisoner
5. Immediate need for tracheal intubation precludes safe performance of study procedures
6. Patient is apneic, hypopneic, or has another condition requiring positive pressure ventilation between enrollment and induction
7. Operator has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with a facemask is required or contraindicated for optimal care of the patient

4. CONSENT
Non-invasive positive pressure ventilation and facemask oxygen are both common approaches to preoxygenation during emergency tracheal intubation in the ED and ICU. Both represent standard of care treatments in current clinical practice.(8, 22) Results from prior clinical trials are conflicting and to not demonstrate superiority of one approach over the other. Consequently, some guidelines recommend non-invasive positive pressure ventilation and other guidelines recommend facemask oxygen.(23-26) As a result, significant variation exists in the approach to

preoxygenation in current clinical practice, with both non-invasive positive pressure ventilation and facemask oxygen used commonly.(8, 27, 28). This trial will enroll patients who are undergoing emergency tracheal intubation as part of their clinical care for whom treating clinicians have determined that preoxygenation with EITHER non-invasive positive pressure ventilation OR facemask oxygen would be consistent with the optimal care of the patient.

We will request a waiver of informed consent because the study involves minimal incremental risk and obtaining informed consent would be impracticable.

Participation in this study involves minimal incremental risk because:

- All patients eligible for the study are already undergoing tracheal intubation with preoxygenation as part of their clinical care
- Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that are commonly used in current clinical care
- No benefits or risks are currently known to differ between the two approaches
- Both approaches have determined to be acceptable options for the optimal care of the patient by treating clinicians (otherwise the patient is excluded from the study)

Obtaining informed consent would be impracticable because:

- **The expected medical condition of patients requiring emergency tracheal intubation in the ED or ICU is critical**. Based on prior trials in the same patient population and setting, approximately 70% of patients eligible for the PREOXI trial will be experiencing encephalopathy (altered mental status) due to their critical illness. The anticipated median Glasgow coma scale score is 11 (equivalent to moderate brain injury). Among the minority of patients whose level of consciousness is not impaired, 45-55% will be experiencing acute delirium. Thus, most patients eligible for PREOXI will not have the capacity to provide informed consent. Further, family members or legally authorized representatives (LAR) are frequently unavailable when critically ill patients undergo intubation in the ED or ICU.
- **The time available for patients or LARs to consider participation will be insufficient.** Even when a patient retains capacity or a LAR is immediately available, a meaningful informed consent process is precluded by the rapid clinical events leading up to emergency tracheal intubation. No published literature has quantified the time from clinicians' decision to perform emergency tracheal intubation (the inclusion criteria for PREOXI) until the initiation of the intubation procedure (completion of the PREOXI intervention). In a convenience sample of 25 consecutive intubations in the VUMC ED or ICU, approximately 50% of intubations occurred within 5 minutes after treating clinicians verbalized the decision to intubate or ordered an induction medication. Obtaining informed consent for research requires study personnel to assess decisional capacity, identify a LAR when appropriate, review the informed consent document in a quiet setting, and provide sufficient time for the patient or LAR to process the information, assess the risks and benefits of participation, and ask questions. Meaningful informed consent cannot be executed in the 5 minutes between the decision to perform emergency tracheal intubation and initiation of the procedure. Emergency tracheal intubation of critically ill adults is a time-sensitive procedure for which every minute of

delay increases the likelihood of hypoxemia, hypotension, and peri-procedural cardiac arrest. Delaying emergency tracheal intubation for a critically ill adult to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, we will request a waiver of informed consent. Numerous previous randomized trials comparing two standards of care for emergency intubation have been completed under a waiver of informed consent [NCT 0040102, NCT 03928925, NCT 02497729, NCT 02051816, NCT 00441792].(7, 29-32)

4.1 Provision of Information after Participation
Information regarding the study will be made available to each patient and family following intubation using a patient and family information sheet. The sheet will inform the patient of his or her enrollment in the PREOXI study, describe the study, and provide contact information for the research team for any questions or concerns.

5. ENROLLMENT AND RANDOMIZATION

5.1 Study Enrollment Locations:
- Participating emergency departments
- Participating intensive care units

5.2 Study Sites:
- **Vanderbilt University Medical Center**
- **Other locations**

5.3 Enrollment and Randomization
All patients requiring emergency tracheal intubation in a participating ED or ICU will be screened for eligibility for the PREOXI trial using the eligibility criteria in Section 3. Patients who do not meet inclusion criteria will be considered 'ineligible'. Patients who meet inclusion criteria but also meet at least one exclusion criterion will be considered 'excluded.' For patients who are excluded, the reason for exclusion will be recorded. For patients who do meet eligibility criteria but are not enrolled, the reason will be recorded.

At enrollment, patients will be randomized in a 1:1 ratio to preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen using randomly permuted blocks of variable size. The randomization will be stratified by study site (i.e., each participating ED or ICU will comprise a different stratum). The study group assignment will be placed in in opaque randomization envelopes, which will be located within participating units. Study group assignment will remain concealed to study personnel and treating clinicians until after the decision has been made to enroll the patient in the study.

To facilitate rapid enrollment during this time-sensitive procedure, sequentially numbered randomization envelopes will be located adjacent to the equipment required for emergency

tracheal intubation (i.e., airway equipment cart, ICU work room). When the need for emergency tracheal intubation is recognized, envelopes will be obtained by the treating clinician performing the intubation (referred to as the "operator") or by a delegate while the operator sets up the equipment required for intubation. Inclusion and exclusion criteria will be posted with randomization envelopes and printed on the outside of enrollment envelopes. As the operator sets up the equipment for emergency tracheal intubation, a verbal "pre-procedural time-out" (described below) will be performed. Based on the experience from our 8 prior randomized clinical trials using the same process to perform randomization and group assignment during emergency tracheal intubation, all enrollment procedures can be completed in less than one minute. For a small number of particularly urgent intubations (e.g., an intubation for cardiac arrest), the urgency of the procedure or the limited availability of clinical personnel will preclude obtaining and opening the randomization envelope. These cases will be excluded using the exclusion criterion that states "Immediate need for tracheal intubation precludes safe performance of study procedures" (see Section 3).

As with all trials conducted to date by our investigators, we will evaluate for the possibility of selection bias via the systematic exclusion of a particular groups of patients. A prospective list of excluded patients will be maintained by site PIs. Data captured on excluded patients will be limited to date of exclusion and reason for exclusion. The number of patients excluded and reasons for excluded will be reported at the time of trial publication via a consort diagram. No patient-level information on excluded patients will be entered into the study database. The coordinating center will not receive any patient-level data on excluded participants.

5.3.1 Pre-Procedural Time-Out to Prevent Enrollment of Ineligible Patients

The enrollment materials for the trial will include instructions for a pre-procedural timeout in which treating clinicians or a delegate recite aloud the inclusion and exclusion criteria and confirm eligibility prior to enrollment. This process requires less than 10 seconds and can be easily completed while the equipment and medications needed for tracheal intubation are being obtained. This approach has been successfully used to confirm eligibility prior to enrollment in multiple prior trials [NCT03928925, NCT03787732]. (33)

5.3.2 Monitoring and Reporting of Eligibility of Enrolled Patients

For all enrolled patients, study personnel will independently verify eligibility criteria at the time of study record creation. In the instance that a patient is enrolled who did not meet eligibility criteria, this will represent a protocol violation. Site investigators will report such a protocol violation to the trial primary investigators and coordinating center **within 24 hours** of becoming aware of the occurrence of a protocol violation. The primary investigators and coordinating center will report the details of such a protocol violation to the IRB **within 7 days** of becoming aware of the occurrence of a protocol violation.

5.3.3 Handling of Patients Found to Be Prisoners after Enrollment

Prisoners typically present with obvious physical signs such as prison uniforms, handcuffs, and the presence of law enforcement. Training of treating clinicians and the enrollment procedures listed above (posting of inclusion and exclusion criteria alongside enrollment envelopes and a "pre-enrollment time-out" with verbal recitation of eligibility criteria) have proven to be effective in preventing the enrollment of prisoners in recent trials.

If a patient who presents to the ED or ICU is not known to be a prisoner at the time of enrollment and following enrollment is discovered to be a prisoner or becomes a prisoner between enrollment and the end of study follow up, all study procedures will stop immediately, the patient will be withdrawn from the study, and the patient's study record will be expunged of all study data. Because both study interventions are one-time, standard-of-care interventions which the patient was likely to receive in clinical care even if not participating in research, no further follow-up will occur.

6. BLINDING

Given the nature of the trial intervention, blinding of patients and treating clinicians to study group assignment is not possible.

7. STUDY INTERVENTIONS

7.1 Treatment of Study Patients

For enrolled patients, study group assignment determines only the approach to preoxygenation. All other aspects of the intubation procedure will be at the discretion of the operator, including patient positioning, choice of sedative agent, use of a neuromuscular blocker, choice of laryngoscope, laryngoscope blade size, use of a bougie to intubate the trachea, use of external laryngeal manipulation to optimize laryngeal view, and endotracheal tube diameter.

The administration of additional supplemental oxygen by nasal cannula is not controlled by the study and is permitted in both groups in any phase of the tracheal intubation procedure, including during laryngoscopy (referred to as "apneic oxygenation"). The administration of ventilation via a bag-mask device will be permitted in both groups between induction and laryngoscopy. Operators may use a non-assigned approach to preoxygenation at any time if it is felt to be required for the safe management of the patient. Use of a non-assigned preoxygenation strategy as the initial approach to preoxygenation will be collected and considered to represent a "crossover." For all patients in the trial, best practices in emergency tracheal intubation will be encouraged according to clinical protocols in the study settings.

7.2 Preoxygenation with Non-Invasive Positive Pressure Ventilation Group

Patients assigned to preoxygenation with non-invasive positive pressure ventilation will receive non-invasive mechanical ventilation via a tight-fitting mask from the initiation of preoxygenation until the initiation of laryngoscopy. Trial protocol will not dictate the brand or type of mechanical ventilator that will be used to deliver non-invasive ventilation.

7.3 Preoxygenation with Facemask Oxygen Group

For patients randomized to preoxygenation with facemask oxygen, supplemental oxygen will be administered via a non-rebreather mask or bag-mask device without manual ventilation from the initiation of preoxygenation until induction. Trial protocol will not dictate the brand or type of facemask. The decision between use of a non-rebreather mask and use of a bag-mask device will be made by treating clinicians. The decision of whether to provide manual ventilation with a bag-mask device between induction and laryngoscopy will be made by treating clinicians.

8. RECORDED STUDY OUTCOMES

8.1 Primary Outcomes

- Hypoxemia, defined as a peripheral oxygen saturation < 85% during the interval between induction and 2 minutes after tracheal intubation

8.2 Secondary Outcomes

- Lowest oxygen saturation during the interval between induction and 2 minutes after tracheal intubation

8.3 Safety Outcomes

- Operator-reported aspiration
- Fraction of inspired oxygen at 24 hours after induction
- Oxygen saturation at 24 hours after induction
- Radiology report of new pneumothorax on chest x-ray in the 24 hours after induction

8. 4 Exploratory Outcomes

- Procedural Characteristics & Complications
    - Severe hypoxemia (lowest oxygen saturation of <80%) between induction and two minutes after tracheal intubation
    - Very severe hypoxemia (lowest oxygen saturation of <70%) between induction and two minutes after tracheal intubation
    - Oxygen saturation at induction
    - Systolic blood pressure at induction
    - Duration from induction to successful intubation (duration of the intubation procedure)
    - Cormack-Lehane grade of glottic view on first attempt
    - Number of laryngoscopy attempts
    - Number of attempts at passing a bougie
    - Number of attempts at passing an endotracheal tube
    - Cardiovascular collapse, defined as a composite of one or more of the following between induction and 2 minutes after intubation:
        1. Systolic blood pressure < 65 mmHg
        2. New or increased vasopressor
        3. Cardiac arrest not resulting in death within 1 hour of induction
        4. Cardiac arrest resulting in death within 1 hour of induction
- Clinical Outcomes
    - 28-day in-hospital mortality
    - Ventilator-free days to 28 days
    - ICU-free days to 28 days

9. DATA COLLECTION

Data collected for the purposes of this study will come from three sources: [1] variables documented in the electronic health record as part of clinical care, [2] variables recorded by clinical staff's bedside observation during the intubation procedure, and [3] variables reported by

the operator immediately following the intubation procedure. Data from the electronic medical record will be collected by trained study personnel (key study personnel) using a standardized electronic case report form. It is infeasible to have research staff present during each emergency tracheal intubation. Therefore, clinical staff not participating in the tracheal intubation procedure will collect data elements relevant to outcomes of emergency tracheal intubation using a standardized electronic case report form. These variables are readily available by bedside observation and do not require interaction with the patient but are not uniformly documented in the electronic health record (e.g., lowest oxygen saturation and lowest blood pressure from induction to two minutes after tracheal intubation). Immediately following the intubation procedure, the operators will record data elements known only to them (e.g., glottic view obtained during the procedure and visualization of gastric aspiration in the oropharynx). Operators and clinical staff observing the procedure at the bedside will not be considered key study personnel. Training will be provided to clinicians who may serve as operators or bedside observers. The activities of these clinicians will be limited to the reporting of data routinely reported as part of clinical care.

The following variables will be recorded:

Baseline:

- age
- sex
- race and ethnicity
- height
- weight
- body mass index
- Acute Physiology and Chronic Health Evaluation (APACHE II) score
- active medical problems at the time of enrollment
- comorbidities
- indication for intubation
- vasopressor receipt in the hour prior to enrollment
- highest FiO2 in the hour prior to enrollment
- lowest SpO2/FIO2 ratio (or PaO2/FIO2 ratio) in the hour prior to enrollment
- Glasgow Coma Scale score
- oxygen delivery device at enrollment
- assessment of the likelihood of a difficult intubation
- presence of difficult airway characteristics
    - limited mouth opening
    - limited anatomic neck mobility
    - cervical immobilization due to trauma
    - increased neck circumference
    - facial trauma
    - obesity
    - body fluids anticipated to obscure laryngeal view
- operator's level of training and specialty
- operator's prior intubation experience

Peri-procedural:

Enrollment to induction

- SpO_2 and FiO_2 at enrollment
- oxygen saturation from enrollment to induction
- approach to preoxygenation
- duration of preoxygenation

Induction to first laryngoscopy attempt

- time of sedative administration (induction)
- sedative agent and dose
- neuromuscular blocking agent and dose
- administration of an intravenous fluid bolus prior to induction
- administration of a vasopressor prior to induction
- SpO_2 at induction
- systolic blood pressure at induction
- approach to oxygen administration and ventilation between induction and laryngoscopy

First laryngoscopy attempt to successful intubation

- time of start of first laryngoscopy attempt
- laryngoscope model, blade size, blade shape on first attempt
- use of video screen (if applicable) on first laryngoscopy attempt
- best Cormack-Lehane grade of glottic view on the first laryngoscopy attempt
- presences of body fluids obstructing laryngeal view
- presence of upper airway obstruction or edema
- receipt of chest compressions at time of first laryngoscopy attempt
- number of intubation attempts
    - number of times laryngoscope entered mouth
    - number of times bougie entered mouth (if applicable)
    - number of times endotracheal tube entered mouth
- reason for failure of first intubation attempt (if applicable)
- device(s) used on subsequent intubation attempts (if applicable)
- necessity of an additional operator
- esophageal intubation
- injury to the teeth
- operator-reported aspiration between induction and intubation
- time of successful tracheal intubation
- endotracheal tube size
- lowest SpO2 from induction until 2 minutes after intubation
- lowest systolic blood pressure from induction until 2 minutes after intubation
- new or increased vasopressor use from induction until 2 minutes after intubation
- cardiac arrest from induction until 2 minutes after intubation not resulting in death within 1 hour of induction
- cardiac arrest from induction until 2 minutes after intubation resulting in death within 1 hour of induction

In-hospital:

24 hours after enrollment

- new pneumothorax detected in the first 24 hours after enrollment
- vasopressor receipt at 24 hours after enrollment
- SpO_2 at 24 hours after enrollment
- FiO_2 at 24 hours after enrollment
- PEEP at 24 hours after enrollment
- systolic blood pressure at 24 hours after enrollment

28 days after enrollment

- 28-day in-hospital mortality
- ventilator-free days
- ICU-free days

10. Risks and Benefits

10.1 Risks of Tracheal Intubation in the ED or ICU

Patients who are severely ill enough to require emergency tracheal intubation in the ED or ICU as part of their clinical care are at high risk of complications. Many patients are undergoing intubation for hypoxemia or hemodynamic instability. Severe hypoxemia or cardiovascular instability occurs during nearly half of intubations in the ED and ICU (1, 2, 4, 5). Hypoxemia and hypotension during intubation are associated with an increased risk of cardiac arrest and death.(9, 10) Cardiac arrest occurs in 1-in-25 cases of emergency tracheal intubation.

Other complications during intubation may include aspiration (approximately 2.8% of cases), esophageal intubation (1.3%) injury to oral or dental structures (0.2%), and pneumothorax (0.1%). The long-term consequences of complications occurring during emergency tracheal intubation are unclear. Neurologic recovery from traumatic brain injury may be worse after hypoxemia due to secondary ischemic insult.(11)

10.2 Potential Risks of Participation in the PREOXI Trial

Participation in the PREOXI trial involves <u>minimal incremental risk</u> because:

- All patients eligible for the study are already experiencing emergency tracheal intubation, with the accompanying risks, as part of their clinical care
- Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that are commonly used in current clinical care. All patients eligible for the study would experience an approach to preoxygenation as part of their clinical care
- No benefits or risks are currently known to differ between the two approaches
- Both approaches have determined to be acceptable options for the optimal care of the patient by treating clinicians (otherwise the patient is excluded from the study)

Although no risks are currently known to differ between preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen (both standard-of-care approaches in currently clinical care), it is possible that the results of the PREOXI trial will ultimately demonstrate a difference between the two approaches in the risk of hypoxemia, hypotension, cardiac arrest, aspiration, or another outcome.

10.3 Potential Benefits of Participation in the PREOXI Trial

The primary benefits of the PREOXI trial will be the indirect benefits to society that would result if one approach to preoxygenation is found to prevent complications. Because millions of critically ill adults undergo emergency tracheal intubation each year, if one of the two approaches were found to prevent serious complications, the findings would immediately improve the care provided to millions of severely ill patients. Compared to the minimal risks of participation in the study, the pursuit of these benefits is reasonable.

10.4 Minimization of Risk

Federal regulations 45 CFR 46.111(a)(1) require that risks to patients are minimized by using procedures which are consistent with sound research design. This trial meets this human subjects protection requirement by incorporating numerous design elements to minimize risk to patients.

Both approaches to preoxygenation have been used in clinical practice for decades with an established safety profile in the same populations included in the PREOXI trial. To further mitigate risk, we will exclude patients with specific risk factors for adverse events such as those already receiving non-invasive positive pressure ventilation and any patient for whom treating clinicians determine that a specific approach to preoxygenation is required or contraindicated for the optimal care of the patient.

The trial protocol includes monitoring of adverse events, robust assessment of clinical outcomes, and an interim analysis by an independent DSMB, empowered to stop the trial or modify the trial protocol at any time.

Finally, to limit the risks associated with the collection of protected health information (PHI), the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. REDCap tools will be used to ensure that the PHI that is collected is only visible to investigators at the healthcare system where the patient was enrolled. To protect participant privacy, REDCap tools will be used to ensure that only deidentified data can be exported for use during analysis.

11. Statistical Considerations

11.1 Initial Sample Size Determination:

The minimum clinically important difference in hypoxemia that would be required to justify routine preoxygenation with non-invasive positive pressure ventilation rather than preoxygenation with facemask oxygen during emergency tracheal intubation of critically ill adults is uncertain. The current trial will be designed to detect a 6% absolute difference between groups in the rate of hypoxemia. An absolute difference of 6% in the incidence of hypoxemia is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.(19, 31) Assuming an incidence of hypoxemia of 17% in the facemask group based on data from two recently completed trials in the same ED and ICU settings, detecting a 6% absolute decrease in the incidence of hypoxemia with 85% power at a two-sided alpha level of 0.05 would require enrollment of 1,264 patients (632 per group). Anticipating missing data for up to 3% of patients, we will plan to enroll a total of 1,300 patients (650 per group). This sample size calculation was performed in PS version 3.1.2.

11.2 Statistical Analysis:
Prior to the conclusion of enrollment, we will make publicly available a complete, final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

11.2.1 Primary Analysis:
The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to preoxygenation with non-invasive positive pressure ventilation versus patients randomized to preoxygenation with facemask oxygen with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.

11.2.2 Secondary Analysis:
We will perform intention-to-treat comparisons of secondary, exploratory, and safety outcomes. Continuous outcomes will be compared with Wilcoxon Rank Sum test and categorical variables with the Chi-squared test. Data on patient characteristics will be summarized as number and proportion for categorical variables and as median and interquartile range for continuous variables.

We will also perform an adjusted comparison of the primary outcome between groups using a generalized linear mixed effects model including a random effect for site and fixed effects for group assignment and the following pre-specified baseline variables:

1. Age;
2. Sex;
3. Race and Ethnicity;
4. Oxygen saturation at enrollment;
5. BMI;
6. Location at enrollment (ED or ICU)
7. Fraction of inspired oxygen at enrollment prior to initiation of preoxygenation;
8. APACHEII score; and
9. Indication for intubation (hypoxemic respiratory failure, other)

11.2.3 Effect Modification (Subgroup Analyses)
To evaluate whether pre-specified baseline variables modify the effect of study group assignment on the primary outcome, we will perform logistic regression modelling with the primary outcome as the dependent variable and independent variables of study group, the proposed effect modifier, and the interaction between the two. Any interaction term with a p-value less than 0.1 will be considered to identify an effect modifier. To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous covariates and the outcome. A full list of prespecified subgroup analyses will be outlined in the detailed Statistical Analysis Plan but will include:

1. Age;
2. Sex;
3. Race and Ethnicity;
4. BMI;
5. Location (ED vs ICU);
6. Fraction of inspired oxygen at enrollment;
7. Indication for intubation (hypoxemic respiratory failure, other) ;
8. APACHEII score; and
9. Baseline risk of the primary outcome

11.3 Interim Analysis

The DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 650 patients. The pre-specified stopping boundary for efficacy will be a P value < 0.001 for the difference between group in the primary outcome using a Chi-square test. This conservative Haybittle–Peto boundary will allow the final analysis to be performed using an unchanged level of significance (two-sided P value < 0.05).
Finally, after the interim analysis, the DSMB will evaluate the rate of the primary outcome in the facemask group. If the incidence of the primary outcome in the facemask group differs from the original estimate, the DSMB may suggest an increase sample size that would maintain the pre-planned statistical power to detect the pre-planned relative risk difference in the primary outcome between groups.

11.4 Correction for Multiple Testing

We will analyze a single pre-specified primary outcome and a single pre-specified secondary outcome. Consistent with recommendations of the Food and Drug Administration[60] and the European Medicines Association,[61] each will be tested using a two-sided P value with a significance level of 0.05. For all other analyses except safety analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors*,[62] and no corrections for multiple comparisons will be performed.

11.5 Handling of Missing Data

No patients will be lost to follow up before the measurement of the primary outcome, but oxygen saturation may be unavailable in some cases (equipment malfunction, observer error during a rapid, emergency procedure, or cardiac arrest). Missing data will not be imputed for the primary outcome, or any of the secondary or exploratory outcomes. In adjusted analyses, missing data for baseline covariates will be imputed using multiple imputations.

12. Privacy and Confidentiality

All patients will be assigned a unique study ID number for use in the coded study database. Study personnel will access patients' electronic health records at three planned time points: immediately following enrollment; when collecting baseline demographics and comorbidities (may occur anytime between enrollment and final data collection); and when collecting clinical outcomes (any time after the first of discharge or 28 days following intubation). The electronic

health record may be accessed again, as needed, between enrollment and study publication to respond to queries from the coordinating center focused on ensuring data completeness and quality. The minimal PHI that is collected will be visible only to site investigators at the site where the patient was enrolled. The dataset for analysis will contain the unique study ID and no other patient identifiers. At the time of publication, a fully de-identified version of the database will be generated.

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Following publication of the study results, all hard copies of data collection forms will be destroyed and the REDCap database will be fully de-identified in accordance with institutional regulations.

13. Follow-up and Record Retention

Patients will be followed after enrollment up to 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. The minimal PHI that is collected will be available only to site investigators at the site where the patient was enrolled. At the time of publication, a fully de-identified version of the database will be generated.

14. Safety Monitoring and Adverse Events

Assuring patient safety is an essential component of this protocol. Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that have been used in clinical practice for decades with an established safety profile. However, any trial conducted during a high-risk, time-sensitive procedure like tracheal intubation of critically ill patients raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen;
2. Systematic collection of outcomes relevant to the safety of preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen;
3. Structured monitoring, assessment, recording, and reporting of adverse events.

14.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the

research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
  - Results in death;
  - Is life-threatening (defined as placing the patient at immediate risk of death);
  - Results in inpatient hospitalization or prolongation of existing hospitalization;
  - Results in a persistent or significant disability or incapacity;
  - Results in a congenital anomaly or birth defect; or
  - Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
  - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
  - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
  - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
  - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".
  - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
  - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
  - Uncertain Relationship: The adverse event does not fit in any of the above categories.

14.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events begins at randomization and ends at the first of hospital discharge or 28 days. Adverse events occurring before randomization or after hospital discharge or 28 days will not be collected. The lead investigator at each enrolling site will have primary responsibility overseeing the

monitoring, assessment, and reporting of adverse events. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record and by communication with treating clinicians. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record at two time points. The first will occur approximately 24 hours after randomization at the time of initial data collection. The second will occur at the first of hospital discharge or 28 days after enrollment at the time of final data collection. Study personnel at each site will also communicate regularly with the treating clinicians who perform tracheal intubation in the study environments between enrollment and 28 days after enrollment to solicit information about any potential adverse events. If study personnel at a site identify a potential adverse event, the lead investigator at the site will be immediately notified. The lead investigator at the site will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. With assistance as needed from the coordinating center and the trial primary investigator, the lead investigator at the site will determine whether the event qualifies for recording and reporting.

14.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the lead investigator at a site assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The lead investigator at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigator **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the lead investigator at the study site will report the adverse event to the coordinating center and the trial principal investigator **within 72 hours** of becoming aware of the adverse event. The coordinating center and the trial principal investigator will coordinate with the lead investigator at the site to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The lead investigator at the site will be responsible for making final determinations regarding seriousness and unexpectedness. The coordinating center and trial principal investigator will be responsible for making final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	**Reporting Period**

Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

The coordinating center will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

14.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of critically ill patients at high risk for death and other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically collected and analyzed for all patients. The primary, secondary, safety, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in ICU trials. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
    - Pulmonary – hypoxemia, aspiration, acute hypoxemic respiratory failure, pneumothorax
    - Cardiac – hypotension, shock, vasopressor receipt, cardiac arrest;
- Duration of mechanical ventilation;
- Duration of ICU admission;
- Duration of hospitalization

Note: A study-specific clinical outcome may also qualify as an adverse event meeting criteria for recording and reporting. For example, a pneumothorax that the investigator considers Definitely Related to preoxygenation with non-invasive positive pressure ventilation would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

14.5 Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel at a site become aware of an event that may represent an Unanticipated problem, they will immediately contact the lead investigator for the site. The lead investigator for the site will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the lead investigator at a site determines that the event represents an Unanticipated Problem, the lead investigator at the site will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The lead investigator at the site will then communicate that an Unanticipated Problem has occurred to the coordinating center and the principal investigator **within 24 hours** of the lead investigator at the site becoming aware of the Unanticipated Problem. The coordinating center and principal investigator will coordinate with the lead investigator at the site to obtain information about the Unanticipated Problem. The coordinating center will report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

15. Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions
- Initial approval of the protocol and subsequent amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will consist of members with expertise in bioethics, emergency medicine, pulmonary and critical care medicine, anesthesia, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The coordinating center, principal investigators, and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event

reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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Tracking of Protocol Versions:

Version 1.0 – Initial Submission (***)

PRagmatic Trial Examining OXygenation prior to Intubation (PREOXI)

Title	Pragmatic trial examining oxygenation prior to intubation
Acronym	PREOXI
Version	Version 1.1
Date	July 7, 2023
Protocol Chairs	Kevin W. Gibbs, MD Wake Forest School of Medicine Jonathan Casey, MD, MSc Vanderbilt University Medical Center Adit A. Ginde, MD, MPH University of Colorado School of Medicine
Coordinating Center	Vanderbilt University Medical Center Director: Jonathan D. Casey, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler MD, MSc
Military Principal Investigators	Maj Brit J Long, MD US Air Force 59MDW MAJ Steven Schauer, DO, MS US Army Institute of Surgical Research and US Air Force 59MDW
Civilian Principal Investigators	Adit A. Ginde, MD, MPH University of Colorado School of Medicine Jonathan Casey, MD, MSc Vanderbilt University Medical Center
Funding	US Department of Defense

Table of Contents

1. TRIAL SUMMARY

Title	Pragmatic Trial Examining Oxygenation prior to Intubation (PREOXI)
Background	Clinicians perform rapid sequence induction, laryngoscopy, and tracheal intubation for more than 5 million critically ill adults as a part of clinical care each year in the United States. One-in-ten emergency tracheal intubations is complicated by life-threatening hypoxemia. Administering supplemental oxygen prior to induction and intubation ("preoxygenation") decreases the risk of life-threatening hypoxemia. In current clinical practice, the most common methods for preoxygenation are non-invasive positive pressure ventilation and facemask oxygen. Prior trials comparing non-invasive positive pressure ventilation and facemask oxygen for preoxygenation have been small and have yielded conflicting results. A better understanding of the comparative effectiveness of these two common, standard-of-care approaches to preoxygenation could improve the care clinicians deliver and patient outcomes.
Study Design	Multicenter, pragmatic, non-blinded, parallel-group, randomized trial
Treatment Groups	• Non-invasive positive pressure ventilation group: Patients will receive preoxygenation with non-invasive mechanical ventilation via a tight-fitting mask. • Facemask oxygen group: Patients will receive preoxygenation via either a non-rebreather mask or a compressed bag-mask device without manual ventilation.
Sample Size	1,300 patients
Inclusion Criteria	1. Patient is located in a participating unit 2. Planned procedure is tracheal intubation using a laryngoscope and sedation 3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.
Exclusion Criteria	1. Patient is receiving positive pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway 2. Patient is known to be less than 18 years old 3. Patient is known to be pregnant 4. Patient is known to be a prisoner 5. Immediate need for tracheal intubation precludes safe performance of study procedures 6. Patient is apneic, hypopneic, or has another condition requiring positive pressure ventilation between enrollment and induction 7. Operator has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen is required or contraindicated for optimal care of the patient
Risks	Participation in this study involves minimal incremental risk because: • All patients eligible for the study are already undergoing tracheal intubation with preoxygenation as part of their clinical care

	• Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are the most common approaches to preoxygenation of critically ill adults in clinical care • No benefits or risks are currently known to differ between the two approaches • If clinicians determine either approach to be required or contraindicated for the optimal care of an individual patient, the patient is excluded from the study
Benefits	The benefits of the PREOXI trial are largely the indirect benefits to future patients that will result by a better understanding of whether preoxygenation with non-invasive positive pressure ventilation or pre-oxygenation with facemask oxygen prevents complications during tracheal intubation of critically ill adults.
Consent	The trial will be conducted with waiver of informed consent because: • Participation in the study involves minimal incremental risk • Obtaining informed consent prior to emergency tracheal intubation of critically ill adults is impracticable
Randomization	Eligible patients will be randomized 1:1 to preoxygenation with non-invasive positive pressure ventilation or pre-oxygenation with facemask oxygen. Randomization will be completed in permuted blocks of variable size and stratified by site.
Blinding	Study group assignment will remain concealed to study personnel and clinicians until after the decision has been made to enroll the patient in the study. Following enrollment, the trial will not blind patients or clinicians to study group assignment.
Primary Outcome	Hypoxemia: Oxygen saturation <85% from induction to 2 minutes after tracheal intubation
Secondary Outcome	Lowest oxygen saturation from induction to 2 minutes after tracheal intubation
Safety Outcomes	• Operator-reported aspiration • Fraction of inspired oxygen at 24 hours after induction • Oxygen saturation at 24 hours after induction • New pneumothorax, defined as a radiology report of new pneumothorax on chest x-ray in the 24 hours after induction • New infiltrate, defined as a radiology report of new infiltrate on chest imaging in the 24 hours after intubation.
Exploratory Outcomes	• Procedural characteristics & complications o Severe hypoxemia (lowest oxygen saturation of <80%) between induction and two minutes after tracheal intubation o Very severe hypoxemia (lowest oxygen saturation of <70%) between induction and two minutes after tracheal intubation o Oxygen saturation at induction o Systolic blood pressure at induction o Duration from induction to successful intubation

	○ Cormack-Lehane grade of glottic view on first attempt ○ Successful intubation on the first attempt ○ Number of laryngoscopy attempts ○ Number of attempts at passing bougie ○ Number of attempts at passing endotracheal tube ○ Cardiovascular collapse, defined as a composite of one or more of the following between induction and 2 minutes after intubation: 1. Systolic blood pressure < 65 mmHg 2. New or increased vasopressor 3. Cardiac arrest not resulting in death 4. Cardiac arrest resulting in death • Clinical Outcomes ○ 28-day in-hospital mortality ○ Ventilator-free days to 28 days ○ ICU-free days to 28 days
Analysis	The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to preoxygenation with non-invasive positive pressure ventilation versus patients randomized to preoxygenation with facemask oxygen with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.
Sample Size	We will plan to enroll 1300 patients, which we estimate will provide 85% power at a two-sided alpha level of 0.05 to detect a 6% absolute difference in the incidence of the primary outcome, assuming an incidence of hypoxemia of 17% in the facemask group and missing data on the primary outcome for up to 3% of patients.
Expected Duration	18 months

2. TRIAL DESCRIPTION

2.1 Background

Clinicians frequently perform tracheal intubation of critically ill patients in the emergency department (ED) or intensive care unit (ICU). Complications of intubation, including hypoxemia and cardiovascular instability, occur in nearly half of intubations performed in these settings (1, 2, 4, 5). Preventing complications during tracheal intubation is a key focus of clinical care and airway management research (4, 6, 7).

2.1.1 Hypoxemia during Intubation of Critically Ill Patients

Life-threatening hypoxemia occurs in 1-in-10 cases of emergency tracheal intubation.(8) Severe hypoxemia during intubation is associated with increased risk of cardiac arrest and death.(9, 10) Severe hypoxemia may be associated with worse outcomes in survivors. For example, neurologic recovery from traumatic brain injury may be worse after hypoxemia due to secondary ischemic insult.(11)

2.1.2 Role of Preoxygenation in Preventing Hypoxemia during Intubation

In current clinical practice, emergency tracheal intubation involves the nearly simultaneous administration of a sedative agent and a neuromuscular blocking agent to optimize the anatomic conditions for intubation. Following medication administration, patients rapidly become hypopneic and then apneic until invasive mechanical ventilation is initiated through the newly-placed endotracheal tube. The oxygen contained in the lungs at the time of neuromuscular blockade (i.e., the patient's functional residual capacity) is the reservoir of oxygen available to the patient's body to prevent hypoxemia and tissue hypoxia during the intubation procedure. For a patient breathing ambient air (i.e., room air), only 21% of the gas in the functional residual capacity is oxygen; 78% is nitrogen. Administering 100% oxygen to a patient prior to induction of anesthesia and tracheal intubation, referred to as "preoxygenation," can replace the nitrogen in the lung with oxygen, increasing up to five-fold the reservoir of oxygen available to the body during the procedure and prolonging the period during which intubation can be performed safely without encountering hypoxemia. In current clinical practice, the two most common methods of providing preoxygenation are:

1. **Non-invasive positive pressure ventilation** - a tight-fitting mask connected to either an invasive ventilator or non-invasive mechanical ventilator.
2. **Facemask oxygen** - with either a non-rebreather mask or a bag-mask device.

2.1.3 Preoxygenation with Non-Invasive Positive Pressure Ventilation

Preoxygenation with non-invasive positive pressure ventilation is common during emergency tracheal intubation of critically ill adults in current clinical practice. During preoxygenation with non-invasive positive pressure ventilation, a tight-fitting mask is connected to a machine capable of providing positive pressure ventilation. Non-invasive positive pressure ventilation delivers up to 95-100% oxygen and can be provided by either a conventional invasive mechanical ventilator or a dedicated non-invasive ventilation machine, commonly referred to as a Bilevel Positive Airway Pressure (BiPAP) machine. In addition to providing high concentrations of oxygen, non-invasive positive pressure ventilation increases mean airway pressure and delivers breaths at a set rate during the period of hyponea/apnea after induction. Because a mechanical ventilator is always required following intubation of a critically ill adult, no specialized equipment is required

to use non-invasive positive pressure ventilation for preoxygenation of critically ill adults undergoing tracheal intubation.

2.1.4 Preoxygenation with Facemask Oxygen

In current clinical practice, preoxygenation with facemask oxygen is commonly performed using one of the following two types of facemask: [1] a non-rebreather mask or [2] a bag-mask device (8, 12). Both a types of facemask (a non-rebreather and a compressed bag-mask device) deliver supplemental oxygen without increasing airway pressures or providing assistance with ventilation.

- A non-rebreather mask is a type of facemask with a loose-fitting mask that sits over a patient's nose and mouth and is connected to an oxygen reservoir. It delivers at least 15 liters per minute of 100% oxygen, but it may not reliably deliver flows of oxygen greater than 15 liters per minute and may allow entrainment of ambient air. Studies show that the while the oxygen content for healthy and calm volunteers may approach 100%, the oxygen content received by critically ill patients with tachypnea may be as low as 50%.(14) It does not provide positive pressure.
- A bag mask device is a type of facemask with a mask that forms a tight seal over the mouth and nose when held in place by the operator, an exhalation port, and a self-inflating bag that serves as a reservoir for oxygen and can be compressed to provide positive pressure ventilation.(13) If the bag of this device is compressed, this device delivers oxygen without providing positive pressure ventilation and can deliver more than 90% oxygen with an ideal mask seal. However, in the setting of emergency intubation leaks may result in the entrainment of ambient air and reduced oxygen delivery.

2.1.5 Potential Advantages of Preoxygenation with Non-Invasive Positive Pressure Ventilation or Preoxygenation with Facemask Oxygen

Preoxygenation with non-invasive positive pressure ventilation has been proposed to offer the following potential advantages compared to preoxygenation with facemask oxygen:

- *Entrainment of ambient air*: The tight-fitting mask used to deliver non-invasive ventilation entrains less ambient air than a non-rebreather or bag-mask device. The higher flow rates of oxygen gas with non-invasive ventilation may also help prevent entrainment of ambient air and increase the fraction of inspired oxygen. (15)
- *Atelectasis and alveolar recruitment*: Preoxygenation and induction of anesthesia rapidly results in the development of atelectasis in both healthy patients and critically ill patients.(16) This atelectasis increases shunt fraction and increases the risk of peri-procedural hypoxia. By delivering positive pressure during both inspiration and expiration, non-invasive ventilation raises mean airway pressure, recruiting alveoli and preventing the development of atelectasis.
- *Hypopnea and Apnea.* Administration of sedation and neuromuscular blocking agents reduces or eliminates spontaneous respiratory effort. This hypoventilation leads to accumulation of alveolar carbon dioxide and reductions in alveolar oxygen, contributing to hypoxemia. Use of non-invasive ventilation before induction and between induction and laryngoscopy provides continuous oxygen to the alveoli, increases the size of breaths taken in the setting of hypopnea, and delivers controlled breaths when patients are apneic.

Preoxygenation with facemask oxygen (via a non-rebreather or compressed bag-mask device) has been proposed to offer the following potential advantages compared with preoxygenation with non-invasive positive pressure ventilation:

Simplicity of use: Preoxygenation with facemask oxygen (using either a non-rebreather or compressed bag-mask device) is simpler to set up than non-invasive positive pressure ventilation.

Low risk of gastric insufflation: Although no clinical evidence exist to suggest that preoxygenation with non-invasive positive pressure ventilation increases the risk of gastric insufflation or aspiration of gastric contents,(19) use of facemask oxygen (without any positive pressure) avoids this hypothetical concern.

2.1.6 Prior Evidence from Clinical Trials.

Two small clinical trials have compared preoxygenation with non-invasive ventilation to preoxygenation with facemask oxygen during the tracheal intubation of critically ill adults.(20, 21) The first trial compared non-invasive ventilation to a facemask among 53 critically ill ICU patients in two hospitals and found that non-invasive ventilation increased the lowest oxygen saturation (93% vs. 81%, $p<0.001$) with no difference in incidence of aspiration (6% vs. 8%). The second trial compared non-invasive ventilation to a facemask oyxgen with regard to severity of illness in the 7 days after intubation among 201 critically ill ICU patients. This trial found no significant difference in the severity of illness between groups and no significant difference in the rate of severe hypoxemia (18.4% vs 27.7%, $p=0.10$). This trial did not have adequate statistical power to detect clinically important differences between groups in the risk of hypoxemia. No large, multicenter trials have compared preoxygenation with non-invasive positive pressure ventilation to preoxygenation with facemask oxygen for critically ill adults undergoing tracheal intubation. Based on the available data from these small randomized clinical trials, preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen both represent acceptable approaches to emergency tracheal intubation. Both approaches are considered standard-of-care and are used commonly in current clinical practice.

2.1.7 Rationale for a Large Multicenter Trial of Preoxygenation

Because of the imperative to optimize emergency tracheal intubation in clinical care, the common use of both preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen in current clinical practice, and the lack of existing data from randomized trials to definitively inform whether preoxygenation strategy effects the rate of hypoxemia, examining the approach to preoxygenation during emergency tracheal intubation represents an urgent research priority. To address this knowledge gap, we propose to conduct a large, multicenter, randomized clinical trial comparing preoxygenation with non-invasive positive pressure ventilation versus preoxygenation with facemask oxygen with regard to hypoxemic during tracheal intubation of critically ill adults in the ED or ICU.

2.2. Primary Aim and Hypothesis

2.2.1 Study Aim:
To compare the effect of preoxygenation with non-invasive positive pressure ventilation versus preoxygenation with facemask oxygen on hypoxemia during tracheal intubation of critically ill adults.

2.2.2 Study Hypothesis:
Among critically ill adults undergoing tracheal intubation, preoxygenation with non-invasive positive pressure ventilation will reduce the incidence of hypoxemia between induction to 2 minutes after tracheal intubation, compared to preoxygenation with facemask oxygen.

2.3 Study Description
We will conduct an investigator-initiated, non-blinded, pragmatic, parallel-group, randomized trial evaluating the effect of preoxygenation with non-invasive ventilation versus preoxygenation with a facemask on the incidence of hypoxemia among critically ill adults undergoing tracheal intubation in the ED and ICU.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria:
1. Patient is located in a participating unit
2. Planned procedure is tracheal intubation using a laryngoscope and sedation
3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.

3.2 Exclusion Criteria:
1. Patient is receiving positive pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway
2. Patient is known to be less than 18 years old
3. Patient is known to be pregnant
4. Patient is known to be a prisoner
5. Immediate need for tracheal intubation precludes safe performance of study procedures
6. Patient is apneic, hypopneic, or has another condition requiring positive pressure ventilation between enrollment and induction
7. Operator has determined that preoxygenation with non-invasive positive pressure ventilation or preoxygenation with a facemask is required or contraindicated for optimal care of the patient

4. CONSENT
Non-invasive positive pressure ventilation and facemask oxygen are both common approaches to preoxygenation during emergency tracheal intubation in the ED and ICU. Both represent standard of care treatments in current clinical practice.(8, 22) Results from prior clinical trials are conflicting and to not demonstrate superiority of one approach over the other. Consequently, some guidelines recommend non-invasive positive pressure ventilation and other guidelines recommend facemask oxygen.(23-26) As a result, significant variation exists in the approach to

preoxygenation in current clinical practice, with both non-invasive positive pressure ventilation and facemask oxygen used commonly.(8, 27, 28). This trial will enroll patients who are undergoing emergency tracheal intubation as part of their clinical care for whom treating clinicians have determined that preoxygenation with EITHER non-invasive positive pressure ventilation OR facemask oxygen would be consistent with the optimal care of the patient.

We will request a waiver of informed consent because the study involves minimal incremental risk and obtaining informed consent would be impracticable.

Participation in this study involves minimal incremental risk because:

- All patients eligible for the study are already undergoing tracheal intubation with preoxygenation as part of their clinical care
- Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that are commonly used in current clinical care
- No benefits or risks are currently known to differ between the two approaches
- Both approaches have determined to be acceptable options for the optimal care of the patient by treating clinicians (otherwise the patient is excluded from the study)

Obtaining informed consent would be impracticable because:

- **The expected medical condition of patients requiring emergency tracheal intubation in the ED or ICU is critical**. Based on prior trials in the same patient population and setting, approximately 70% of patients eligible for the PREOXI trial will be experiencing encephalopathy (altered mental status) due to their critical illness. The anticipated median Glasgow coma scale score is 11 (equivalent to moderate brain injury). Among the minority of patients whose level of consciousness is not impaired, 45-55% will be experiencing acute delirium. Thus, most patients eligible for PREOXI will not have the capacity to provide informed consent. Further, family members or legally authorized representatives (LAR) are frequently unavailable when critically ill patients undergo intubation in the ED or ICU.
- **The time available for patients or LARs to consider participation will be insufficient.** Even when a patient retains capacity or a LAR is immediately available, a meaningful informed consent process is precluded by the rapid clinical events leading up to emergency tracheal intubation. No published literature has quantified the time from clinicians' decision to perform emergency tracheal intubation (the inclusion criteria for PREOXI) until the initiation of the intubation procedure (completion of the PREOXI intervention). In a convenience sample of 25 consecutive intubations in the VUMC ED or ICU, approximately 50% of intubations occurred within 5 minutes after treating clinicians verbalized the decision to intubate or ordered an induction medication. Obtaining informed consent for research requires study personnel to assess decisional capacity, identify a LAR when appropriate, review the informed consent document in a quiet setting, and provide sufficient time for the patient or LAR to process the information, assess the risks and benefits of participation, and ask questions. Meaningful informed consent cannot be executed in the 5 minutes between the decision to perform emergency tracheal intubation and initiation of the procedure. Emergency tracheal intubation of critically ill adults is a time-sensitive procedure for which every minute of

delay increases the likelihood of hypoxemia, hypotension, and peri-procedural cardiac arrest. Delaying emergency tracheal intubation for a critically ill adult to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, we will request a waiver of informed consent. Numerous previous randomized trials comparing two standards of care for emergency intubation have been completed under a waiver of informed consent [NCT 0040102, NCT 03928925, NCT 02497729, NCT 02051816, NCT 00441792].(7, 29-32)

4.1 Provision of Information after Participation
Information regarding the study will be made available to each patient and family following intubation using a patient and family information sheet. The sheet will inform the patient of his or her enrollment in the PREOXI study, describe the study, and provide contact information for the research team for any questions or concerns.

5. ENROLLMENT AND RANDOMIZATION

5.1 Study Enrollment Locations:
- Participating emergency departments
- Participating intensive care units

5.2 Study Sites:
- **Vanderbilt University Medical Center**
- **Other locations**

5.3 Enrollment and Randomization
All patients requiring emergency tracheal intubation in a participating ED or ICU will be screened for eligibility for the PREOXI trial using the eligibility criteria in Section 3. Patients who do not meet inclusion criteria will be considered 'ineligible'. Patients who meet inclusion criteria but also meet at least one exclusion criterion will be considered 'excluded.' For patients who are excluded, the reason for exclusion will be recorded. For patients who do meet eligibility criteria but are not enrolled, the reason will be recorded.

At enrollment, patients will be randomized in a 1:1 ratio to preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen using randomly permuted blocks of variable size. The randomization will be stratified by study site (i.e., each participating ED or ICU will comprise a different stratum). The study group assignment will be placed in in opaque randomization envelopes, which will be located within participating units. Study group assignment will remain concealed to study personnel and treating clinicians until after the decision has been made to enroll the patient in the study.

To facilitate rapid enrollment during this time-sensitive procedure, sequentially numbered randomization envelopes will be located adjacent to the equipment required for emergency

tracheal intubation (i.e., airway equipment cart, ICU work room). When the need for emergency tracheal intubation is recognized, envelopes will be obtained by the treating clinician performing the intubation (referred to as the "operator") or by a delegate while the operator sets up the equipment required for intubation. Inclusion and exclusion criteria will be posted with randomization envelopes and printed on the outside of enrollment envelopes. As the operator sets up the equipment for emergency tracheal intubation, a verbal "pre-procedural time-out" (described below) will be performed. Based on the experience from our 8 prior randomized clinical trials using the same process to perform randomization and group assignment during emergency tracheal intubation, all enrollment procedures can be completed in less than one minute. For a small number of particularly urgent intubations (e.g., an intubation for cardiac arrest), the urgency of the procedure or the limited availability of clinical personnel will preclude obtaining and opening the randomization envelope. These cases will be excluded using the exclusion criterion that states "Immediate need for tracheal intubation precludes safe performance of study procedures" (see Section 3).

As with all trials conducted to date by our investigators, we will evaluate for the possibility of selection bias via the systematic exclusion of a particular groups of patients. A prospective list of excluded patients will be maintained by site PIs. Data captured on excluded patients will be limited to date of exclusion and reason for exclusion. The number of patients excluded and reasons for excluded will be reported at the time of trial publication via a consort diagram. No patient-level information on excluded patients will be entered into the study database. The coordinating center will not receive any patient-level data on excluded participants.

5.3.1 Pre-Procedural Time-Out to Prevent Enrollment of Ineligible Patients

The enrollment materials for the trial will include instructions for a pre-procedural timeout in which treating clinicians or a delegate recite aloud the inclusion and exclusion criteria and confirm eligibility prior to enrollment. This process requires less than 10 seconds and can be easily completed while the equipment and medications needed for tracheal intubation are being obtained. This approach has been successfully used to confirm eligibility prior to enrollment in multiple prior trials [NCT03928925, NCT03787732]. (33)

5.3.2 Monitoring and Reporting of Eligibility of Enrolled Patients

For all enrolled patients, study personnel will independently verify eligibility criteria at the time of study record creation. In the instance that a patient is enrolled who did not meet eligibility criteria, this will represent a protocol violation. Site investigators will report such a protocol violation to the trial primary investigators and coordinating center **within 24 hours** of becoming aware of the occurrence of a protocol violation. The primary investigators and coordinating center will report the details of such a protocol violation to the IRB **within 7 days** of becoming aware of the occurrence of a protocol violation.

5.3.3 Handling of Patients Found to Be Prisoners after Enrollment

Prisoners typically present with obvious physical signs such as prison uniforms, handcuffs, and the presence of law enforcement. Training of treating clinicians and the enrollment procedures listed above (posting of inclusion and exclusion criteria alongside enrollment envelopes and a "pre-enrollment time-out" with verbal recitation of eligibility criteria) have proven to be effective in preventing the enrollment of prisoners in recent trials.

If a patient who presents to the ED or ICU is not known to be a prisoner at the time of enrollment and following enrollment is discovered to be a prisoner or becomes a prisoner between enrollment and the end of study follow up, all study procedures will stop immediately, the patient will be withdrawn from the study, and the patient's study record will be expunged of all study data. Because both study interventions are one-time, standard-of-care interventions which the patient was likely to receive in clinical care even if not participating in research, no further follow-up will occur.

6. BLINDING

Given the nature of the trial intervention, blinding of patients and treating clinicians to study group assignment is not possible.

7. STUDY INTERVENTIONS

7.1 Treatment of Study Patients

For enrolled patients, study group assignment determines only the approach to preoxygenation. All other aspects of the intubation procedure will be at the discretion of the operator, including patient positioning, choice of sedative agent, use of a neuromuscular blocker, choice of laryngoscope, laryngoscope blade size, use of a bougie to intubate the trachea, use of external laryngeal manipulation to optimize laryngeal view, and endotracheal tube diameter.

The administration of additional supplemental oxygen by nasal cannula is not controlled by the study and is permitted in both groups in any phase of the tracheal intubation procedure, including during laryngoscopy (referred to as "apneic oxygenation"). The administration of ventilation via a bag-mask device will be permitted in both groups between induction and laryngoscopy. Operators may use a non-assigned approach to preoxygenation at any time if it is felt to be required for the safe management of the patient. Use of a non-assigned preoxygenation strategy as the initial approach to preoxygenation will be collected and considered to represent a "crossover." For all patients in the trial, best practices in emergency tracheal intubation will be encouraged according to clinical protocols in the study settings.

7.2 Preoxygenation with Non-Invasive Positive Pressure Ventilation Group

Patients assigned to preoxygenation with non-invasive positive pressure ventilation will receive non-invasive mechanical ventilation via a tight-fitting mask from the initiation of preoxygenation until the initiation of laryngoscopy. Trial protocol will not dictate the brand or type of mechanical ventilator that will be used to deliver non-invasive ventilation.

7.3 Preoxygenation with Facemask Oxygen Group

For patients randomized to preoxygenation with facemask oxygen, supplemental oxygen will be administered via a non-rebreather mask or bag-mask device without manual ventilation from the initiation of preoxygenation until induction. Trial protocol will not dictate the brand or type of facemask. The decision between use of a non-rebreather mask and use of a bag-mask device will be made by treating clinicians. The decision of whether to provide manual ventilation with a bag-mask device between induction and laryngoscopy will be made by treating clinicians.

8. RECORDED STUDY OUTCOMES

8.1 Primary Outcomes

- Hypoxemia, defined as a peripheral oxygen saturation < 85% during the interval between induction and 2 minutes after tracheal intubation

8.2 Secondary Outcomes

- Lowest oxygen saturation during the interval between induction and 2 minutes after tracheal intubation

8.3 Safety Outcomes

- Operator-reported aspiration
- Fraction of inspired oxygen at 24 hours after induction
- Oxygen saturation at 24 hours after induction
- New pneumothorax, defined as radiology report of new pneumothorax on chest imaging in the 24 hours after induction.
- New infiltrate, defined as radiology report of new infiltrate on chest imaging in the 24 hours after intubation.

8. 4 Exploratory Outcomes

- Procedural Characteristics & Complications
    - Severe hypoxemia (lowest oxygen saturation of <80%) between induction and two minutes after tracheal intubation
    - Very severe hypoxemia (lowest oxygen saturation of <70%) between induction and two minutes after tracheal intubation
    - Oxygen saturation at induction
    - Systolic blood pressure at induction
    - Duration from induction to successful intubation (duration of the intubation procedure)
    - Cormack-Lehane grade of glottic view on first attempt
    - Successful intubation on the first attempt
    - Number of laryngoscopy attempts
    - Number of attempts at passing a bougie
    - Number of attempts at passing an endotracheal tube
    - Cardiovascular collapse, defined as a composite of one or more of the following between induction and 2 minutes after intubation:
        1. Systolic blood pressure < 65 mmHg
        2. New or increased vasopressor
        3. Cardiac arrest not resulting in death within 1 hour of induction
        4. Cardiac arrest resulting in death within 1 hour of induction
- Clinical Outcomes
    - 28-day in-hospital mortality
    - Ventilator-free days to 28 days
    - ICU-free days to 28 days

9. DATA COLLECTION

Data collected for the purposes of this study will come from three sources: [1] variables documented in the electronic health record as part of clinical care, [2] variables recorded by clinical staff's bedside observation during the intubation procedure, and [3] variables reported by the operator immediately following the intubation procedure. Data from the electronic medical record will be collected by trained study personnel (key study personnel) using a standardized electronic case report form. It is infeasible to have research staff present during each emergency tracheal intubation. Therefore, clinical staff not participating in the tracheal intubation procedure will collect data elements relevant to outcomes of emergency tracheal intubation using a standardized electronic case report form. These variables are readily available by bedside observation and do not require interaction with the patient but are not uniformly documented in the electronic health record (e.g., lowest oxygen saturation and lowest blood pressure from induction to two minutes after tracheal intubation). Immediately following the intubation procedure, the operators will record data elements known only to them (e.g., glottic view obtained during the procedure and visualization of gastric aspiration in the oropharynx). Operators and clinical staff observing the procedure at the bedside will not be considered key study personnel. Training will be provided to clinicians who may serve as operators or bedside observers. The activities of these clinicians will be limited to the reporting of data routinely reported as part of clinical care.

The following variables will be recorded:

Baseline:

- age
- sex
- race and ethnicity
- height
- weight
- body mass index
- Acute Physiology and Chronic Health Evaluation (APACHE II) score
- active medical problems at the time of enrollment
- comorbidities
- indication for intubation
- vasopressor receipt in the hour prior to enrollment
- highest FiO2 in the hour prior to enrollment
- lowest SpO2/FIO2 ratio (or PaO2/FIO2 ratio) in the hour prior to enrollment
- Glasgow Coma Scale score
- oxygen delivery device at enrollment
- assessment of the likelihood of a difficult intubation
- presence of difficult airway characteristics
    - limited mouth opening
    - limited anatomic neck mobility
    - cervical immobilization due to trauma
    - increased neck circumference
    - facial trauma
    - obesity

    - body fluids anticipated to obscure laryngeal view
- operator's level of training and specialty
- operator's prior intubation experience

Peri-procedural:

Enrollment to induction

- SpO_2 and FiO_2 at enrollment
- oxygen saturation from enrollment to induction
- approach to preoxygenation
- duration of preoxygenation

Induction to first laryngoscopy attempt

- time of sedative administration (induction)
- sedative agent and dose
- neuromuscular blocking agent and dose
- administration of an intravenous fluid bolus prior to induction
- administration of a vasopressor prior to induction
- SpO_2 at induction
- systolic blood pressure at induction
- approach to oxygen administration and ventilation between induction and laryngoscopy

First laryngoscopy attempt to successful intubation

- time of start of first laryngoscopy attempt
- laryngoscope model, blade size, blade shape on first attempt
- use of video screen (if applicable) on first laryngoscopy attempt
- best Cormack-Lehane grade of glottic view on the first laryngoscopy attempt
- presences of body fluids obstructing laryngeal view
- presence of upper airway obstruction or edema
- receipt of chest compressions at time of first laryngoscopy attempt
- number of intubation attempts
    - number of times laryngoscope entered mouth
    - number of times bougie entered mouth (if applicable)
    - number of times endotracheal tube entered mouth
- reason for failure of first intubation attempt (if applicable)
- device(s) used on subsequent intubation attempts (if applicable)
- necessity of an additional operator
- esophageal intubation
- injury to the teeth
- operator-reported aspiration between induction and intubation
- time of successful tracheal intubation
- endotracheal tube size
- lowest SpO2 from induction until 2 minutes after intubation
- lowest systolic blood pressure from induction until 2 minutes after intubation
- new or increased vasopressor use from induction until 2 minutes after intubation
- cardiac arrest from induction until 2 minutes after intubation not resulting in death within 1 hour of induction

- cardiac arrest from induction until 2 minutes after intubation resulting in death within 1 hour of induction

In-hospital:

24 hours after enrollment

- new pneumothorax detected in the first 24 hours after enrollment
- vasopressor receipt at 24 hours after enrollment
- SpO_2 at 24 hours after enrollment
- FiO_2 at 24 hours after enrollment
- PEEP at 24 hours after enrollment
- systolic blood pressure at 24 hours after enrollment

28 days after enrollment

- 28-day in-hospital mortality
- ventilator-free days
- ICU-free days

10. Risks and Benefits

10.1 Risks of Tracheal Intubation in the ED or ICU

Patients who are severely ill enough to require emergency tracheal intubation in the ED or ICU as part of their clinical care are at high risk of complications. Many patients are undergoing intubation for hypoxemia or hemodynamic instability. Severe hypoxemia or cardiovascular instability occurs during nearly half of intubations in the ED and ICU (1, 2, 4, 5). Hypoxemia and hypotension during intubation are associated with an increased risk of cardiac arrest and death.(9, 10) Cardiac arrest occurs in 1-in-25 cases of emergency tracheal intubation.

Other complications during intubation may include aspiration (approximately 2.8% of cases), esophageal intubation (1.3%) injury to oral or dental structures (0.2%), and pneumothorax (0.1%). The long-term consequences of complications occurring during emergency tracheal intubation are unclear. Neurologic recovery from traumatic brain injury may be worse after hypoxemia due to secondary ischemic insult.(11)

10.2 Potential Risks of Participation in the PREOXI Trial

Participation in the PREOXI trial involves <u>minimal incremental risk</u> because:

- All patients eligible for the study are already experiencing emergency tracheal intubation, with the accompanying risks, as part of their clinical care
- Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that are commonly used in current clinical care. All patients eligible for the study would experience an approach to preoxygenation as part of their clinical care
- No benefits or risks are currently known to differ between the two approaches
- Both approaches have determined to be acceptable options for the optimal care of the patient by treating clinicians (otherwise the patient is excluded from the study)

Although no risks are currently known to differ between preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen (both standard-of-care

approaches in currently clinical care), it is possible that the results of the PREOXI trial will ultimately demonstrate a difference between the two approaches in the risk of hypoxemia, hypotension, cardiac arrest, aspiration, or another outcome.

10.3 Potential Benefits of Participation in the PREOXI Trial

The primary benefits of the PREOXI trial will be the indirect benefits to society that would result if one approach to preoxygenation is found to prevent complications. Because millions of critically ill adults undergo emergency tracheal intubation each year, if one of the two approaches were found to prevent serious complications, the findings would immediately improve the care provided to millions of severely ill patients. Compared to the minimal risks of participation in the study, the pursuit of these benefits is reasonable.

10.4 Minimization of Risk

Federal regulations 45 CFR 46.111(a)(1) require that risks to patients are minimized by using procedures which are consistent with sound research design. This trial meets this human subjects protection requirement by incorporating numerous design elements to minimize risk to patients.

Both approaches to preoxygenation have been used in clinical practice for decades with an established safety profile in the same populations included in the PREOXI trial. To further mitigate risk, we will exclude patients with specific risk factors for adverse events such as those already receiving non-invasive positive pressure ventilation and any patient for whom treating clinicians determine that a specific approach to preoxygenation is required or contraindicated for the optimal care of the patient.

The trial protocol includes monitoring of adverse events, robust assessment of clinical outcomes, and an interim analysis by an independent DSMB, empowered to stop the trial or modify the trial protocol at any time.

Finally, to limit the risks associated with the collection of protected health information (PHI), the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. REDCap tools will be used to ensure that the PHI that is collected is only visible to investigators at the healthcare system where the patient was enrolled. To protect participant privacy, REDCap tools will be used to ensure that only deidentified data can be exported for use during analysis.

11. Statistical Considerations

11.1 Initial Sample Size Determination:

The minimum clinically important difference in hypoxemia that would be required to justify routine preoxygenation with non-invasive positive pressure ventilation rather than preoxygenation with facemask oxygen during emergency tracheal intubation of critically ill adults is uncertain. The current trial will be designed to detect a 6% absolute difference between groups in the rate of hypoxemia. An absolute difference of 6% in the incidence of hypoxemia is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.(19, 31) Assuming an incidence of hypoxemia of 17% in the facemask group based on data from two recently completed trials in the same ED and ICU

settings, detecting a 6% absolute decrease in the incidence of hypoxemia with 85% power at a two-sided alpha level of 0.05 would require enrollment of 1,264 patients (632 per group). Anticipating missing data for up to 3% of patients, we will plan to enroll a total of 1,300 patients (650 per group). This sample size calculation was performed in PS version 3.1.2.

11.2 Statistical Analysis:

Prior to the conclusion of enrollment, we will make publicly available a complete, final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

11.2.1 Primary Analysis:

The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to preoxygenation with non-invasive positive pressure ventilation versus patients randomized to preoxygenation with facemask oxygen with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.

11.2.2 Secondary Analysis:

We will perform intention-to-treat comparisons of secondary, exploratory, and safety outcomes. Continuous outcomes will be compared with Wilcoxon Rank Sum test and categorical variables with the Chi-squared test. Data on patient characteristics will be summarized as number and proportion for categorical variables and as median and interquartile range for continuous variables.

We will also perform an adjusted comparison of the primary outcome between groups using a generalized linear mixed effects model including a random effect for site and fixed effects for group assignment and the following pre-specified baseline variables:

1. Age;
2. Sex;
3. Race and Ethnicity;
4. BMI;
5. Location at enrollment (ED or ICU)
6. Highest fraction of inspired oxygen in the hour prior to initiation of preoxygenation;
7. APACHEII score; and
8. Indication for intubation (hypoxemic respiratory failure: Yes vs No)
9. Operator experience (number of previous intubations the operator has performed)

11.2.3 Effect Modification (Subgroup Analyses)

To evaluate whether pre-specified baseline variables modify the effect of study group assignment on the primary outcome, we will perform logistic regression modelling with the primary outcome as the dependent variable and independent variables of study group, the proposed effect modifier, and the interaction between the two. Any interaction term with a p-value less than 0.1 will be considered to identify an effect modifier. To account for non-linear relationships, continuous variables will be analyzed using restricted cubic splines with between 3 and 5 knots. Forest plots will be used to graphically display the adjusted analyses, and locally weighted regression or partial effects plots will be used to portray the association between continuous

covariates and the outcome. A full list of prespecified subgroup analyses will be outlined in the detailed Statistical Analysis Plan but will include:

1. BMI;
2. Location (ED vs ICU);
3. Highest fraction of inspired oxygen in the hour prior to initiation of preoxygenation)
4. Indication for intubation (hypoxemic respiratory failure, other) ;
5. APACHEII score; and
6.

11.3 Interim Analysis

The DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrollment of 650 patients. The pre-specified stopping boundary for efficacy will be a P value < 0.001 for the difference between group in the primary outcome using a Chi-square test. This conservative Haybittle–Peto boundary will allow the final analysis to be performed using an unchanged level of significance (two-sided P value < 0.05).
Finally, after the interim analysis, the DSMB will evaluate the rate of the primary outcome in the facemask group. If the incidence of the primary outcome in the facemask group differs from the original estimate, the DSMB may suggest an increase sample size that would maintain the pre-planned statistical power to detect the pre-planned relative risk difference in the primary outcome between groups.

11.4 Correction for Multiple Testing

We will analyze a single pre-specified primary outcome and a single pre-specified secondary outcome. Consistent with recommendations of the Food and Drug Administration[60] and the European Medicines Association,[61] each will be tested using a two-sided P value with a significance level of 0.05. For all other analyses except safety analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors*,[62] and no corrections for multiple comparisons will be performed.

11.5 Handling of Missing Data

No patients will be lost to follow up before the measurement of the primary outcome, but oxygen saturation may be unavailable in some cases (equipment malfunction, observer error during a rapid, emergency procedure, or cardiac arrest). Missing data will not be imputed for the primary outcome, or any of the secondary or exploratory outcomes. In adjusted analyses, missing data for baseline covariates will be imputed using multiple imputations.

12. Privacy and Confidentiality

All patients will be assigned a unique study ID number for use in the coded study database. Study personnel will access patients' electronic health records at three planned time points: immediately following enrollment; when collecting baseline demographics and comorbidities (may occur anytime between enrollment and final data collection); and when collecting clinical

outcomes (any time after the first of discharge or 28 days following intubation). The electronic health record may be accessed again, as needed, between enrollment and study publication to respond to queries from the coordinating center focused on ensuring data completeness and quality. The minimal PHI that is collected will be visible only to site investigators at the site where the patient was enrolled. The dataset for analysis will contain the unique study ID and no other patient identifiers. At the time of publication, a fully de-identified version of the database will be generated.

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Following publication of the study results, all hard copies of data collection forms will be destroyed and the REDCap database will be fully de-identified in accordance with institutional regulations.

13. Follow-up and Record Retention

Patients will be followed after enrollment up to 28 days or until hospital discharge, whichever occurs first. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. The minimal PHI that is collected will be available only to site investigators at the site where the patient was enrolled. At the time of publication, a fully de-identified version of the database will be generated.

14. Safety Monitoring and Adverse Events

Assuring patient safety is an essential component of this protocol. Preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen are both standard-of-care interventions that have been used in clinical practice for decades with an established safety profile. However, any trial conducted during a high-risk, time-sensitive procedure like tracheal intubation of critically ill patients raises unique safety considerations. This protocol addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from preoxygenation with non-invasive positive pressure ventilation or preoxygenation with facemask oxygen;
2. Systematic collection of outcomes relevant to the safety of preoxygenation with non-invasive positive pressure ventilation and preoxygenation with facemask oxygen;
3. Structured monitoring, assessment, recording, and reporting of adverse events.

14.1 Adverse Event Definitions

Adverse Event – An adverse event will be defined as any untoward or unfavorable medical occurrence in a human subject temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. Any adverse event occurring during the research will be classified according to the following characteristics:

- **Seriousness** – An adverse event will be considered "serious" if it:
    - Results in death;
    - Is life-threatening (defined as placing the patient at immediate risk of death);
    - Results in inpatient hospitalization or prolongation of existing hospitalization;
    - Results in a persistent or significant disability or incapacity;
    - Results in a congenital anomaly or birth defect; or
    - Based upon appropriate medical judgment, may jeopardize the patient's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- **Unexpectedness** – An adverse event will be considered "unexpected" if the nature, severity, or frequency is neither consistent with:
    - The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol; nor
    - The expected natural progression of any underlying disease, disorder, or condition of the subject experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

- **Relatedness** – The strength of the relationship of an adverse event to a study intervention or study procedure will be defined as follows:
    - Definitely Related: The adverse event follows (1) a reasonable, temporal sequence from a study procedure AND (2) cannot be explained by the known characteristics of the patient's clinical state or other therapies AND (3) evaluation of the patient's clinical state indicates to the investigator that the experience is definitely related to study procedures.
    - Probably or Possibly Related: The adverse event meets some but not all of the above criteria for "Definitely Related".
    - Probably Not Related: The adverse event occurred while the patient was on the study but can reasonably be explained by the known characteristics of the patient's clinical state or other therapies.
    - Definitely Not Related: The adverse event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
    - Uncertain Relationship: The adverse event does not fit in any of the above categories.

14.2 Monitoring for Adverse Events

The time interval during which patients will be monitored for the occurrence of adverse events

begins at randomization and ends at the first of hospital discharge or 28 days. Adverse events occurring before randomization or after hospital discharge or 28 days will not be collected. The lead investigator at each enrolling site will have primary responsibility overseeing the monitoring, assessment, and reporting of adverse events. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record and by communication with treating clinicians. Site study personnel will evaluate for the occurrence of adverse events by manual review of the electronic health record at two time points. The first will occur approximately 24 hours after randomization at the time of initial data collection. The second will occur at the first of hospital discharge or 28 days after enrollment at the time of final data collection. Study personnel at each site will also communicate regularly with the treating clinicians who perform tracheal intubation in the study environments between enrollment and 28 days after enrollment to solicit information about any potential adverse events. If study personnel at a site identify a potential adverse event, the lead investigator at the site will be immediately notified. The lead investigator at the site will assess the seriousness, unexpectedness, and relatedness of the potential adverse event. With assistance as needed from the coordinating center and the trial primary investigator, the lead investigator at the site will determine whether the event qualifies for recording and reporting.

14.3 Recording and Reporting Adverse Events

The following types of adverse events will be recorded and reported:

- Adverse events that are Serious and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.
- Adverse events that are Unexpected and Definitely Related, Probably or Possibly Related, or of Uncertain Relationship.

Adverse events that do not meet the above criteria will not be recorded or reported. Adverse events that the lead investigator at a site assesses to meet the above criteria for recording and reporting will be entered into the adverse event electronic case report form in the trial database. The lead investigator at the site will record an assessment of each characteristic for the adverse event, including seriousness, unexpectedness, and relatedness. For any adverse event that is **serious AND unexpected**, and definitely related, probably or possibly related, or of uncertain relationship, the lead investigator at the site will report the adverse event to the coordinating center and the trial primary investigator **within 24 hours** of becoming aware of the adverse event. For any other adverse event requiring recording and reporting, the lead investigator at the study site will report the adverse event to the coordinating center and the trial principal investigator **within 72 hours** of becoming aware of the adverse event. The coordinating center and the trial principal investigator will coordinate with the lead investigator at the site to obtain information about the adverse event regarding each characteristic for the adverse event, including seriousness, expectedness, and relatedness. The lead investigator at the site will be responsible for making final determinations regarding seriousness and unexpectedness. The coordinating center and trial principal investigator will be responsible for making final determinations regarding relatedness.

For adverse events that meet the above criteria for recording and reporting, the coordinating center will notify the DSMB, the IRB, and the sponsor in accordance with the following reporting plan:

Characteristics of the Adverse Event	Reporting Period
Fatal or life-threatening (and therefore serious), unexpected, and definitely related, probably or possibility related, or of uncertain relationship.	Report to the DSMB, IRB, and sponsor within 7 days after notification of the event.
Serious but non-fatal and non-life-threatening, unexpected, and definitely related, probably or possibly related, or of uncertain relationship.	Report to DSMB, IRB, and sponsor within 15 days of notification of the event.
All other adverse events meeting criteria for recording and reporting.	Report to DSMB in regularly scheduled DSMB safety reports.

The coordinating center will distribute the written summary of the DSMB's periodic review of reported adverse events to the IRB in accordance with NIH guidelines: (http://grants.nih.gov/grants/guide/notice-files/not99-107.html).

14.4 Clinical Outcomes that may be Exempt from Adverse Event Recording and Reporting

In this study of critically ill patients at high risk for death and other adverse outcomes due to their underlying critical illness, clinical outcomes, including death and organ dysfunction, will be systematically collected and analyzed for all patients. The primary, secondary, safety, and exploratory outcomes will be recorded and reported as clinical outcomes and not as adverse events unless treating clinicians or site investigators believe the event is Definitely Related or Probably or Possibly Related to the study intervention or study procedures. This approach – considering death and organ dysfunction as clinical outcomes rather than adverse events and systemically collecting these clinical outcomes for analysis – is common in ICU trials. This approach ensures comprehensive data on death and organ dysfunction for all patients, rather than relying on sporadic adverse event reporting to identify these important events. The following events are examples of study-specific clinical outcomes that would not be recorded and reported as adverse events unless treating clinicians or site investigators believe the event was Definitely Related or Probably or Possibly Related to the study intervention or study procedures:

- Death (all deaths occurring prior to hospital discharge or 28 days will be recorded);
- Organ dysfunction
    - Pulmonary – hypoxemia, aspiration, acute hypoxemic respiratory failure, pneumothorax
    - Cardiac – hypotension, shock, vasopressor receipt, cardiac arrest;
- Duration of mechanical ventilation;
- Duration of ICU admission;
- Duration of hospitalization

Note: A study-specific clinical outcome may also qualify as an adverse event meeting criteria for recording and reporting. For example, a pneumothorax that the investigator considers Definitely Related to preoxygenation with non-invasive positive pressure ventilation would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

14.5 Unanticipated Problems involving Risks to Subjects or Others

Investigators must also report Unanticipated Problems Involving Risks to Subjects or Others ("Unanticipated Problems"), regardless of severity, associated with study procedures **within 24 hours** of the site investigator becoming aware of the Unanticipated Problem. An Unanticipated Problem is defined as any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol; and (b) the characteristics of the subject population being studied; AND
- Definitely Related or Probably or Possibly Related to participation in the research (as defined above in the section on characteristics of adverse events); AND
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

If any study personnel at a site become aware of an event that may represent an Unanticipated problem, they will immediately contact the lead investigator for the site. The lead investigator for the site will assess whether the event represents an Unanticipated Problem by applying the criteria described above. If the lead investigator at a site determines that the event represents an Unanticipated Problem, the lead investigator at the site will record the Unanticipated Problem in the Unanticipated Problem electronic case report form in the trial database. The lead investigator at the site will then communicate that an Unanticipated Problem has occurred to the coordinating center and the principal investigator **within 24 hours** of the lead investigator at the site becoming aware of the Unanticipated Problem. The coordinating center and principal investigator will coordinate with the lead investigator at the site to obtain information about the Unanticipated Problem. The coordinating center will report the Unanticipated Problem to the DSMB, IRB, and sponsor within 15 days of becoming aware of the Unanticipated Problem.

15. Data and Safety Monitoring Board (DSMB)

The principal role of the DSMB is to assure the safety of patients in the trial. They will regularly monitor data from this trial, review and assess the performance of its operations, and make recommendations to the steering committee and sponsor with respect to:

- Participant safety and risk/benefit ratio of study procedures and interventions
- Initial approval of the protocol and subsequent amendments (with specific attention to study population, intervention, and study procedures)
- Adherence to the protocol requirements
- Completeness, quality, and planned analysis of data
- Ancillary study burden on participants and main study
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance

The DSMB will consist of members with expertise in bioethics, emergency medicine, pulmonary and critical care medicine, anesthesia, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The coordinating center, principal investigators, and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event

reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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Tracking of Protocol Versions:

Version 1.0 – Initial Submission

Version 1.1: July 7, 2023:

- Minor protocol revisions to align with prespecified statistical analysis plan:
    - Addition of new "New infiltrate" as a safety outcome and "Successful intubation on the first attempt" as an exploratory procedural outcome
    - Updated covariables in adjusted analysis of the primary outcome (a secondary analysis) to match prespecified statistical analysis plan
    - Updated prespecified variables to be evaluated in effect modification (subgroup analysis) to match prespecified statistical analysis plan

Summary of Changes to the PREOXI Trial Protocol

Tracking of Protocol Versions:

Version 1.0 – Initial Protocol (February 21, 2022)

Version 1.1: Final Trial Protocol (July 7, 2023):

- Changes in this version: Minor protocol revisions to align with prespecified statistical analysis plan:
    - Addition of new "New infiltrate" as a safety outcome and "Successful intubation on the first attempt" as an exploratory procedural outcome;
    - Updated covariables in adjusted analysis of the primary outcome (a secondary analysis) to match prespecified statistical analysis plan;
    - Updated prespecified variables to be evaluated in effect modification (subgroup analysis) to match prespecified statistical analysis plan.

Protocol and statistical analysis plan for the PREOXI trial of preoxygenation with noninvasive ventilation vs oxygen mask.

Short Title: Protocol and Analysis Plan for the PREOXI Trial

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Sources of Funding: The research was funded primarily by the Department of Defense, Defense Health Agency, J9 Office, RESTORAL program. Kevin P. Seitz was supported in part by the NIH (T32HL087738). Jessica A. Palakshappa was supported in part by the NIA (K23AG073529) Matthew W. Semler was supported in part by the NHLBI (K23HL143053). Jonathan D. Casey was supported in part by the NHLBI (K23HL153584). Derek Russell was supported in part by the NHLBI (K08HL148514-01A1). Data collection utilized the Research Electronic Data Capture (REDCap) tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR000445 from NCATS/NIH). The funding institutions had no role in (1) conception, design, or conduct of the study, (2) collection, management, analysis, interpretation, or presentation of the data. The views expressed are those of the author and do not reflect the official views or policy of the Department of Defense, its Components. The authors do not have any financial interest in the companies whose

materials are discussed in this publication, and no federal endorsement of the companies and materials is intended.

Conflicts of Interest and Financial Disclosures: Kevin W. Gibbs MD reports financial support and travel were provided by US Department of Defense. Adit. A. Ginde MD MPH reports financial support was provided by US Department of Defense. Matthew E. Prekker MD MPH reports financial support was provided by US Department of Defense. Kevin P. Seitz MD MSc reports financial support was provided by National Heart Lung and Blood Institute. Susan B. Stempek PA MBA reports financial support was provided by American College of Chest Physicians. Akram Khan MD reports financial support was provided by United Therapeutics Corporation. Akram Khan MD reports financial support was provided by 4D Medicine Ltd. Akram Khan MD reports financial support was provided by Regeneron Pharmaceuticals Inc. Akram Khan MD reports financial support was provided by Roche. Akram Khan MD reports financial support was provided by Dompé pharmaceutical. Jessica A. Palakshappa MD MS reports financial support was provided by National Institute on Aging. Joanne M. Wozniak PA MS reports was provided by American College of Chest Physicians. Matthew C. Exline MD, MPH reports financial support was provided by Abbott Laboratories. Derek W. Russell MD reports financial support was provided by National Heart Lung and Blood Institute. Shekar Ghamande MD reports financial support was provided by US Department of Defense. Ari Moskowitz MD MPH reports financial support was provided by National Heart Lung and Blood Institute. Jill Bastman BSN reports financial support was provided

by US Department of Defense. Micah T. Long MD reports financial support was provided by pocket cards. Steven G. Schauer DO MS reports was provided by US Department of Defense. David Janz MD MSc reports financial support was provided by US Department of Defense. Matthew W. Semler MD MSc reports financial support was provided by US Department of Defense. Matthew W. Semler MD MSc reports financial support was provided by National Heart Lung and Blood Institute. Jonathan D. Casey MD MSc reports was provided by US Department of Defense. Jonathan D. Casey MD MSc reports was provided by National Heart Lung and Blood Institute. Jonathan D. Casey MD MSc reports travel was provided by Fisher & Paykel Healthcare Inc. Todd W Rice MD MSc reports a relationship with Cumberland Pharmaceuticals Inc that includes: consulting or advisory and equity or stocks. Derek W. Russell MD reports a relationship with Achieve Life Science Inc that includes: equity or stocks. Matthew W. Semler MD MSc reports a relationship with Baxter International Inc that includes: consulting or advisory.

Keywords for indexing: Endotracheal intubation, non-invasive positive pressure ventilation, critical illness, respiratory failure, oxygen

Subject Descriptor Number: 4.4 Clinical Trials in Critical Care Medicine

Manuscript Word Count (body only): 4060

Abstract Word Count: 243

Supplemental digital content is available for this article.

HIGHLIGHTS

- Hypoxemia is common during emergency tracheal intubation
- Supplemental oxygen prior to intubation (preoxygenation) reduces risk of hypoxemia
- The PREOXI trial compares noninvasive ventilation vs oxygen mask preoxygenation
- This protocol describes the design, methods, and planned analyses
- PREOXI is the largest trial of preoxygenation for emergency intubation to date

ABSTRACT

Background: Hypoxemia is a common and life-threatening complication during emergency tracheal intubation of critically ill adults. The administration of supplemental oxygen prior to the procedure ("preoxygenation") decreases the risk of hypoxemia during intubation.

Research Question: Whether preoxygenation with noninvasive ventilation prevents hypoxemia during tracheal intubation of critically ill adults, compared to preoxygenation with oxygen mask, remains uncertain.

Study Design and Methods: The PRagmatic trial Examining OXygenation prior to Intubation (PREOXI) is a prospective, multicenter, non-blinded randomized comparative effectiveness trial being conducted in 7 emergency departments and 17 intensive care units across the United States. The trial compares preoxygenation with noninvasive ventilation versus oxygen mask among 1300 critically ill adults undergoing emergency tracheal intubation. Eligible patients are randomized in a 1:1 ratio to receive either noninvasive ventilation or an oxygen mask prior to induction. The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation <85% between induction and 2 minutes after intubation. The secondary outcome is the lowest oxygen saturation between induction and 2 minutes after intubation. Enrollment began on 10 March 2022 and is expected to conclude in 2023.

Interpretation: The PREOXI trial will provide important data on the effectiveness of noninvasive ventilation and oxygen mask preoxygenation for the prevention of hypoxemia during emergency tracheal intubation. Specifying the protocol and statistical

analysis plan prior to the conclusion of enrollment increases the rigor, reproducibility, and interpretability of the trial.

Clinical trial registration number: NCT05267652

INTRODUCTION

Life-threatening hypoxemia occurs in 10-20% of emergency tracheal intubations in the Emergency Department (ED) and Intensive Care Unit (ICU).[1,2] Hypoxemia during intubation is associated with an increased risk of cardiac arrest and death.[3,4] Identifying interventions to prevent hypoxemia during emergency tracheal intubation is a high priority for clinicians and researchers.[5,6] Because patients are typically apneic between induction of anesthesia and intubation but continue to consume oxygen, the oxygen content in the lungs at the time of induction is a primary determinant of whether the patient will experience hypoxemia. Preoxygenation, the administration of supplemental oxygen prior to induction of anesthesia, increases the oxygen content in the lung at induction and decreases the risk of hypoxemia.[7,8] In current clinical practice, preoxygenation for emergency tracheal intubation of critically ill adults is most commonly administered using either an oxygen mask or noninvasive ventilation.[1]

Preoxygenation with an oxygen mask is typically performed using either a non-rebreather mask or a bag-mask device. A non-rebreather mask is a loose-fitting mask with an oxygen reservoir connected to an oxygen source. A bag-mask device is a mask capable of forming a tight seal over the mouth when held in place by a clinician and can be used to provide supplemental oxygenation alone, or both supplemental oxygen and manual ventilation.[9] Both types of oxygen mask can deliver up to 100% oxygen, are simple to set up, and have low potential for gastric insufflation. However, oxygen masks may deliver oxygen less effectively in critically ill patients when tachypnea, high minute ventilation, and poor mask seal allow the entrainment of ambient air with resulting alveolar oxygen concentrations as low as 50%.[7,10]

Preoxygenation is also routinely administered via noninvasive ventilation, in which a tight-fitting mask is connected to a machine capable of providing both 100% oxygen and positive pressure ventilation. Compared to an oxygen mask, noninvasive ventilation may reduce air entrainment by delivering a higher inspiratory flow rate of oxygen and by minimizing leaks. Additionally, noninvasive ventilation increases the mean airway pressure and recruits atelectatic lung, potentially reducing shunting. Compared with an oxygen mask, noninvasive ventilation may take longer to initiate and may potentially increase the risk of gastric insufflation and aspiration.

Two small, randomized trials have compared these two approaches to preoxygenation. The first trial found that, among 53 ICU patients undergoing tracheal intubation in two hospitals in France, noninvasive ventilation increased the lowest oxygen saturation compared to an oxygen mask (mean lowest oxygen saturation 93% vs. 81%, respectively, P<0.001) with no difference between groups in the incidence of aspiration (6% vs. 8%).[11] Among 201 ICU patients in 6 hospitals in France, the second trial found no difference in the severity of illness in the 7 days after intubation and an incidence of hypoxemia during intubation of 18.4% in the noninvasive ventilation group versus 27.7% in the oxygen mask group (P = 0.10).[12] Thus, whether noninvasive ventilation for preoxygenation in critically ill adults undergoing emergency tracheal intubation decreases the incidence of hypoxemia compared to an oxygen mask remains unknown. Therefore, we designed the PRagmatic trial Examining OXygenation prior to Intubation (PREOXI) to test the hypothesis that, among critically ill adults undergoing emergency tracheal intubation in the ED and ICU, preoxygenation with noninvasive

ventilation will decrease the incidence of hypoxemia compared to preoxygenation with an oxygen mask.

METHODS AND ANALYSIS

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see Table 1 and online supplement file 1, section 1). [13]

Funding:

Funding for this trial was provided by the Department of Defense, Defense Health Agency, J9 Office, RESTORAL program. The funder has no role in study design or conduct, data collection or analysis.

Patient and public involvement:

Materials used to communicate about the study with patients and families were developed with input from the Vanderbilt Community Engaged Research Core, which includes input from patients and community members. Study authors will disseminate the results of this study online and via social media in forms suitable for public understanding.

Study Design:

PREOXI is a pragmatic, multicenter, non-blinded, parallel-group, randomized trial comparing preoxygenation with noninvasive ventilation to preoxygenation with an oxygen mask among critically ill adults undergoing emergency tracheal intubation in the ED and ICU. The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation < 85% between induction of anesthesia and two minutes after intubation. The trial is conducted by the Pragmatic Critical Care Research Group (www.pragmaticcriticalcare.org). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. The trial was registered prior to initiation of enrollment (ClinicalTrials.gov identifier: NCT05267652).

Study Population:

Patients located in a participating ED or ICU who are undergoing tracheal intubation using a laryngoscope and sedation are eligible. Patients are excluded if they are known to be less than 18 years old, are known to be pregnant or a prisoner, require positive pressure ventilation for apnea or hypopnea, or have an immediate need for tracheal intubation that precludes performance of study procedures, or if the clinician performing the procedure (referred to as the “operator”) determines that preoxygenation with noninvasive ventilaton or an oxygen mask is either required or contraindicated. Complete lists of inclusion and exclusion criteria are provided in Table 2.

Randomization and treatment allocation:

Patients are randomized in a 1:1 ratio to undergo preoxygenation with noninvasive ventilaton vs oxygen mask in permuted blocks of variable size, stratified by

study site. Study-group assignments are generated using a computerized randomization sequence, placed in sequentially numbered opaque envelopes, and distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets eligibility criteria. Study group assignment remains concealed to study personnel and treating clinicians until after the decision has been made to enroll the patient and the envelope is opened. Patients are considered to be enrolled once the operator opens the opaque trial envelope to reveal study group assignment. After randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment due to the nature of the study intervention.

STUDY INTERVENTIONS

Training:

Before beginning enrollment at each site, study investigators provide training on study procedures including instructional videos with consensus best practice recommendations for preoxygenation with noninvasive ventilation and preoxygenation with an oxygen mask. Observers receive in-person training on the collection of data during the intubation procedure using example data collection sheets. Descriptions of the training videos and website links can be found in the supplementary appendix.

Noninvasive ventilation group:

For patients assigned to the noninvasive ventilation group, operators are instructed to administer noninvasive ventilation via a tight-fitting mask covering the nose and mouth connected to either a conventional mechanical ventilator or a dedicated

noninvasive ventilator (i.e., BiPAP machine) from the initiation of preoxygenation until the initiation of laryngoscopy. The trial protocol does not dictate brand or type of ventilator, ventilator settings, or duration of preoxygenation. Operators receive the following best practice recommendations for the administration of preoxygenation using noninvasive ventilation:

1. Preoxygenate ≥ 3 minutes (if feasible)
2. Continue noninvasive ventilation until initiation of laryngoscopy
3. Fraction of Inspired Oxygen (FiO2) of 100%
4. Expiratory pressure ≥ 5 cm of water
5. Inspiratory pressure ≥ 10 cm of water
6. Respiratory rate of ≥ 10

Oxygen mask group:

For patients assigned to the oxygen mask group, clinicians are instructed to administer supplemental oxygen via a non-rebreather mask or bag-mask device without manual ventilation from the initiation of preoxygenation until the induction of anesthesia. The operator determines whether to use a non-rebreather mask or a bag-mask device without manual ventilation. The trial protocol does not dictate the brand or type of non-rebreather or bag-mask device or duration of preoxygenation. Between induction of anesthesia and initiation of laryngoscopy, the operator determines whether to provide oxygen with a non-rebreather mask, oxygen with a bag-mask device without manual ventilation, or oxygen with a bag-mask device with manual ventilation.[2] Operators

receive the following best practice recommendations for the administration of preoxygenation using an oxygen mask:

1. Preoxygenate ≥ 3 minutes (if feasible)
2. Maximal oxygen flow rate possible (≥ 15 liters per minute)
3. Continue oxygenation from induction to laryngoscopy

Cointerventions:

Study group assignment determines only the initial method of preoxygenation. Treating clinicians determine all other aspects of the intubation procedure including: [1] the co-administration of supplemental oxygen by nasal cannula (either standard nasal cannula, large bore nasal cannula, or heated high flow nasal cannula) before induction, between induction an initiation of laryngoscopy, and between initiation of laryngoscopy and intubation of the trachea; [2] choice of induction medication and timing of administration; [3] use of neuromuscular blockade; [4] choice of laryngoscope; [5] use of additional airway management equipment and adjuncts; and [6] post-intubation ventilator settings.

Data Collection

An observer not directly involved with the intubation procedure collects data for key periprocedural outcomes, including oxygen saturation at induction and the lowest value for oxygen saturation between induction and two minutes after successful intubation. Observers may be clinical personnel on the enrolling unit (e.g., physicians or nurses) or research personnel. Immediately after the intubation procedure, the operator

completes a paper data collection form to record the device used for preoxygenation, the duration of preoxygenation, the devices used for oxygenation and ventilation between induction and laryngoscopy, and complications of intubation.[14] Study personnel at each site review the medical record to collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes. A complete list of baseline, peri-procedural, and in-hospital variables are provided in Supplemental Table 1.

Data on pneumothorax and new pulmonary infiltrates are collected by study staff from clinical radiology reports using a structured case report form. The clinical radiologist who interprets the chest imaging is unaware of study group assignment. A lung infiltrate is considered to be present if the clinical radiologist identifies on the chest imaging the presence of air bronchograms, centrilobular nodules, consolidation, ground-glass opacity, infiltrate, opacity, parenchymal opacification, pneumonia, pneumonitis pulmonary edema, or a tree-in-bud pattern. A pneumothorax or lung infiltrate present on chest imaging in the 24 hours after intubation will be assumed to be new if it was not present on chest imaging in the 24 hours prior to intubation. If no chest imaging is available in the 24 hours prior to intubation, any pneumothorax or lung infiltrate on chest imaging will be assumed to be new.

Primary Outcome

The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation <85% during the interval between induction and 2 minutes after intubation.

We selected hypoxemia (as a binary variable) rather than lowest oxygen saturation (a continuous variable) as the primary outcome for the trial for several reasons. First, experiencing hypoxemia in the range associated with an increased risk of adverse clinical outcomes (e.g., cardiac arrest) may be more clinically relevant than changes in oxygen saturation within the normal range. For example a change in oxygen saturation of 5 percentage points from 87% to 82% may be more closely associated with adverse outcomes than a change in oxygen saturation of 10 percentage points from 100% to 90%. Second, values for oxygen saturation are "right-censored" because oxygen saturation reaches 100% with a partial pressure of oxygen in arterial blood (PaO_2) of approximately 100 mmHg but patients may have a higher PaO_2 following preoxygenation. The approach of analyzing hypoxemia as a binary variable rather than lowest oxygen saturation has been used by many prior trials and endorsed by airway experts.[15-20]

We selected an oxygen saturation of <85% as the threshold for the primary outcome based on several physiologic and procedural factors. First, an oxygen saturation of 85% corresponds with the inflection point on the oxyhemoglobin dissociation curve, at which further decrements in arterial oxygen concentrations result in rapid and critical desaturation.[9] Second, an oxygen saturation <85% has been associated with an increased risk of cardiac arrest during tracheal intubation[21] and may be associated with increased mortality.[5]

Secondary Outcome:

The sole secondary outcome is the lowest oxygen saturation during the interval between induction and 2 minutes after tracheal intubation.

Additional Outcomes:

Table 3 reports the safety outcomes, exploratory outcomes, and clinical outcomes.

Sample Size Estimation

The minimum clinically important difference in the incidence of hypoxemia that would be required to justify routine preoxygenation with noninvasive ventilation rather than preoxygenation with an oxygen mask during the emergency tracheal intubation of critically ill adults is uncertain. The current trial is designed to detect a 6% absolute difference between groups in the incidence of hypoxemia, a difference that is similar to or smaller than the difference considered to be clinically meaningful in the design of prior trials of oxygenation strategies during tracheal intubation.[2,24] Assuming an incidence of hypoxemia of 17% in the oxygen mask group based on data from two recently completed trials by this network in similar ED and ICU settings, detecting a 6% absolute decrease in the incidence of hypoxemia with 85% power at a two-sided alpha level of 0.05 would require enrollment of 1,264 patients (632 per group).[25,26] Anticipating missing data for up to 3% of patients, we will plan to enroll a maximum of 1,300 total

patients (650 per group). This sample size calculation was performed in PS version 3.1.2 (Nashville, Tennessee).

Data and Safety Monitoring Board and Interim Analysis

A data and safety monitoring board (DSMB) consisting of members with expertise in bioethics, emergency medicine, pulmonary and critical care medicine, anesthesiology, biostatistics, and clinical trial methodology has overseen the design of the trial and is monitoring its conduct. The DSMB will review a single interim analysis, prepared by the study biostatistician at the anticipated halfway point of the trial after enrolment of 650 patients. The pre-specified stopping boundary for efficacy is a P value < 0.001 using a Chi-square test for the difference between groups in the primary outcome. This conservative Haybittle–Peto boundary will allow the final analysis to be performed using an unchanged level of significance (two-sided P value < 0.05).

The DSMB has the authority to recommend that the trial stop at any point, request additional data, request additional interim analyses, or request modifications to the study protocol.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables will be presented as number and percentage and compared between groups using a Chi-square text. Continuous variables will be presented as mean ± SD or median and IQR and compared between groups using a Wilcoxon Rank Sum test. We will also present

absolute between-group differences with associated 95% confidence intervals. A two-sided P-value of < 0.05 will define a statistically significant between-group difference in the primary outcome. With a single primary outcome, no adjustment for multiplicity will be made. For secondary, safety, and exploratory analyses, emphasis will be placed on the magnitude of differences between groups with 95% confidence intervals rather than statistical significance.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted, intention-to-treat comparison of the primary outcome of hypoxemia between patients randomized to the noninvasive ventilation group versus patients randomized to the oxygen mask group, using a chi-square test. The absolute difference in proportions, associated 95% confidence interval, and a P value for the comparison will be presented. The primary analysis will be conducted among patients for whom the primary outcome is available without imputation of missing data.

Additional Analyses of the Primary Outcome

Multivariable analysis

To account for relevant baseline covariates, we will fit a generalized linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group and the following prespecified baseline covariates: age, sex, race and ethnicity, body mass index (BMI), location at enrollment (ED or ICU), highest fraction of inspired oxygen in

the hour prior to initiation of preoxygenation, Acute Physiology and Chronic Health Evaluation (APACHE) II score[27], and indication for intubation (hypoxemic respiratory failure: Yes vs No). All continuous variables will be modelled assuming a non-linear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect modification

We will examine whether prespecified baseline variables modify the effect of study group assignment (noninvasive ventilation vs oxygen mask) on the primary outcome using a formal test of statistical interaction in a generalized linear mixed-effects model with the primary outcome as the dependent variable, study site as a random effect and fixed effects of study group, the prespecified proposed effect modifier and the interaction between the two. For categorical variables, we will present the OR and 95% CIs within each prespecified subgroup. Continuous variables will not be dichotomized for analysis of effect modification but may be dichotomized for data presentation. In accordance with the Instrument for assessing the Credibility of effect Modification Analyses (ICEMAN) recommendations, we have prespecified the following baseline variables as potential effect modifiers and hypothesized the direction of effect modification for each:

1. Patient location (ED vs ICU). We hypothesize that patient location will not modify the effect of study group assignment on the primary outcome.
2. Body Mass Index (kg/m^2). We hypothesize that Body Mass Index (BMI) will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia with preoxygenation within the

noninvasive ventilation group compared to the oxygen mask group among patients with higher BMIs, as compared to patients with lower BMIs. This hypothesis of effect modification is supported by evidence from multiple prior studies that patients with obesity are more likely to have early airway closure and atelectasis-dependent shunting that is likely to improve with positive pressure ventilation. [28,29]

3. Fraction of inspired oxygen in the hour prior to intubation. We hypothesize that the fraction of inspired oxygen received in the hour prior to intubation will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia in the noninvasive ventilation group compared to the oxygen mask group among patients with higher fractions of inspired oxygen in the hour prior to intubation, compared to patients with lower fractions of inspired oxygen. This hypothesis of effect modification is supported by evidence from multiple prior studies that patients requiring higher fractions of inspired oxygen have more atelectasis-dependent shunting that is likely to improve with positive pressure ventilation.[5,11,30]
4. APACHE II score. We hypothesize that APACHE II score will not modify the effect of study group assignment on the primary outcome.
5. Hypoxemic respiratory failure as the indication for intubation (Yes vs No). We hypothesize that hypoxemic respiratory failure as the indication for intubation will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia in the noninvasive ventilation group compared to the oxygen mask group among patients with hypoxemic

respiratory failure, compared to patients without. This hypothesis of effect modification is supported by evidence from two prior randomized trials suggesting a potential benefit for noninvasive ventilation among patients with acute hypoxemic respiratory failure.[11,12]

Analysis of the Secondary Outcome

We will perform an unadjusted, intention-to-treat comparison of patients randomized to the noninvasive ventilation group versus the oxygen mask group with regard to the secondary outcome of lowest oxygen saturation between induction and 2 minutes after intubation using the Wilcoxon rank sum test.

Analyses of Additional Outcomes:

We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the noninvasive ventilation group versus the oxygen mask group with regard to all pre-specified safety, clinical, and exploratory outcomes. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with the chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Handling of missing data:

We anticipate that no patients will be lost to follow up before assessment of the primary outcome. In some cases, the oxygen saturation between induction and 2 minutes after intubation will be unmeasurable (e.g., poor plethysmography of pulse

oximetry, shock, cardiac arrest, peripheral arterial disease, or other reasons) or unavailable. We anticipate that data will be missing in less than 3% of cases based on the rates of missing data in prior trials in similar settings.[25,26] Missing data will not be imputed for the primary outcome or for any of the secondary or exploratory outcomes. In adjusted analyses, missing data for baseline covariates will be imputed using multiple imputations.

Trial status:

PREOXI is a pragmatic, multi-center, non-blinded randomized clinical trial comparing preoxygenation with noninvasive ventilation to preoxygenation with an oxygen mask during the tracheal intubation of critically ill adults. Enrollment began on 10 March 2022 and is expected to conclude in 2023.

ETHICS AND DISSEMINATION

Waiver of Informed Consent:

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive preoxygenation with either noninvasive ventilation or an oxygen mask. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrollment in PREOXI, the patient's treating clinician must determine that either preoxygenation with noninvasive

ventilation or preoxygenation with an oxygen mask would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly in the context of a pragmatic trial, rather than by a clinician who thinks either approach is safe and reasonable for the patient, is expected to pose no more than minimal additional risk.

Obtaining informed consent from potential study participants or their legally authorized representatives would be impracticable. The majority of critically ill patients undergoing emergency tracheal intubation lack decisional capacity due to their critical illness and surrogate decision makers are frequently unavailable. Further, emergency tracheal intubation is a time-sensitive procedure with only minutes between the decision to intubate and the completion of the procedure. Meaningful informed consent could not be executed in this brief window. Attempting to obtain informed consent could lead to potentially deleterious delays in intubation which would increase the risk of hypoxemia, hypotension, and cardiac arrest.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, a waiver of informed consent was requested from and approved by the single institutional review board at Vanderbilt University Medical Center (reference number VUMC IRB# 211271). Conduct of this trial with waiver of informed consent is consistent with previous randomized trials comparing alternative approaches to tracheal intubation in widespread clinical use.[2,24-26,31,32] This approach was secondarily approved by the US Department of Defense Health Agency Human Research Protection Office). IRBs at participating sites reviewed the protocol,

addressed any local contextual factors with the site principal investigator, and ceded responsibility for ethics approval and study oversight to the single IRB.

Information for Patients and Families

Information regarding the study is made available to patients and families following intubation using a patient and family information sheet. The patient and family information sheet contains information on the purpose of the PREOXI trial, study procedures, risks and discomforts, benefits, use of protected health information, confidentiality, and investigator contact information. The Defense Health Agency Human Research Protection Office determined that this procedure meets the requirement of 32 CFR 219 and DODI 3216.02_AFI40-402. At centers with a significant population of non-English speaking patients, the patient and family information sheet has been translated into Spanish and Somali languages.

Protocol Changes

In accordance with SPIRIT guidelines, changes to the study protocol will be documented on clinicaltrials.gov (see online supplementary file) and submitted to the sIRB for approval.

Data Handling

Privacy protocols and data handling are reported in the online supplement.

Dissemination Plan

We will submit the trial results to a peer-reviewed journal for publication. Trial results will also be presented at scientific conferences and disseminated online and via social media in forms suitable for public understanding.

Conclusion

The PREOXI trial will provide important data on the effectiveness of common preoxygenation strategies for the prevention of hypoxemia during emergency tracheal intubation with a goal of improving outcomes for critically ill adults. To aid in the transparency and interpretation of trial results, this protocol and statistical analysis plan for the PREOXI trial has been finalized prior to the conclusion of patient enrollment.

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	Table 1: Schedule of Enrollment, Interventions, and Assessments in PREOXI						
	Eligibility Screen	**Randomization and Allocation**	**Peri-Procedural**				**Final Outcome Assessment**
Timepoint	Decision to perform tracheal intubation	Before tracheal intubation	Induction	Tracheal intubation	0-2 min after tracheal intubation	0-24 hours after tracheal intubation	Discharge or 28 days after enrollment
Enrollment:		**X**					
Eligibility screen	**X**						
Allocation		**X**					
Interventions:							
Preoxygenation with NIPPV		**X**	**X**				
Preoxygenation with facemask oxygen		**X**	**X**				
Screening for contraindications	**X**	**X**					
Assessments:							
Baseline variables	**X**	**X**					
Peri-procedural variables		**X**	**X**	**X**	**X**		
Adverse events		**X**	**X**	**X**	**X**	**X**	**X**
Clinical outcomes					**X**	**X**	**X**

Table 2: Inclusion/Exclusion Criteria

Inclusion Criteria
Patient is located in a participating unit.
Planned procedure is tracheal intubation using a laryngoscope and sedation.
Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit.
Exclusion Criteria
Patient is receiving positive pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway.
Patient is known to be less than 18 years old.
Patient is known to be pregnant.
Patient is known to be a prisoner.
Immediate need for tracheal intubation precludes safe performance of study procedures.
Patient is apneic, hypopneic, or has another condition requiring positive pressure ventilation between enrollment and induction.
Operator has determined that preoxygenation with noninvasive ventilation or preoxygenation with an oxygen mask is required or contraindicated for optimal care of the patient.

Table 3: Study outcomes

Primary Outcome	Incidence of hypoxemia, defined as a peripheral oxygen saturation <85% during the interval between induction and 2 minutes after tracheal intubation.
Secondary Outcome	Lowest oxygen saturation during the interval between induction and 2 minutes after tracheal intubation.
Safety Outcomes	Incidence of operator-reported aspiration.
	Fraction of inspired oxygen at 24 hours after induction.
	Oxygen saturation at 24 hours after induction.
	Incidence of pneumothorax, defined as radiology report of new pneumothorax on chest imaging in the 24 hours after induction. If no chest imaging available pre-induction, any pneumothorax in the 24 hours after induction will be assumed to be new.
	New infiltrate, defined as radiology report of new infiltrate on chest imaging in the 24 hours after intubation. If no chest imaging available pre-induction, any infiltrate in the 24 hours after induction will be assumed to be new.
Exploratory Outcomes	Incidence of severe hypoxemia, defined as the lowest oxygen saturation of <80% between induction and 2 minutes after tracheal intubation.

	Incidence of very severe hypoxemia, defined as the lowest oxygen saturation of <70% between induction and 2 minutes after tracheal intubation.
	Oxygen saturation at induction.
	Systolic blood pressure at induction.
	Duration from induction to successful intubation (duration of the intubation procedure).
	Cormack-Lehane grade of glottic view on first attempt.
	Number of laryngoscopy attempts.
	Number of attempts at passing a bougie.
	Number of attempts at passing an endotracheal tube.
	Incidence of cardiovascular collapse, defined as a composite of one or more of the following between induction and 2 minutes after intubation: Systolic blood pressure <65 mmHg, new or increased vasopressor, cardiac arrest not resulting in death within 1 hour of induction, cardiac arrest resulting in death within 1 hour of induction.
	28 day in-hospital mortality.
	Ventilator-free days to 28 days.
	ICU-free days to 28 days.

Protocol and Statistical Analysis Plan for the Pragmatic Trial Examining Oxygenation Prior to Intubation of Preoxygenation With Noninvasive Ventilation vs Oxygen Mask in Critically Ill Adults

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BACKGROUND: Hypoxemia is a common and life-threatening complication during emergency tracheal intubation of critically ill adults. The administration of supplemental oxygen before the procedure (ie, preoxygenation) decreases the risk of hypoxemia during intubation.

RESEARCH QUESTION: Does preoxygenation with noninvasive ventilation prevent hypoxemia during tracheal intubation of critically ill adults compared with preoxygenation with an oxygen mask?

STUDY DESIGN AND METHODS: The Pragmatic Trial Examining Oxygenation Prior to Intubation (PREOXI) is a prospective, multicenter, nonmasked randomized comparative effectiveness trial being conducted in seven EDs and 17 ICUs across the United States. The trial compares preoxygenation with noninvasive ventilation vs oxygen mask among 1,300 critically ill adults undergoing emergency tracheal intubation. Eligible patients are randomized in a 1:1 ratio to receive either noninvasive ventilation or an oxygen mask before induction. The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation of $< 85\%$ between induction and 2 min after intubation. The secondary outcome is the lowest oxygen saturation between induction and 2 min after intubation. Enrollment began on March 10, 2022, and is expected to conclude in 2023.

INTERPRETATION: The PREOXI investigation will provide important data on the comparative effectiveness of preoxygenation with noninvasive ventilation vs oxygen mask for the prevention of hypoxemia during emergency tracheal intubation. Specifying the protocol and statistical analysis plan before the conclusion of enrollment increases the rigor, reproducibility, and interpretability of the trial.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT05267652; URL: www.clinicaltrials.gov

CHEST Critical Care 2023; 1(2):100014

KEY WORDS: critical illness; endotracheal intubation; noninvasive positive-pressure ventilation; oxygen; respiratory failure

Take-home Points

Study Question: Does preoxygenation with noninvasive ventilation prevent hypoxemia during tracheal intubation of critically ill adults compared with preoxygenation with an oxygen mask?

Results: This article describes the protocol and statistical analysis plan for the Pragmatic Trial Examining Oxygenation Prior to Intubation investigation of preoxygenation with noninvasive ventilation vs with oxygen mask.

Interpretation: Prespecifying the full statistical analysis plan before completion of enrollment increases rigor, reproducibility, and transparency of the trial results.

Life-threatening hypoxemia occurs in 10% to 20% of emergency tracheal intubations in the ED and ICU.[1,2] Hypoxemia during intubation is associated with an increased risk of cardiac arrest and death.[3,4] Identifying interventions to prevent hypoxemia during emergency tracheal intubation is a high priority for clinicians and researchers.[5,6] Because patients typically are apneic between induction of anesthesia and intubation, but continue to consume oxygen, the oxygen content in the lungs at the time of induction is a primary determinant of whether the patient will experience hypoxemia.

Preoxygenation, the administration of supplemental oxygen before induction of anesthesia, increases lung oxygen content at induction and decreases the risk of hypoxemia.[7,8] In clinical practice, preoxygenation for emergency tracheal intubation of critically ill adults is most commonly administered using either an oxygen mask or noninvasive ventilation.[1]

Preoxygenation with an oxygen mask typically is performed using either a non-rebreather mask or a bag-mask device. A non-rebreather mask is a loose-fitting mask with an oxygen reservoir connected to an oxygen source. A bag-mask device is a mask capable of forming a tight seal over the mouth when held in place by a clinician and can be used to provide supplemental oxygenation alone, or both supplemental oxygen and ventilation.[9] Both types of oxygen mask can deliver up to 100% oxygen, are simple to set up, and have low potential for gastric insufflation. However, oxygen masks may deliver oxygen less effectively in critically ill patients when high minute ventilation and poor mask seal allow the entrainment of ambient air, with resulting alveolar oxygen concentrations as low as 50%.[7,10]

Preoxygenation also is administered routinely via noninvasive ventilation, in which a tight-fitting mask is connected to a machine capable of providing both 100% oxygen and positive-pressure ventilation. Compared with an oxygen mask, noninvasive

ABBREVIATIONS: PREOXI = Pragmatic Trial Examining Oxygenation Prior to Intubation

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DOI: https://doi.org/10.1016/j.chstcc.2023.100014

ventilation may reduce air entrainment by delivering a higher inspiratory flow rate of oxygen and by minimizing leaks. Additionally, noninvasive ventilation increases the mean airway pressure and recruits atelectatic lung, potentially reducing shunting. Compared with an oxygen mask, noninvasive ventilation may take longer to initiate and potentially may increase the risk of gastric insufflation and aspiration.

Two small randomized trials have compared these two approaches to preoxygenation. The first trial found that, among 53 patients in the ICU undergoing tracheal intubation in two hospitals, noninvasive ventilation increased the lowest oxygen saturation compared with the effects of an oxygen mask (mean lowest oxygen saturation, 93% vs 81%, respectively; $P < .001$) with no difference between groups in the incidence of aspiration (6% vs 8%).[11] Among 201 patients in the ICUs of six hospitals, the second trial found no difference in the severity of illness in the 7 days after intubation and an incidence of hypoxemia during intubation of 18.4% in the noninvasive ventilation group vs 27.7% in the oxygen mask group ($P = .10$).[12] Thus, whether noninvasive ventilation for preoxygenation in critically ill adults undergoing emergency tracheal intubation decreases the incidence of hypoxemia compared with an oxygen mask remains unknown. We designed the Pragmatic Trial Examining Oxygenation Prior to Intubation (PREOXI) to test the hypothesis that, among critically ill adults undergoing emergency tracheal intubation in the ED and ICU, preoxygenation with noninvasive ventilation decreases the incidence of hypoxemia compared with preoxygenation with an oxygen mask.

Study Design and Methods

This article was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines (Table 1, e-Appendix 1).[13]

Study Design

PREOXI is a pragmatic, multicenter, nonmasked, parallel-group randomized trial comparing preoxygenation using noninvasive ventilation with preoxygenation using an oxygen mask among critically ill adults undergoing emergency tracheal intubation in

TABLE 1] Schedule of Enrollment, Interventions, and Assessments in PREOXI

Time Point	Eligibility Screening, Decision to Perform Tracheal Intubation	Randomization and Allocation, Before Tracheal Intubation	During the Procedure				Final Outcome Assessment, Discharge or 28 d After Enrollment
			Induction	Tracheal Intubation	0-2 min After Tracheal Intubation	0-24 h After Tracheal Intubation	
Enrollment							
Eligibility screen	X	. . .	. . .	. . .	. . .	. . .	. . .
Enrollment	. . .	X	. . .	. . .	. . .	. . .	. . .
Allocation	. . .	X	. . .	. . .	. . .	. . .	. . .
Interventions							
Preoxygenation with NIPPV	. . .	X	X	. . .	. . .	. . .	. . .
Preoxygenation with face mask oxygen	. . .	X	X	. . .	. . .	. . .	. . .
Screening for contraindications	X	X	X	. . .	. . .	. . .	. . .
Assessments							
Baseline variables	X	X	. . .	. . .	. . .	. . .	. . .
Periprocedural variables	. . .	X	X	X	X	. . .	. . .
Adverse events	. . .	X	X	X	X	X	X
Clinical outcomes	. . .	. . .	. . .	. . .	X	X	X

Table entries without data mean that data elements were not collected at that time. NIPPV = noninvasive positive-pressure ventilation; PREOXI = Pragmatic Trial Examining Oxygenation Prior to Intubation.

the ED and ICU. The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation of < 85% between induction of anesthesia and 2 min after intubation. The trial is conducted by the Pragmatic Critical Care Research Group (www.pragmaticcriticalcare.org). The trial was registered before initiation of enrollment (ClinicalTrials.gov Identifier: NCT05267652).

Study Population

Patients located in a participating ED or ICU who are undergoing tracheal intubation using a laryngoscope and sedation are eligible. Complete lists of inclusion and exclusion criteria are provided in Table 2.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo preoxygenation with noninvasive ventilaton vs oxygen mask in permuted blocks of variable size, stratified by study site. Study-group assignments are generated using a computerized randomization sequence, placed in sequentially numbered opaque envelopes and distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets eligibility criteria. Study group assignment remains concealed to study personnel and clinicians until after the decision has been made to enroll the patient and the envelope is opened. Patients are enrolled as soon as the operator opens the trial envelope to reveal study group assignment. After randomization, patients, clinicians, and study personnel are not masked to group assignment because of the nature of the intervention.

Study Interventions

Training

Before beginning enrollment at each site, study investigators provide training on study procedures including instructional videos with consensus best practice recommendations for preoxygenation. Descriptions of the training videos and website links can be found in e-Appendix 1.

Noninvasive Ventilation Group

For patients assigned to the noninvasive ventilation group, operators are instructed to administer noninvasive ventilation using either a conventional mechanical ventilator or a dedicated noninvasive ventilator (ie, a bilevel positive airway pressure machine). The operator determines the ventilator type, ventilator mode, inspiratory and expiratory pressures, and mandatory respiratory rate. Operators receive the following best practice recommendations for the administration of preoxygenation using noninvasive ventilation: (1) preoxygenate ≥ 3 min (if feasible); (2) continue noninvasive ventilation until initiation of laryngoscopy, (3) F_{IO_2} of 100%, (4) expiratory pressure of ≥ 5 cm H_2O; (5) use an inspiratory pressure of ≥ 10 cm H_2O, and (6) respiratory rate of ≥ 10 breaths per minute.

TABLE 2] Inclusion and Exclusion Criteria

Inclusion criteria
Patient is located in a participating unit.
Planned procedure is tracheal intubation using a laryngoscope and sedation.
Planned operator is a clinician expected to perform tracheal intubation routinely in the participating unit.
Exclusion criteria
Patient is receiving positive-pressure ventilation by a mechanical ventilator, bag-mask device, or laryngeal mask airway.
Patient is known to be younger than 18 years.
Patient is known to be pregnant.
Patient is known to be in prison.
Immediate need for tracheal intubation precludes safe performance of study procedures.
Patient is apneic, is hypopneic, or has another condition requiring positive-pressure ventilation between enrollment and induction.
Operator has determined that preoxygenation with noninvasive ventilation or preoxygenation with an oxygen mask is required or contraindicated for optimal care of the patient.

Oxygen Mask Group

For patients assigned to the oxygen mask group, clinicians are instructed to administer supplemental oxygen via a non-rebreather mask or bag-mask device without bag-mask ventilation from the initiation of preoxygenation until the induction of anesthesia. The operator determines whether to use a non-rebreather mask or a bag-mask device (without ventilation). Operators receive the following best practice recommendations for the administration of preoxygenation using an oxygen mask: (1) preoxygenate ≥ 3 min (if feasible), (2) use the maximum oxygen flow rate possible (≥ 15 L/min), and (3) continue oxygenation from induction to laryngoscopy.

Cointerventions

In both trial groups, trial protocol allows the administration of supplemental oxygen by standard nasal cannula or high-flow nasal cannula during preoxygenation, between induction of anesthesia and initiation of laryngoscopy, and between initiation of laryngoscopy and intubation of the trachea. Bag-mask ventilation between induction and laryngoscopy also may be provided at the discretion of the operator in both groups. Figure 1 shows the interventions, cointerventions, and phases of the intubation process during which these interventions are applied.

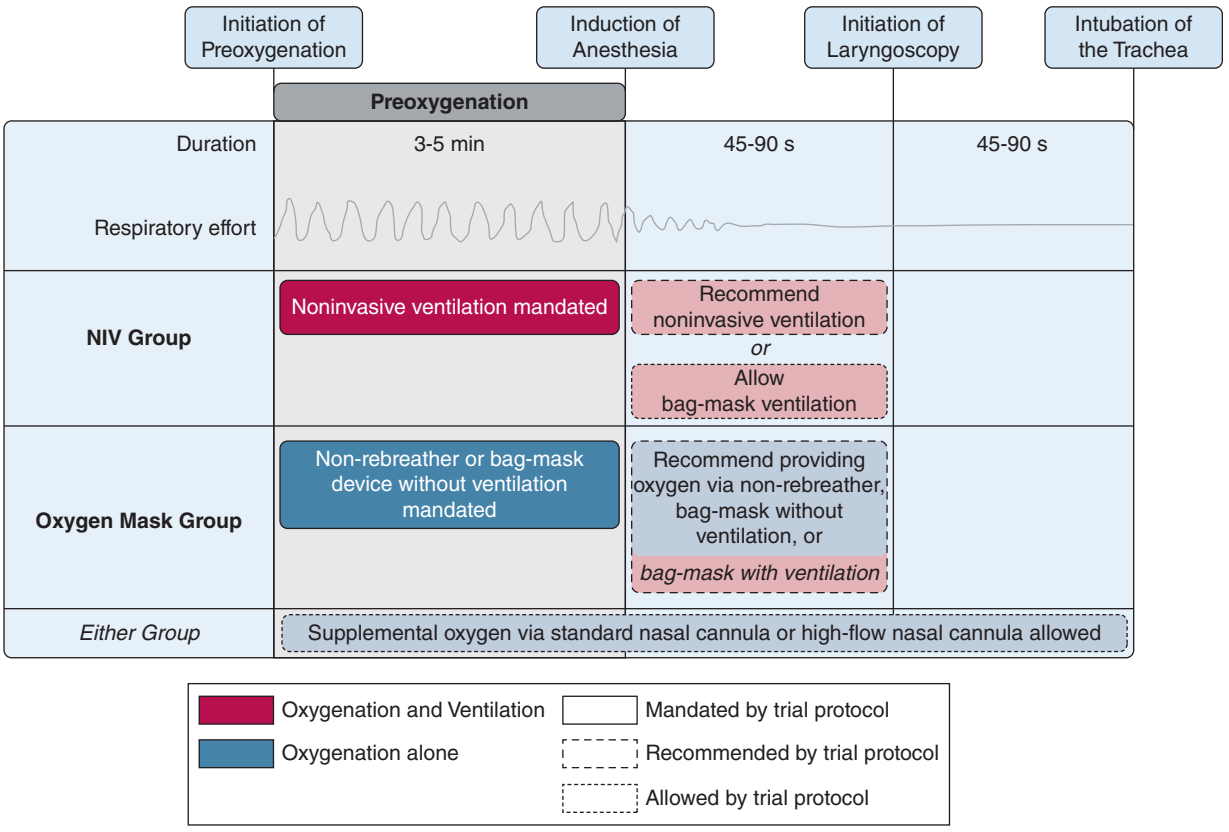

Figure 1 – *Diagram showing oxygenation and ventilation interventions in each trial group. The methods of oxygen delivery and ventilation allowed, recommended, and mandated during each phase of the tracheal intubation procedure are displayed for the noninvasive ventilation group and the oxygen mask group. For patients assigned to the noninvasive ventilation group, clinicians are instructed to administer noninvasive ventilation via either a dedicated noninvasive ventilator or an invasive ventilator connected to a tight-fitting mask from the initiation of preoxygenation until induction of anesthesia. Trial protocol recommends that noninvasive ventilation be continued between induction of anesthesia and the initiation of laryngoscopy. For patients assigned to the oxygen mask group, clinicians are instructed to administer supplemental oxygen without ventilation via either a non-rebreather mask or a bag-mask device from the initiation of preoxygenation until induction of anesthesia. Trial protocol recommends that the administration of supplemental oxygen by mask be continued between induction of anesthesia and the initiation of laryngoscopy. In either trial group, trial protocol allows the administration of supplemental oxygen by high-flow nasal cannula or standard nasal cannula in any phase of the intubation procedure, including under a mask during preoxygenation. In either trial group, trial protocol allows ventilation using a bag-mask device between induction and the initiation of laryngoscopy in place of noninvasive ventilation or an oxygen mask. NIV = noninvasive ventilation.*

Data Collection

An observer not directly involved with the intubation procedure collects data for key periprocedural outcomes, including oxygen saturation at induction and the lowest value for oxygen saturation between induction and 2 min after successful intubation. Observers may be trained clinical personnel (eg, physicians or nurses) or research personnel. Immediately after the intubation procedure, the operator completes a paper data collection form to record the device used for preoxygenation, the duration of preoxygenation, the devices used for oxygenation and ventilation between induction and laryngoscopy, and complications of intubation (eg, aspiration).[14] Study personnel at each site review the medical record to collect data on baseline characteristics, management before and after laryngoscopy, and clinical outcomes. A complete list of baseline, periprocedural, and in-hospital variables are provided in e-Table 1.

Primary Outcome

The primary outcome is the incidence of hypoxemia, defined as a peripheral oxygen saturation of $< 85\%$ during the interval between induction and 2 min after intubation.

Secondary Outcome

The sole secondary outcome is the lowest oxygen saturation during the interval between induction and 2 min after tracheal intubation.

Additional Outcomes

Table 3 reports the safety outcomes, exploratory procedural outcomes, and exploratory clinical outcomes.

TABLE 3] Study Outcomes

Outcome Type	Description
Primary	Incidence of hypoxemia, defined as a peripheral oxygen saturation of < 85% during the interval between induction and 2 min after tracheal intubation.
Secondary	Lowest oxygen saturation during the interval between induction and 2 min after tracheal intubation.
Safety	Incidence of operator-reported aspiration.
	F_{IO_2} at 24 h after induction.
	Oxygen saturation at 24 h after induction.
	Incidence of pneumothorax, defined as radiology report of new pneumothorax on chest imaging in the 24 h after induction. If no chest imaging is available before induction, any pneumothorax in the 24 h after induction will be assumed to be new.
	New infiltrate, defined as radiology report of new infiltrate on chest imaging in the 24 h after intubation. If no chest imaging is available before induction, any infiltrate in the 24 h after induction will be assumed to be new.
Exploratory procedural	Incidence of severe hypoxemia, defined as the lowest oxygen saturation of < 80% between induction and 2 min after tracheal intubation.
	Incidence of very severe hypoxemia, defined as the lowest oxygen saturation of < 70% between induction and 2 min after tracheal intubation.
	Oxygen saturation at induction.
	Systolic BP at induction.
	Duration from induction to successful intubation (duration of the intubation procedure).
	Cormack-Lehane grade of glottic view on first attempt.
	Successful intubation on the first attempt
	No. of laryngoscopy attempts.
	No. of attempts at passing a bougie.
	No. of attempts at passing an endotracheal tube.
	Incidence of cardiovascular collapse, defined as a composite of ≥ 1 of the following between induction and 2 min after intubation: systolic BP < 65 mm Hg, new or increased vasopressor administration, cardiac arrest not resulting in death within 1 h of induction, cardiac arrest resulting in death within 1 h of induction.
Exploratory clinical	28-d in-hospital mortality.
	Ventilator-free days to 28 d.
	ICU-free days to 28 d.

Sample Size Estimation

The current trial is designed to detect a 6% absolute difference between groups in the incidence of hypoxemia, a difference that is similar to or smaller than the difference considered to be clinically meaningful in the design of prior trials of oxygenation strategies during tracheal intubation.[2,15] Assuming an incidence of hypoxemia of 17% in the oxygen mask group based on data from two recently completed trials by this network in similar ED and ICU settings, detecting a 6% absolute decrease in the incidence of hypoxemia with 85% power at a two-sided α level of .05 would require enrollment of 1,264 patients (632 per group).[16,17] Anticipating missing data for up to 3% of patients, we plan to enroll a maximum of 1,300 total patients (650 per group). This sample size calculation was performed in PS version 3.1.2 software (Vanderbilt University Medical Center).

Data and Safety Monitoring Board and Interim Analysis

The data and safety monitoring board and interim analysis are described in e-Appendix 1.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R software (R Foundation for Statistical Computing). Categorical variables will be presented as number and percentage and will be compared between groups using a χ^2 test. Continuous variables will be presented as mean ± SD or median

(interquartile range) and will be compared between groups using a Wilcoxon rank-sum test. We will present absolute between-group differences with associated 95% CIs. A two-sided P value of $< .05$ will define a statistically significant between-group difference in the primary outcome. With a single primary outcome, no adjustment for multiplicity will be made. For secondary, safety, and exploratory analyses, emphasis will be placed on the magnitude of differences between groups with 95% CIs, rather than statistical significance.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted intention-to-treat comparison of the primary outcome of hypoxemia between patients randomized to the noninvasive ventilation group vs patients randomized to the oxygen mask group using a χ^2 test. The absolute difference in proportions, associated 95% CI, and a P value for the comparison will be presented. The primary analysis will be conducted among patients for whom the primary outcome is available without imputation of missing data. Planned tables of baseline characteristics, procedural characteristics, and outcomes are presented in e-Tables 2 and 3.

Additional Analyses of the Primary Outcome

Multivariable Analysis: To account for relevant baseline covariates, we will fit a generalized linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group and the following prespecified baseline covariates: age, sex, race and ethnicity, BMI, location at enrollment (ED or ICU), highest F_{IO_2} 1 h before initiation of preoxygenation, Acute Physiology and Chronic Health Evaluation II score,[18] indication for intubation (hypoxemic respiratory failure: yes vs no), and operator experience (number of previous intubations the operator has performed). All continuous variables will be modelled assuming a nonlinear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect Modification: We will examine whether prespecified baseline variables modify the effect of study group assignment on the primary outcome using a formal test of statistical interaction in a logistic regression model with the primary outcome as the dependent variable and independent variables of study group, the proposed effect modifier, and the interaction between the two. For categorical variables, we will present the OR and 95% CIs within each prespecified subgroup. Continuous variables will not be dichotomized for analysis of effect modification, but may be dichotomized for data presentation. In accordance with the Instrument for Assessing the Credibility of Effect Modification Analyses recommendations, we have prespecified the following baseline variables as potential effect modifiers and hypothesized the direction of effect modification for each.

Patient Location (ED vs ICU): We hypothesize that patient location will not modify the effect of study group assignment on the primary outcome.

BMI (kg/m^2): We hypothesize that BMI will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia in the noninvasive ventilation group compared with the oxygen mask group among patients with higher BMIs, as compared with patients with lower BMIs. This hypothesis is supported by evidence from multiple prior studies that patients with obesity are more likely to have early airway closure and atelectasis-dependent shunting that is likely to improve with positive-pressure ventilation.[19,20]

F_{IO_2} 1 h Before Intubation: We hypothesize that F_{IO_2} 1 h before intubation will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia in the noninvasive ventilation group compared with the oxygen mask group among patients with higher F_{IO_2} 1 h before intubation compared with patients with lower F_{IO_2}. This hypothesis is supported by evidence from multiple prior studies that patients requiring higher F_{IO_2} have more atelectasis-dependent shunting that is likely to improve with positive-pressure ventilation.[5,11,21]

Acute Physiology and Chronic Health Evaluation II Score: We hypothesize that Acute Physiology and Chronic Health Evaluation II score will not modify the effect of study group assignment on the primary outcome.

Hypoxemic Respiratory Failure as the Indication for Intubation (Yes vs No): We hypothesize that hypoxemic respiratory failure as the indication for intubation will modify the effect of study group assignment on the primary outcome, with a greater decrease in the incidence of hypoxemia in the noninvasive ventilation group compared with the oxygen mask group among patients with hypoxemic respiratory failure compared with patients without. This hypothesis is supported by evidence from two prior

randomized trials suggesting a potential benefit for noninvasive ventilation among patients with acute hypoxemic respiratory failure.[11,12]

Analysis of the Secondary Outcome

We will perform an unadjusted intention-to-treat comparison of patients randomized to the noninvasive ventilation group vs the oxygen mask group regarding the secondary outcome of lowest oxygen saturation between induction and 2 min after intubation using the Wilcoxon rank-sum test.

Analyses of Additional Outcomes

The analysis plan for additional outcomes is described in e-Appendix 1.

Handling of Missing Data

The plan for handling of missing data is described in e-Appendix 1.

Ethics and Dissemination

Critically ill patients undergoing tracheal intubation are at significant risk for morbidity and mortality from the underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive preoxygenation with either noninvasive ventilation or an oxygen mask. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrollment in PREOXI, the patient's treating clinician must determine that either preoxygenation with noninvasive ventilation or preoxygenation with an oxygen mask would be a safe and reasonable approach for the patient. Otherwise, the patient is excluded. Therefore, making the decision between the two approaches randomly in the context of a trial, rather than by a clinician who thinks either approach is safe, is expected to pose no more than minimal additional risk.

Obtaining informed consent from potential study participants or their legally authorized representatives would be impracticable. Most critically ill patients undergoing emergency tracheal intubation lack decisional capacity because of the critical illness and surrogate decision-makers frequently are unavailable. Further, emergency tracheal intubation is a time-sensitive procedure with only minutes between the decision to intubate and the completion of the procedure. Meaningful informed consent could not be executed in this brief window.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and because obtaining informed consent would be impracticable, a waiver of informed consent was requested from and approved by the single institutional review board at Vanderbilt University Medical Center (Identifier: 211271). Conduct of this trial with waiver of informed consent is consistent with previous randomized trials comparing alternative approaches to tracheal intubation in widespread clinical use.[2,15-17,22,23] This approach was approved secondarily by the US Department of Defense Health Agency Human Research Protection Office. Institutional review boards at participating sites reviewed the protocol, addressed any local contextual factors, and ceded responsibility for ethics approval and study oversight to the single institutional review board.

Discussion

Herein, we report the rationale, design, and analysis plan for PREOXI, a 1,300-patient randomized trial of preoxygenation with noninvasive ventilation vs preoxygenation with oxygen mask among critically ill adults undergoing emergency tracheal intubation in the ED or ICU. Several important trial design elements bear additional consideration.

We selected hypoxemia (as a binary variable), rather than lowest oxygen saturation (a continuous variable), as the primary outcome for the trial for several reasons. First, experiencing hypoxemia in the range associated with an increased risk of adverse clinical outcomes (eg, cardiac arrest) may be more clinically relevant than changes in oxygen saturation within the normal range. For example, a change in oxygen saturation of 5 percentage points from 87% to 82% may be associated more closely with adverse outcomes than a change in oxygen saturation of 10 percentage points from 100% to 90%. Second, values for oxygen saturation are right-censored because oxygen saturation reaches 100% with a Pao_2 of approximately 100 mm Hg, but patients may have a higher Pao_2 after preoxygenation. The approach of analyzing hypoxemia as a binary variable, rather than lowest oxygen saturation, has been used by many prior trials and has been endorsed by airway experts.[24-29]

We selected an oxygen saturation of $< 85\%$ as the threshold for the primary outcome based on several physiologic and procedural factors. First, an oxygen saturation of 85% corresponds with the inflection point on the oxyhemoglobin dissociation curve, at which

further decrements in arterial oxygen concentrations result in rapid and critical desaturation.[9] Second, an oxygen saturation of < 85% has been associated with an increased risk of cardiac arrest during tracheal intubation[30] and may be associated with increased mortality.[5]

Another trial design element that warrants consideration is the decision to allow the use of either a non-rebreather mask or a bag-mask device to provide preoxygenation in the oxygen mask group. Both devices can be used to provide supplemental oxygen without positive-pressure ventilation, but differ in some respects. A non-rebreather mask uses a loose-fitting interface and requires no provider involvement, whereas a bag-mask device requires a provider to hold the mask in place and can provide a tight mask seal. A bag-mask device also can be used to provide positive-pressure ventilation, which in the oxygen mask group of the current trial was allowed only after induction of anesthesia. Although these differences theoretically could affect preoxygenation, available evidence suggests that the two devices perform similarly.[31] Any theoretical difference in preoxygenation between two devices providing oxygen is likely to be much smaller than the difference between these devices, which provide supplemental oxygen alone, and devices that provide both supplemental oxygen and positive-pressure ventilation (ie, the noninvasive ventilation group in PREOXI). Allowing both types of oxygen masks routinely used in clinical care also increases the generalizability of trial results.

The use of positive-pressure ventilation after induction of anesthesia (the end of preoxygenation) is allowed in both trial groups. Evidence from a prior randomized trial conducted among patients in the ICU suggests that bag-mask ventilation between induction and laryngoscopy reduces the risk of hypoxemia.[2] However, the safety and efficacy of bag-mask ventilation has not been evaluated among patients in the ED. Some experts have advocated avoiding bag-mask ventilation among patients in the ED who are less likely to have fasted than patients in the ICU and therefore may be at higher risk of aspiration.[32] Because PREOXI enrolls patients in both the ED and ICU and focuses on preoxygenation and not management between induction and laryngoscopy, trial protocol allows bag-mask ventilation after induction of anesthesia, but does not mandate it.

The final design consideration is the administration of supplemental oxygen via standard nasal cannula and high-flow nasal cannula. Because oxygen facemasks and facemasks for noninvasive ventilation must be removed during laryngoscopy, some experts advocate for the administration of supplemental oxygen via standard nasal cannula oxygen or high-flow nasal cannula during laryngoscopy. The randomized trials available to date have not demonstrated consistently a benefit from administration of supplemental oxygen via standard nasal cannula or high-flow nasal cannula during tracheal intubation.[15,33-38] Therefore, the trial protocol for PREOXI allows, but does not require, the administration of supplemental oxygen via standard nasal cannula and high-flow nasal cannula in both trial groups.

Interpretation

PREOXI will provide important evidence regarding the effectiveness of common preoxygenation strategies for the prevention of hypoxemia during emergency tracheal intubation. To aid in the transparency and interpretation of trial results, this article detailing the protocol and statistical analysis plan for PREOXI has been finalized before the conclusion of patient enrollment.

Funding/Support

The research was funded primarily by the United States Department of Defense, Defense Health Agency, J9 Office, Restoral program. K. P. S. was supported in part by the National Institutes of Health [Grant T32HL087738]. J. A. P. was supported in part by the National Institute on Aging [Grant K23AG073529]. M. W. S. was supported in part by the National Heart, Lung, and Blood Institute [Grant K23HL143053]. J. D. C. was supported in part by the National Heart, Lung, and Blood Institute [Grant K23HL153584]. D. R. was supported in part by the National Heart, Lung, and Blood Institute [Grant K08HL148514-01A1]. Data collection used the Research Electronic Data Capture tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support [Grant UL1 TR000445 from the National Center for Advancing Translational Sciences, National Institutes of Health).

Financial/Nonfinancial Disclosures

The authors have reported to *CHEST Critical Care* the following: K. W. G. reports financial support and travel were provided by US Department of Defense. A. A. G. reports financial support was provided by US Department of Defense. M. E. P. reports financial support

was provided by US Department of Defense. K. P. S. reports financial support was provided by National Heart, Lung, and Blood, Institute. S. B. S. reports financial support was provided by CHEST. A. K. reports financial support was provided by United Therapeutics Corporation, 4D Medicine, Ltd., Regeneron Pharmaceuticals, Inc., Roche, and Dompé Pharmaceutical. J. A. P. reports financial support was provided by the National Institute on Aging. J. M. W. reports financial support was provided by CHEST. M. C. E. reports financial support was provided by Abbott Laboratories. D. W. R. reports financial support was provided by the National Heart, Lung, and Blood Institute and a relationship with Achieve Life Science, Inc., that includes equity or stocks. S. G. reports financial support was provided by US Department of Defense. A. M. reports financial support was provided by the National Heart, Lung, and Blood Institute. J. B. reports financial support was provided by US Department of Defense. M. T. L. reports financial support was provided by pocket cards. S. G. S. reports was provided by US Department of Defense. D. R. J. reports financial support was provided by US Department of Defense. M. W. S. reports financial support was provided by US Department of Defense and the National Heart, Lung, and Blood Institute and a relationship with Baxter International, Inc., that includes consulting or advisory. J. D. C. reports financial support was provided by US Department of Defense. T. W. R. reports a relationship with Cumberland Pharmaceuticals, Inc., that includes consulting or advisory and equity or stocks. J. D. C. reports financial support was provided by the National Heart, Lung, and Blood Institute and travel was provided by Fisher & Paykel Healthcare, Inc.

Acknowledgments

Author contributions: K. W. G. , A. A. G., M. W. S., and J. D. C. helped with study concept and design, acquisition of data, drafting and critical revision of the manuscript, and study supervision. M. E. P., K. P. S., S. B. S., C. T., S. G., H. W., D. R.-A., N. R. A., M. R. W., S. J. H., J. P. G., V. B., B. E. D., J. A. P., B. D. L., J. M. W., M. C. E., D. W. R., S. G., C. W., K. A. H., A. M., J. B., L. A., P. D. S., D. B. P., M. T. L., J. K. G., R. M., B. J. L., S. G. S., E. A., K. M., J. P. R., K. W., D. R. J., S. A. T., W. H. S., and T. W. R. helped with acquisition of data and critical revision of the manuscript for important intellectual content. A. C. helped with development of training videos and critical revision of the manuscript for important intellectual content. B. I. helped with acquisition of data, statistical analysis, and critical revision of the manuscript for important intellectual content.

Collaborators for the PREOXI Investigators and the Pragmatic Critical Care Research Group: Listed in e-Appendix 1.

Role of sponsors: The funding institutions had no role in (1) conception, design, or conduct of the study; or (2) collection, management, analysis, interpretation, or presentation of the data.

Disclaimer: The views expressed are those of the authors and do not reflect the official views or policy of the Department of Defense or its components. The authors do not have any financial interest in the companies whose materials are discussed in this publication, and no federal endorsement of the companies and materials is intended.

Additional information: The e-Appendix and e-Tables are available online under "Supplementary Data."

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PREOXI Trial Statistical Analysis Plan Revision Sequence

March 24, 2023 Statistical Analysis Plan posted on preprint server

April 13, 2023 Statistical Analysis Plan submitted for publication

August 11, 2023 Statistical Analysis Plan completed peer review

September 1, 2023 Statistical Analysis Plan* published:

Gibbs KW, Ginde AA, Prekker ME, Seitz Kevin P, Stempek SB, Taylor C, Gandotra S, White H, Resnick-Ault D, Khan A, Mohmed A, Brainard JC, Fein DG, Aggarwal NR, Whitson MR, Halliday SJ, Gaillard JP, Blinder V, Driver BE, Palakshappa JA, Lloyd BD, Wozniak JM, Exline MC, Russell DW, Ghamande S, Withers C, Hubel KA, Moskowitz A, Bastman J, Andrea L, Sottile PD, Page DB, Long MT, Goranson JK, Malhotra R, Long BJ, Schauer SG, Connor A, Anderson E, Maestas K, Rhoads JP, Womack K, Imhoff B, Janz DR, Trent SA, Self WH, Rice TW, Semler MW, Casey JD for the PREOXI investigators and the Pragmatic Critical Care Research Group. Protocol and Statistical Analysis Plan for the Pragmatic Trial Examining Oxygenation Prior to Intubation of Preoxygenation With Noninvasive Ventilation vs Oxygen Mask in Critically Ill Adults. CHEST Critical Care. 2023 Sep 1;1(2):100014. https://doi.org/10.1016/j.chstcc.2023.100014.

October 14, 2023 Final patient enrolled

**No changes to the statistical analysis plan occurred between initial posting of the Statistical Analysis Plan on a preprint server and its publication.*