Randomized Trial of Sedative Choice for Intubation

Protocol and Statistical Analysis Plan

Clinicaltrials.gov: NCT 05277896

This Supplementary Appendix contains the following items:

1) Initial Trial Protocol -Version 1.0 [dated March 9, 2022]

2) Final Trial Protocol -Version 2.2 [dated March 7, 2025]

3) Summary of changes to Trial Protocol

4) Original Statistical Analysis Plan [posted January 18, 2025]

5) Final Statistical Analysis Plan [published May 21, 2025]

6) RSI Trial Statistical Analysis Plan Revision Sequence

Randomized Trial of Sedative Choice for Intubation ("RSI") Trial Protocol

The Pragmatic Critical Care Research Group Investigators

Title:	**R**andomized Trial of **S**edative Choice for **I**ntubation
Acronym:	RSI
Funder:	The National Heart, Lung, and Blood Institute (NHLBI)
Network:	Pragmatic Critical Care Research Group
Protocol:	Version 1.0
Date:	March 9, 2022
Study Chair:	Jonathan Casey MD, MSc, Vanderbilt University Medical Center

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REVISIONS TO THE PROTOCOL

Protocol Version 1
Date: March 9, 2022
Initial protocol

ABBREVIATIONS

AE	Adverse event
SOFA score	Sequential Organ Failure Assessment score
DSMB	Data safety monitoring board
ED	Emergency department
EFIC	Exception from Informed Consent (21 CFR 50.24.7)
ICU	Intensive care unit
IV	Intravenous
LAR	Legally authorized representative
PI	Principal investigator (the clinician leading the study across all sites)
RCT	Randomized control trial
SAE	Serious adverse events
S/F	SpO_2/FiO_2 ratio
SOP	Standard operating procedure

1. STUDY SUMMARY

Title	Randomized Trial of Sedative Choice for Intubation (RSI)
Background	Among critically ill adults undergoing emergency tracheal intubation, one in five experience hypotension, cardiac arrest, or death. The sedatives used to rapidly induce anesthesia for emergency tracheal intubation have been hypothesized to effect cardiovascular complications and patient outcomes, but the optimal sedative medication for intubation of critically ill adults remains unknown. Ketamine and etomidate are the two most commonly used sedatives during intubation of critically ill adults. Data from a randomized clinical trial are urgently needed to determine the effect of ketamine versus etomidate on cardiovascular complications and clinical outcomes of emergency tracheal intubation.
Study Design	Multi-center non-blinded, parallel-group, randomized clinical trial
Treatment Groups	Ketamine group: Patients will receive intravenous ketamine at a recommended dose of 2 mg/kg for induction of anesthesia for emergency tracheal intubation. Etomidate group: Patients will receive intravenous etomidate at a recommended dose of 0.3 mg/kg for the induction of anesthesia for emergency tracheal intubation. In this investigator-initiated, multi-center, non-blinded, randomized trial comparing two commonly used medications within their approved indications, the assigned sedative medication will be dispensed from the clinical pharmacy and administered by clinical personnel as would occur in clinical care.
Sample Size	Stage 1 (feasibility): 464 patients Stage 2 (effectiveness): 1,900 patients
Inclusion Criteria	1. Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit 2. Planned procedure is orotracheal intubation using a laryngoscope 3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
Exclusion Criteria	1. Patient is known to be less than 18 years old 2. Patient is known to be pregnant 3. Patient is known to be a prisoner 4. Patient is known to have an allergy to ketamine or etomidate 5. Patient is presenting to the emergency department with a primary diagnosis of trauma 6. Patient or LAR declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI trial 7. Clinician feels ketamine is required or contraindicated for the optimal care of the patient

	8. Clinician feels etomidate is required or contraindicated for the optimal care of the patient 9. Clinician feels an induction medication other than ketamine or etomidate is required for the optimal care of the patient 10. Immediate need for tracheal intubation precludes safe performance of study procedures
Consent	Emergency tracheal intubation of critically ill patients is a time-sensitive procedure with a brief therapeutic window between the decision to perform intubation and the completion of the procedure. A written informed consent is available and will be used when feasible in RSI. However, it is expected that written consent will be infeasible in most, if not all, cases because delaying the emergency tracheal intubation of critically ill adults would cause irreparable harm to patients. Therefore, it is expected that most, if not all, patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC). In conformance with EFIC requirements, measures to protect the rights and welfare of subjects will include: a) community consultation, b) public disclosure of plans to conduct the trial, c) public disclosure of trial results, d) independent data monitoring, and e) opportunity for pre-randomization opt-out (when feasible) and notification of the patient, legally authorized representative, or a family member of a patient's enrollment in the trial with an opportunity to discontinue trial participation.
Randomization	Eligible patients will be randomized 1:1 to ketamine versus etomidate. 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 operators until after the decision has been made to enroll the patient in the study. Following enrollment, the trial will not blind patients or treating clinicians to study group assignment.
Primary Outcome	Stage 1 (if trial terminates during or at the end of the feasibility stage): • Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation: o Systolic blood pressure < 65 mmHg o New or increased vasopressors o Cardiac arrest not resulting in death within 1 hour of induction o Cardiac arrest resulting in death within 1 hour of induction Stage 2: 28-day in-hospital mortality
Secondary Outcome	Stage 1 (if trial terminates during or at the end of the feasibility stage): 28-day in-hospital mortality Stage 2: • Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation: o Systolic blood pressure < 65 mmHg

	○ New or increased vasopressors ○ Cardiac arrest not resulting in death within 1 hour of induction ○ Cardiac arrest resulting in death within 1 hour of induction
Exploratory Outcomes	• Procedural Characteristics & Complications ○ Cormack-Lehane Grade of glottic view ○ Number of attempts at tracheal intubation ○ Time from induction to successful tracheal intubation ○ Operator-assessed difficulty of intubation ○ Lowest oxygen saturation between induction and two minutes after intubation ○ Lowest oxygen saturation < 80% between induction to two minutes after intubation ○ Highest and lowest systolic blood pressure from induction to two minutes after intubation ○ Systolic blood pressure > 180 between induction and two minutes after intubation ○ Systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation ○ New or increased vasopressor between induction and 2 minutes after intubation ○ Cardiac arrest within 2 minutes of intubation not resulting in death ○ Cardiac arrest within 2 minutes of intubation resulting in death • Short-term Clinical Outcomes ○ Ventilator-free days to study day 28 ○ Vasopressor-free days to study day 28 ○ ICU-free days to study day 28
Safety Outcomes	• Systolic blood pressure at 24 hours after induction • Receipt of vasopressors at 24 hours after induction • Cardiac arrest receiving cardiopulmonary resuscitation between induction and hospital discharge
Analysis	The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to ketamine versus patients randomized to etomidate with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.

2. TRIAL DESCRIPTION

2.1 Background

Each year more than 1.5 million critically ill adults receive invasive mechanical ventilation in the United States,[1–3] at a cost of nearly $30 billion dollars annually.[1,2] Recent research has dramatically improved patient safety during the maintenance, weaning, and liberation stages of invasive mechanical ventilation.[4,5] In contrast, the optimal approach to the initiation of mechanical ventilation remains an important knowledge gap in the care of adults with respiratory failure. Among critically ill adults, life-threatening complications during tracheal intubation and initiation of invasive mechanical ventilation remain common. One in five patients experiences hypotension and one-in-forty experiences cardiac arrest during the two-minute tracheal intubation procedure.[6–10]

2.1.1 Cardiovascular Collapse during Intubation

Cardiovascular collapse is a peri-procedural outcome defined as severe hypotension, new or increased vasopressors, cardiac arrest or death. The occurrence of cardiovascular collapse during tracheal intubation of critically ill adults increases patients' risk of in-hospital mortality.[11] Randomized trials examining intubation technique commonly target cardiovascular collapse as an outcome.[12–14] Adherence to recommended best-practices for tracheal intubation (e.g., preoxygenation,[15,16] optimization of patient positioning,[9] and procedural checklists[8]) are insufficient to prevent 20-40% of critically ill adults from experiencing cardiovascular collapse during tracheal intubation.[12,14,17–19]

2.1.2 Sedative Medications Contribute to the Risk of Cardiovascular Collapse

Rapid sequence induction and tracheal intubation, the most common method of intubation for critically ill patients, is the nearly simultaneous administration of a sedative medication and neuromuscular blocking medication. The ideal sedative agent for rapid sequence intubation would rapidly provide a deep state of unconsciousness and analgesia without causing hemodynamic side effects. No available agent meets all of these criteria.[20] The administration of any of the available sedative agents at a dose large enough to rapidly induce unconsciousness contributes to cardiovascular collapse through vasodilation, decreased cardiac filling pressures from sedation-induced venodilation, and decreased endogenous catecholamines.[21–24] While all sedatives commonly used during emergency tracheal intubation of critically ill patients have been associated with unsatisfactory hypotension (21 CFR 50.24(a)(1)), ketamine and etomidate are the medications used most commonly in clinical practice due to their rapid onset and favorable hemodynamic profiles relative to the other available sedatives.[25,26] Other sedatives that have been used in some settings during rapid sequence intubation include benzodiazepines, propofol, and barbiturates. Benzodiazepines do not provide any analgesia and are associated with an unsatisfactory degree of hypotension, with a drop in mean arterial blood pressure of 10 to 25 percent, even among healthy patients.[27–29] At present, barbiturates are rarely used for tracheal intubation in the US because of unsatisfactorily high rates of post-intubation hypotension and evidence of negative cardiac ionotropy.[30] While propofol is commonly used to induce anesthesia among healthy patients, and is commonly administered as a continuous infusion to maintain sedation for critically ill patients, it is used less commonly as a bolus during tracheal intubation of critically ill patients because it has been suggested to cause unsatisfactorily high rates of hypotension and cardiac depression, compared to ketamine or etomidate.[31,32]

2.1.3 Ketamine as a Sedative during Tracheal Intubation.

Ketamine is a phencyclidine derivative that provides anesthesia via its effect at the NMDA receptors. Ketamine has been approved by the United States Food and Drug Administration (FDA) with approved indications including "use as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation" and "induction of anesthesia prior to the administration of other general anesthetic agents." In addition to sedation, ketamine provides significant amnesia and analgesia via action at the opioid receptors, and is commonly used for procedural sedation and as a continuous infusion to control pain.[33]

Ketamine activates the sympathetic nervous system, stimulating the release of catecholamines,[34] which may increase heart rate and blood pressure during intubation and prevent peri-procedural cardiovascular collapse.[33] Conversely ketamine has direct negative ionotropic effects, leading to myocardial depression.[30,35,36] While the myocardial depression may be counteracted by increased catecholamine release, ketamine could cause cardiovascular collapse among patients with depleted catecholamine stores, and case reports of unexpected cardiac arrest during intubations with ketamine have been published.[37] Despite stimulating the release of catecholamines, using ketamine as the induction agent during emergency tracheal intubation does not appear to frequently cause or worsen hypertensive urgency or emergency; however, the literature on this topic is limited to case reports.[38]

Historically, concerns have been raised that ketamine might increase intracranial pressure and cause deleterious decreases in cranial perfusion pressure. Recent studies have suggested, however, that ketamine may be associated with a beneficial increase in cranial perfusion pressure as a result of increased mean arterial pressure,[39,40] and a recent, large before-after study showed no significant differences in clinical outcomes for trauma patients intubated with ketamine versus etomidate.[41]

2.1.4 Etomidate as a Sedative during Tracheal Intubation.

Etomidate is an imidazole derivative that acts at gamma-aminobutyric acid "A" (GABA) receptors. Etomidate has been approved by the FDA with an indication for "induction of general anesthesia." In a recent review of more than 19,000 intubations by a large, multicenter emergency medicine registry, etomidate was the most commonly used sedative during emergency tracheal intubation.[26]

Etomidate causes less hemodynamic instability than propofol[42] and midazolam,[27] but the data regarding the relative risk of hemodynamical instability with etomidate, compared to ketamine, is unclear. It was initially suggested that ketamine might cause less hypotension than etomidate, given ketamine's ability to stimulate the release of catecholamines,[43,44] but a recent observational study comparing ketamine and etomidate among nearly 7,000 critically ill adults undergoing tracheal intubation in emergency departments suggested that ketamine was independently associated with an increased risk of peri-intubation hypotension.[26]

Etomidate was initially used both for induction of anesthesia and as a continuous drip for maintenance of anesthesia. Its use as a continuous drip for maintenance of anesthesia was halted after it was discovered that prolonged use of etomidate causes inhibition of adrenal cortisol production by blockade of 11-β-hydroxylase, leading to adrenal insufficiency, and increased mortality.[45–47] Etomidate use as a single bolus for induction of anesthesia has continued, but numerous studies have demonstrated that even a single dose of etomidate can cause transient adrenal insufficiency.[48–53] The clinical significance of this relative

adrenal insufficiency, however, remains unclear. Contrasting observational studies have suggested that etomidate may have positive,[41,54] negative [47,52,55–57] or neutral impacts[41,48,49,51,58,59] on mortality.

2.1.5 Prior Evidence from Clinical Trials.

Two randomized trials have directly compared ketamine to etomidate for RSI among critically ill adults.[60,61]

The Ketased trial, published in 2009, was a 469-patient trial conducted across 12 emergency medical services and emergency departments in France.[60] Because many patients were enrolled in the pre-hospital setting without continuous blood pressure monitoring, peri-procedural outcomes such as cardiovascular collapse were not collected, and the results were indeterminate, in regards to the primary outcome, average Sequential Organ Failure Assessment (SOFA) scores in the 72 hours after intubation. The results, however, demonstrated significant heterogeneity. Patients with trauma (for whom increased intracranial pressure from ketamine may be important) experienced a non-significant 4% absolute increase in mortality when intubated with ketamine compared to etomidate. All other patients experienced a non-significantly lower mortality when intubated with ketamine, particularly patients with sepsis who experienced a non-significant 7% absolute mortality benefit (and in whom adrenal insufficiency from etomidate may be particularly important).

The EvK trial, published in January 2022, was a single-center, 801-patient trial conducted among hospitalized patients at a single hospital in Texas.[61] Survival at 7 days, the primary outcome of the EvK trial, was higher in the ketamine group, compared to the etomidate group (85.1% vs 77.3%; p=0.005), but this difference was attenuated by day 28, at which point it was no longer significant (66.8% vs 64.1%, p=0.294). The conclusion of this single-center trial was that "there was no significant difference in survival by Day 28", however it was noted that this "could represent a small but durable long-term survival effect, one which our trial was under-powered to detect."[61]

2.1.6 Rationale for a Trial of Ketamine vs Etomidate in Non-Traumatic Critical Illness.

Experts have pointed out that the currently available data on sedative choice during tracheal intubation of critically ill patients are inadequate and have called for additional randomized clinical trials.[48,49,62] Because (1) cardiovascular collapse is common during tracheal intubation of critically ill adults (2) sedatives are a driver of cardiovascular collapse, (3) use of ketamine or etomidate varies between centers, specialties, and operators, and (4) prior data suggests the potential for ketamine to significantly decrease mortality for patients without trauma, a large, multicenter trial is needed to determine the effects of ketamine and etomidate on mortality in non-traumatic critical illness.

2.1.7 Rationale for Two Stages of the RSI trial.

Stage 1 of the RSI trial will focus on feasibility and short-term, peri-procedural outcomes. This stage is required to demonstrate the feasibility of performing a pragmatic trial comparing ketamine to etomidate during emergency tracheal intubation of critically ill adults under exception from informed-consent (EFIC) requirements for emergency research (under FDA code of regulations 21 CFR 50.24.7).[99,100] Stage 1 of the RSI trial (funded by the National Heart, Lung, and Blood Institute; grant number, K23HL153584) is designed to be of sufficient size to inform the effects of ketamine and etomidate on the short-term, peri-procedural outcome of cardiovascular collapse.

Stage 2 of the RSI trial will focus on the effect of ketamine vs etomidate on in-hospital mortality. Data on the effects of ketamine and etomidate on the short-term, peri-procedural outcome of cardiovascular collapse (the primary outcome of stage 1) could make an immediate impact on the use of these medications in clinical practice. However, the effects of ketamine and etomidate on in-hospital mortality may be mediated by mechanisms presenting after the peri-procedural period (e.g. adrenal insufficiency or increased intracranial pressure), and the effects of ketamine and etomidate on cardiovascular collapse may, therefore, be discordant with their effects on in-hospital mortality. A finding in stage 1 of the RSI trial that ketamine decreases, increases, or has no impact on cardiovascular collapse would in no way detract from the need for definitive data on the effect of ketamine and etomidate on in-hospital mortality.

Completing a feasibility trial, closing enrollment, and subsequently initiating a separate, new, definitive trial using the same study design is inefficient. Such an approach introduces delays in enrollment between the stages and fails to make use of data on clinical outcomes from patients enrolled during the feasibility stage. This increases the total number of patients who must experience the potential risks of trial participation to obtain a definitive answer to the research question. The RSI trial is, therefore, planned as a single, adaptive trial with two stages.

To increase efficiency and minimize the number of patients exposed to the potential risks of trial participation, the RSI trial is designed to allow progress from the stage assessing feasibility (Stage 1) to the stage assessing effectiveness (Stage 2) if the following criteria are met: (1) the data and safety monitoring board (DSMB) determines that the feasibility and safety of conducting the trial have been demonstrated; (2) the investigators determine that the observed enrollment rate, protocol compliance, separation between groups in receipt of the assigned therapy, and data completeness and quality permit progression to Stage 2; and (3) funding for a multicenter trial is available. Additional details regarding the progression from Stage 1 to Stage 2 are providing in section 10.3 of the protocol.

2.2 Study Aims and Hypotheses

2.2.1 Study aims

Stage 1: To compare the effects of ketamine versus etomidate on cardiovascular collapse during tracheal intubation of critically ill adults. To evaluate the feasibility of conducting a pragmatic trial of ketamine versus etomidate during tracheal intubation of critically ill adults in the ED or ICU using EFIC.

Stage 2: To compare the effects of ketamine versus etomidate on in-hospital mortality among non-traumatic critically ill adults undergoing tracheal intubation in the ED or ICU

2.2.2 Study hypothesis

Stage 1: Conducting a pragmatic trial comparing ketamine versus etomidate during tracheal intubation of non-traumatic critically ill adults in the ED or ICU using EFIC will be feasible. Ketamine will decrease the incidence of cardiovascular collapse.

Stage 2: Ketamine will decrease the incidence of in-hospital mortality among non-traumatic critically ill adults undergoing intubation in the ED or ICU.

2.3 Study Design

We will conduct an investigator-initiated non-blinded, pragmatic, parallel-group, randomized clinical trial evaluating the effect of ketamine versus etomidate on clinical outcomes of non-traumatic critically ill adults undergoing tracheal intubation in the ED and ICU.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria

1. Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit
2. Planned procedure is orotracheal intubation using a laryngoscope
3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit

3.2 Exclusion Criteria

1. Patient is known to be less than 18 years old
2. Patient is known to be pregnant
3. Patient is known to be a prisoner
4. Patient is known to have an allergy to ketamine or etomidate
5. Patient is presenting to the emergency department with a primary diagnosis of trauma
6. Patient or LAR declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI trial
7. Clinician feels ketamine is required or contraindicated for the optimal care of the patient
8. Clinician feels etomidate is required or contraindicated for the optimal care of the patient
9. Clinician feels an induction medication other than ketamine or etomidate is required for the optimal care of the patient
10. Immediate need for intubation precludes safe performance of study procedures

3.3 Justification of Exclusion Criteria

The RSI trial is intended to be broadly inclusive of critically ill patients who would receive ketamine or etomidate during intubation in usual care. The purpose of the exclusion criteria is to prevent the enrollment of patients who should not be enrolled under EFIC, patients who have a contraindication to study medications, or patients who have an indication for an alternative treatment. Pregnant women and prisoners are explicitly excluded from studies performed under EFIC. Patients with trauma are excluded from the RSI trial given the concern that ketamine may cause increased intracranial pressure among patients with head trauma. No patients will be excluded on the basis of race, ethnicity, or sex.

4.0 Process of Obtaining Informed Consent

Respect for human subjects and their safety is paramount in clinical research. Clinical research aiming to evaluate optimal care for critically ill adults during an emergency procedure presents unique ethical challenges. Protecting patient autonomy through the informed consent process is an ethical cornerstone of human subjects research.

An informed consent document is available and will be used to obtain written informed consent from the patient or legally authorized representative for participation in the trial, when feasible. However, it is expected that obtaining written informed consent will be infeasible in most, if not all, cases due to:

1. **The expected medical condition of the patient.** Based on prior trials in the same patient population and setting, approximately 70% of patients eligible for the trial will be experiencing encephalopathy (altered mental status) and the median Glasgow coma scale score will be 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 the trial will not have the capacity to provide informed consent.
2. **Sufficient time for the patient or legally authorized representative to consider participation & circumstances for consent that minimize the possibility of undue influence.** Even in instances in which a patient retains decisional capacity, or a legally authorized representative (LAR) is immediately available, the rapidity with which emergency tracheal intubation is clinically required (and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation) precludes execution of a meaningful informed consent process. Although no published literature quantifies the time from the decision to perform emergency tracheal intubation (the inclusion criteria for the trial) until the initiation of intubation (the trial intervention), among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the VUMC ED or ICU, approximately 50% of intubations occurred within 5 minutes, 75% of intubations occurred within 10 minutes, and no intubations occurred longer than 30 minutes after treating clinicians verbalized the decision to intubate (or placed a written order for an induction medication). Obtaining informed consent for research requires research personnel to assess decisional capacity, identify an 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 for cannot be executed in the 5 minutes before emergency tracheal intubation of a critically ill adult or their LAR in the ED or ICU. Moreover, obtaining informed consent for participation in research in the minutes before emergency tracheal intubation from a distressed patient or LAR places the informed consent process for research adjacent to the receipt of life-saving care and risks blurring the distinction between treatment and research. Emergency tracheal intubation of critically ill adults is, definitionally, 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.

The RSI trial comparing ketamine versus etomidate during tracheal intubation of critically ill adults can, therefore, only be conducted with exception from informed consent (EFIC) for emergency research, and it is expected that most, if not all, patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC).

Complete details of the plan for conducting the RSI trial in compliance with FDA regulation for EFIC are provided in Appendix B. In coordination with the IRB, investigators for the RSI trial will conduct community consultation and public disclosure prior to beginning enrollment (see Community Consultation and Public Disclosure Plan). The trial will be overseen by the IRB and an independent data and safety monitoring board.

While the nature of emergency tracheal intubation precludes a full, written, informed consent process in most, if not all, cases, the RSI trial will provide an opportunity for patients, LARs, or family members to object to participation based on more limited information whenever feasible using a pre-enrollment opt-out script (details in section 13.3).

After enrollment of each patient, study personnel will attempt to notify the patients, LAR, or family members of enrollment in the trial in person. Notification of enrollment will be performed by research team members trained in informed consent processes, HIPAA laws, and the trial protocol. Patients or family members will be provided with a notification document approved by the Institutional Review Board (IRB). In the event that the patient, LAR, or family member cannot be contacted in person (for example, if they are outside of the state), study personnel will notify by telephone or by registered mail. There is no single timeline that is appropriate for all patients or families who are dealing with issues surrounding emergency tracheal intubation in the setting of critical illness. Study personnel will coordinate with treating clinicians to incorporate the judgement of treating clinicians as to the appropriate timing of notification for a given patient. For cases in which a LAR or family member cannot be reached and the patient does not survive their critical illness, study personnel will send a letter approved by the IRB. Study personnel will keep a log that reflects the required steps for contacting the LAR or family member. The notification tracking log will be completed for each patient enrolled and included in the patient's research records.

Patients or their LARs may decline follow-up or access to medical record review, as stated in the notification document. If a patient or LAR declines follow up or access to medical record review, this information will be documented in the patient's research record, along with the date and reason for withdrawal. As suggested in federal regulations for EFIC, the study investigators may examine data collected prior to patient withdrawal as this is necessary to maximize understanding of the safety of the study intervention.

5.0 Enrollment and Randomization

Patients will be enrolled at the time that treating clinicians have decided to pursue tracheal intubation and confirmed that the patient meets eligibility criteria. The enrollment materials for the RSI trial will include instructions for a pre-procedural timeout to review the inclusion and exclusion criteria prior to enrollment.

This process requires less than 10 seconds and can be easily completed during the 2-minute preoxygenation period. This approach has been successfully used in multiple prior trials.[7–10]

Patients who are enrolled will be randomized 1:1 to ketamine or etomidate using random permuted blocks of two, four, and six. Study group assignment will be stored and concealed prior to enrollment using opaque envelopes or the Randomization Module in the online database REDCap.

6.0 Blinding

The trial will not blind patients or treating clinicians to study group assignment. Obscuring treatment assignment in a controlled trial is particularly important when the outcomes are subjective, such as alleviation of pain, but less important for objective criteria, such as hypotension, cardiac arrest, or death.[63] Treating clinician's awareness of study group assignment in the current trial may predispose to differential administration of co-interventions. For example, patients in the etomidate group may be more likely to be treated by clinicians with corticosteroid replacement therapy. In an explanatory trial focused on the mechanistic effects of a medication, such a difference in co-intervention could be viewed as confounding. In a pragmatic trial, the intent is to compare the manner in which the two interventions of interest would be administered as a part of routine clinical practice. Therefore, if patients in the etomidate group are administered corticosteroids at a higher rate than in the ketamine group, but the clinical outcomes in such circumstances are not different between groups, this provides the most robust answer to the question of the comparative effectiveness of ketamine versus etomidate for RSI as a part of routine clinical care.

7.0 STUDY INTERVENTIONS

7.1 Treatment of Study Patients

Timing of study procedures is based on the time of the administration of sedative medication (e.g., ketamine or etomidate), which is the first step of rapid sequence induction and tracheal intubation and will be defined as "Time 0.".

Study medications will be administered by the same treating clinicians (e.g., registered nurse, physician, pharmacist) who would administer those medications as part of routine clinical care.

7.2 Ketamine Group

Patients in the ketamine group will be assigned to receive intravenous ketamine for induction of anesthesia during tracheal intubation. A dose of 2 mg/kg will be recommended, and the group assignment sheet will contain a nomogram providing the recommended dose for a range of patient weights (in pounds and kg). In this pragmatic trial, treating clinicians will be able elect to give a lesser or greater dose of ketamine than recommended if felt to be required for optimal patient care.

7.3 Etomidate Group

Patients in the etomidate group will be assigned to receive intravenous etomidate for induction of anesthesia during tracheal intubation. A dose of 0.3 mg/kg will be recommended, and the group assignment sheet will contain a nomogram providing the recommended dose for a range of patient weights (in pounds and kg). In this pragmatic trial, treating clinicians will be able elect to give a lesser or greater dose of etomidate than recommended if felt to be required for optimal patient care.

7.4 Co-Interventions

The RSI trial will control only the first sedative medication administered during the intubation procedure. Subsequent sedative boluses or drips will be determined by treating clinicians. Other aspects of tracheal intubation (e.g., pre-intubation fluid management, pre-oxygenation, choice of neuromuscular blocking medication, choice of laryngoscopy device) will be performed by treating clinicians according to standardized clinical protocols already in place in the study units. Co-interventions that could modify the effect of ketamine or etomidate on cardiovascular collapse or clinical outcomes (e.g., vasopressors, corticosteroids) will be prospectively recorded.

7.5 Packaging and Labeling

Ketamine and etomidate will be packaged and labeled by the manufacturers of the medications. The labeling will not be altered. As the study is unblinded, concealment of the study medication after randomization is not necessary.

Ketamine has been approved by the United States Food and Drug Administration (FDA) and is commercially available with approved indications including “use as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation” and “induction of anesthesia prior to the administration of other general anesthetic agents.” Etomidate has been approved by the FDA and is commercially available with an indication for “induction of general anesthesia.”

Because both agents are FDA-approved and will be used in a manner consistent with FDA-labeling and standard of care for tracheal intubation in the ED and ICU, labeling ketamine and etomidate as investigational drugs is unnecessary. At all times and all study sites, study medications will already include standard labeling applied by the manufacturer.

The IND application for the RSI trial will, therefore, request a waiver of 21 CFR 312.6, which requires labeling of investigational new drugs with the statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” Given ED and ICU staff familiarity with the current labeling applied by the manufacturer, lack of investigational labeling will not pose a significant or unreasonable risk for any patient. In fact, investigational labeling could introduce increased risk to patients by introducing a new and unfamiliar label to a commonly used medication during a high-risk, time-sensitive procedure.

7.6 Storage and Accountability

The medications administered in this investigation will be stored and handled as they are in routine clinical care in the study units, in accordance with institutional policies for each medication. This will

include secure storage in pharmacy and in study units with the use of a password-protected secure medication storage devices (e.g. Omnicell machine). When treatment allocation is revealed at the time of enrollment, the assigned medication will be ordered, procured, prepared, and administered by clinical pharmacists, registered nurses, or physicians as it would be as part of routine clinical care.

7.7 On-Study Monitoring

This study will take place in high-acuity clinical care environments (EDs and ICUs) at the time of a procedure routinely performed as part of usual care. Thus, at the time of the study intervention, the patient will have in the room: a physician trained in the care of critically ill adults, a critical care or emergency medicine nurse, and usually a respiratory therapist and pharmacist. The patient will be receiving continuous invasive or non-invasive monitoring.

The intravenous injection of either ketamine or etomidate produces anesthetic effects that last for less than 10 minutes. Therefore, patients will be intensely monitored, with treating clinicians at the bedside for the duration of the primary effects of the study agents. Following intubation, no additional monitoring is planned beyond what occurs in the usual care of critically ill patients who have received these medications.

8. OUTCOMES

8.1 Stage 1 Primary Outcome

- Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation:
  - Systolic blood pressure < 65 mmHg
  - New or increased vasopressors
  - Cardiac arrest not resulting in death within 1 hour of induction
  - Cardiac arrest resulting in death within 1 hour of induction

8.2 Stage 1 Secondary Outcomes

- All-cause 28-day in-hospital mortality
- Feasibility, defined as meeting all the following:
  - Enrollment of at least 16 patients per month
  - Appropriate documentation of patient eligibility and adherence to EFIC requirements for notification of enrollment for **all** patients
  - Greater than 95% of enrolled patients receiving the induction medication assigned by the trial
  - Appropriate mechanisms for ongoing monitoring of EFIC compliance, tracking of excluded patients, and protocol adherence
  - Adequate completeness and timeliness of data entry

8.3 Stage 2 Primary Outcome

- All-cause, 28-day, in-hospital mortality

8.4 Stage 2 Secondary Outcome

- Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation:
  - Systolic blood pressure < 65 mmHg
  - New or increased vasopressors
  - Cardiac arrest not resulting in death within 1 hour of induction
  - Cardiac arrest resulting in death within 1 hour of induction

8.5 Exploratory Outcomes (for both Stage 1 and Stage 2)

- Procedural Characteristics & Complications
  - Cormack-Lehane Grade of glottic view
  - Number of attempts at tracheal intubation
  - Time from induction to successful tracheal intubation
  - Operator-assessed difficulty of intubation
  - Lowest oxygen saturation between induction and two minutes after intubation
  - Lowest oxygen saturation < 80% between induction to two minutes after intubation
  - Highest and lowest systolic blood pressure from induction to two minutes after intubation
  - Systolic blood pressure > 180 between induction and two minutes after intubation
  - Systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 2 minutes of intubation not resulting in death within 1 hour of induction
  - Cardiac arrest within 2 minutes of intubation resulting in death within 1 hour of induction
- Short-term Clinical Outcomes
  - Ventilator-free days to study day 28
  - Vasopressor-free days to study day 28
  - ICU-free days to study day 28

8.6 Safety outcomes (for both Stage 1 and Stage 2)

- Systolic blood pressure at 24 hours after induction
- Receipt of vasopressors at 24 hours after induction
- Cardiac arrest receiving cardiopulmonary resuscitation between induction and hospital discharge

9. DATA COLLECTION

Data will be stored in the secure, online database REDCap. A trained independent observer, not involved in the performance of the procedure, will collect peri-procedural outcomes, including oxygen saturation

and systolic blood pressure at the time of induction, lowest oxygen saturation and lowest systolic blood pressure between induction and two minutes after tracheal intubation, peri-procedural cardiac arrest, and time from induction to intubation. This process for outcome collection has been used by the primary investigator during multiple prior trials with nearly perfect agreement with the reference standard of direct observation by research staff (Spearman's rho rank correlation coefficient = 0.998).[9] Immediately after each intubation, the operator will report approach to preoxygenation, pre-intubation fluid boluses or vasopressors, Cormack-Lehane grade of glottic view,[64] subjective difficulty of tracheal intubation, airway complications during the procedure, and the level of operator experience. Study personnel will manually collect data from the medical record on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes.

9.1 Baseline Variable Collection

- Presence or absence of inclusion and exclusion criteria
- Date and time of induction
- Admission data: date and time of presentation, location at enrollment (ED, hospital ward, ICU)
- Demographics (age, sex, race, ethnicity, height, weight)
- Severity of illness score prior to induction
- Active medical problems at the time of induction
- Active comorbidities complicating induction
- Vasopressor use in the hour prior to induction
- Noninvasive ventilator use in the 1 hour prior to induction
- High flow nasal cannula use in the 1 hour prior to induction
- Highest FiO2 delivered in the 1 hour prior to induction
- Indication for intubation
- Preoxygenation technique
- Operator experience (number of prior intubations performed)
- Receipt of corticosteroids in the 48 hours prior to induction
- Vasopressor administration prior to or with induction
- Oxygen saturation by pulse oximetry at time of induction
- Systolic blood pressure at time of induction

9.2 Peri-Procedural Variables

- Lowest arterial oxygen saturation from induction to two minutes after intubation
- Lowest systolic blood pressure from induction to two minutes after intubation
- Highest systolic blood pressure from induction to two minutes after intubation
- Vasopressor administration from induction to two minutes after intubation
- Cardiac arrest from induction to one hour after intubation
- Time from induction to tracheal intubation
- Total number of attempts at intubation
- Sedative agent and dose

- Neuromuscular blocking agent and dose
- Use of nasal cannula, high flow nasal cannula, oxygen by bag-valve-mask, ventilation by bag mask, non-invasive ventilation, or ventilation by laryngeal mask airway between sedative administration and intubation
- Laryngoscope type
- Use of a bougie
- Presence of aspiration between induction and intubation
- Cormack-Lehane grade of glottic view
- Rescue device use
- Need for additional operators
- Mechanical complications (esophageal intubation)
- Self-reported difficulty of the intubation

9.3 Assessments between Hospital Presentation and Hospital Discharge

- Cardiac arrest between one hour after intubation and hospital discharge
- Oxygen saturation at 24 hours after intubation
- FiO2 at 24 hours after intubation
- PEEP at 24 hours after intubation
- Systolic blood pressure at 24 hours after intubation
- Vasopressor receipt at 24 hours after intubation
- Receipt of corticosteroids between induction and hospital discharge
- Clinically recorded Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scores on days 1-7
- SOFA Score on days 1-7
- Clinically recorded Glasgow Coma Scale on days 1-7
- Date and time of final receipt of invasive mechanical ventilation
- Date and time of first and final receipt of vasopressors following sedative administration (if applicable)
- Date and time of final ICU discharge (if applicable)
- Date and time of hospital discharge (if applicable)
- Date of death (if applicable)

9.4 REDCap Clinical Data Interoperability Services

This project will utilize the REDCap platform for data collection and management. Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative (or local equivalents) and/or directly from the EHR into REDCap.

10.1 Stage 1 Sample Size Calculation

Stage 1 of the RSI trial is primarily focused on feasibility. However, stage 1 will be of sufficient size to provide critical data on the short-term periprocedural outcome of cardiovascular collapse. Assuming that cardiovascular collapse will occur in 19% of patients in the etomidate group (a similar incidence as observed in a prior trial of airway management in which etomidate was the primary sedative),[12] we calculate that enrolling 464 patients will provide 80% statistical power (at a two-sided alpha of 0.05) to demonstrate a relative risk reduction of 50% in the primary outcome of cardiovascular collapse in the ketamine group, compared to the etomidate group.

10.2 Stage 2 Sample Size Calculation

To estimate the incidence of in-hospital mortality in the etomidate group of stage 2 of the RSI trial, we used data from 656 adults undergoing tracheal intubation for non-traumatic critical illness who were recently enrolled from EDs and ICUs in two recent randomized trials in the ED and ICU. Among these patients, the incidence of 28-day in-hospital mortality was 31%. The minimum clinically important difference (MCID) in mortality used in the design of prior critical care RCTs has been an absolute risk reduction of a median of 8 percent (IQR, 6-10).[65] We powered the RSI trial to detect a more conservative absolute risk reduction of 6 percent. This equates to an incidence of the primary outcome of 25% in the ketamine group and a relative risk of mortality with ketamine compared to etomidate of 0.81 – comparable to the relative risk of 0.827 among adults with non-traumatic critical illness observed in the only prior RCT comparing ketamine vs etomidate.[60] Achieving 80% statistical power at a two-sided alpha of 0.05 to detect a 6 percent absolute difference between groups in the primary outcome would require enrolling 911 patients per group (1,822 overall). Anticipating that, like prior EFIC trials, less than 5% of patients will discontinue participation after enrollment, we aim to enroll a total of 1,900 patients.

10.3 Progression from Stage 1 to Stage 2 of RSI

If, between initiation of enrollment in Stage 1 and enrollment of 464 patients in Stage 1, funding becomes available for Stage 2, the DSMB will perform a formal assessment of feasibility and issue a recommendation of whether the trial should progress from Stage 1 to Stage 2. To perform this assessment of feasibility, the DSMB will meet to review data from at least 100 patients enrolled in Stage 1. The DSMB will review: 1) the rate of enrollment, 2) the number, proportion, and reasons for exclusion, 3) protocol adherence, 4) data quality, 5) compliance with the requirements of EFIC (under FDA code of regulations 21 CFR 50.24.7) including a review of the timeliness and success of patient or LAR notification,[99,100] and 6) adverse events. Metrics upon which the DSMB may base their recommendation to progress to Stage 2 will include:

1. Enrollment of at least 16 patients per month.
2. Appropriate documentation of patient eligibility and adherence to EFIC requirements for notification of enrollment for **all** patients.
3. Greater than 95% of enrolled patients receiving the induction medication assigned by the trial
4. Appropriate mechanisms for ongoing monitoring of EFIC compliance, tracking of excluded patients, and protocol adherence.
5. Adequate completeness and timeliness of data entry.

If the DSMB recommends the trial progress to Stage 2 and the investigators accept the DSMB's recommendation, no analysis of Stage 1 outcomes (primary outcome of cardiovascular collapse) will be performed. At the end of enrollment in Stage 2, all patients enrolled in the trial will be included in a single planned analysis of the Stage 2 outcomes (primary outcome of 28-day in-hospital mortality). If the trial does not progress to Stage 2 for any reason, the planned analysis of Stage 1 outcomes (primary outcome of cardiovascular collapse) will be performed and reported.

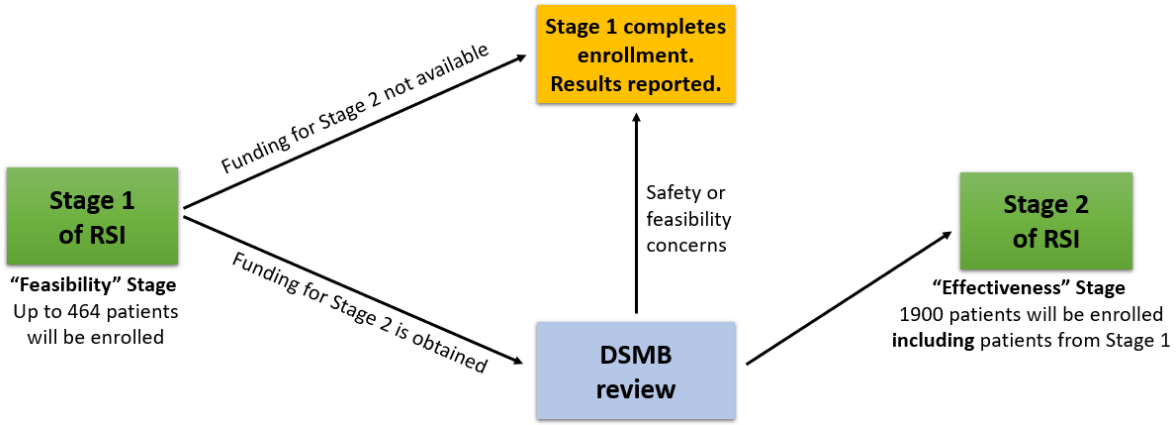

Figure 1. Flow diagram for Adaptation from Stage 1 to Stage 2 of RSI

10.4 Primary Analysis

Whether the trial stops at the end of stage 1 or progresses to the completion of stage 2, the approach to analysis will be the same. The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to ketamine versus patients randomized to etomidate with regard to the primary outcome. The difference between the two study groups will be compared using a Chi-squared test.

10.5 Secondary Analyses

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 (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and fixed effects for group assignment and the following pre-specified baseline variables:

1. Age;
2. Sex;
3. Race;
4. Systolic blood pressure at induction;
5. Receipt of vasopressors in the 1 hour prior to induction;
6. Sequential Organ Failure Assessment score prior to induction; and
7. Diagnosis of sepsis at the time of intubation.

10.6 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. Pre-specified effect modifiers will include:

1. Age;
2. Location (ED vs ICU);
3. Systolic blood pressure at induction;
4. Receipt of vasopressors in the 1 hour prior to induction;
5. Sequential Organ Failure Assessment score prior to induction;
6. Diagnosis of sepsis at the time of intubation;
7. Indication for intubation; and
8. Baseline risk of the primary outcome.

10.7 Interim Analysis

If the RSI trial does not progress to Stage 2, no interim analysis will be performed as Stage 1 is primarily focused on feasibility and a finding that ketamine or etomidate reduced the incidence of the short-term peri-procedural outcome of cardiovascular collapse would not negate the need for a definitive trial evaluating the effect of ketamine and etomidate on mortality. If the RSI trial progresses to Stage 2, the DSMB will review an interim analysis performed after the enrollment of 950 patients (50% of the anticipated trial enrollment). 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).

10.8 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[66] and the European Medicines Association,[67] each will be tested using a two-sided P value with a significance level of 0.05. For all other 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*,[68] and no corrections for multiple comparisons will be performed.

10.9 Handling of Missing Data

No patients will be lost to follow up before the measurement of the primary outcome, except those that choose to withdraw from the study. 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.

11. DATA QUALITY MONITORING AND STORAGE

11.1 Data Quality Monitoring

Data quality will be reviewed using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools connecting the online database to statistical software to generate data reports. The coordinating center will perform remote monitoring of documentation of eligibility criteria, completion of EFIC requirements, and the completeness of study outcome collection.

11.2 Data Storage

Data will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

12. RISK ASSESSMENT

12.1 Potential Risks of Receiving Ketamine

Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. At an intravenous dose of 2 mg/kg of body weight, the onset of ketamine is rapid, usually producing surgical anesthesia within 30 seconds after injection. The anesthetic effect usually lasts five to ten minutes and the duration of action of the medication is less than fifteen minutes.

Potential risks of receiving ketamine can be classified based on their severity as major or minor. Major potential risks of receiving ketamine include:

1) Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred. Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes, and usually returns to preanesthetic values within 15 minutes after injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10% to 50% above preanesthetic levels shortly after induction of anesthesia. Regardless of which sedative is used, cardiovascular complications including hypotension and cardiac arrest are common during the tracheal intubation of critically ill adults. Determining whether or not use of ketamine for

induction of anesthesia during intubation of critically ill adults effects the risk of cardiovascular events compared to etomidate is a key objective of the RSI trial.

2) Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasm has also been reported. Given that ketamine will be used in this trial only as part of the process of tracheal intubation and initiation of invasive mechanical ventilation, respiratory suppression from ketamine is not a significant concern in the RSI trial.

3) Anaphylaxis: Allergic reactions to ketamine are extremely rare and only a few cases of anaphylaxis have been reported. Patients with known allergy to ketamine are excluded from the RSI trial.[69,70]

4) Psychological: According to the FDA package insert for ketamine, adverse psychological manifestations with ketamine are common, reportedly occurring in up to 12% of patients. The psychological manifestations vary in severity from pleasant dream-like states to hallucinations and emergence delirium. The duration is reported to be no more than several hours for most patients with rare occurrences up to 24 hours post postoperatively. Because patients in the RSI trial are critically ill and will receive ketamine at the time of tracheal intubation with a median duration of invasive mechanical ventilation and accompanying sedation and analgesia of 2-3 days,[10,12] psychological manifestations are unlikely to represent significant risk to patients in the RSI trial.

5) Increased intracranial pressure: An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride and caution is recommended for patients with preanesthetic elevated cerebrospinal fluid pressure. However, the original evidence supporting this assertion is anecdotal and recent studies have contraindicated these findings, suggesting that ketamine may be associated with a beneficial increase in cranial perfusion pressure as a result of increased mean arterial pressure.[39,40] Ketamine is routinely administered to patients with head trauma in routine clinical care in the study settings. However, to maximize patient safety, patients presenting with a primary diagnosis of trauma are excluded from the RSI trial.

Minor potential risks of receiving ketamine include: diplopia, nystagmus, temporary increase in intraocular pressure, anorexia, nausea, and vomiting. Lower urinary tract and bladder symptoms have also been reported with chronic use.

12.2 Potential Risks of Receiving Etomidate

Etomidate is a rapidly acting general anesthetic without analgesic activity. At a dose of 0.3 mg/kg body weight, onset of action is usually within one minute with a duration of action of three to five minutes.

Potential risks of receiving etomidate can be classified based on their severity as major or minor. Major potential risks of receiving etomidate include:

1) Endocrine: Reduced plasma cortisol and aldosterone levels have been reported following the induction doses of etomidate that will be recommended in the RSI trial. These reductions in plasma cortisol and aldosterone persist for approximately 6-8 hours and appear to be unresponsive to ACTH stimulation. They are likely related to blockage of 11 beta-hydroxylation within the adrenal cortex. Determining whether or not these transient reduction in cortisol and aldosterone levels influence clinical outcomes for patients is a key objective of the RSI trial.

2) Circulatory: Hypertension, hypotension, tachycardia, bradycardia, and other arrhythmias have occasionally been observed during induction with etomidate. Geriatric patients, particularly those with hypertension, may be at increased risk for the development of cardiac depression following etomidate administration. Regardless of which sedative is used, cardiovascular complications including hypotension and cardiac arrest are common during the tracheal intubation of critically ill adults. Determining whether or not use of etomidate for induction of anesthesia during intubation of critically ill adults effects the risk of cardiovascular events compared to ketamine is a key objective of the RSI trial.

3) Respiration: Hyperventilation, hypoventilation, apnea of short duration (5 to 90 seconds with spontaneous recovery), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients. Given that etomidate will be used in this trial only as part of the process of tracheal intubation and initiation of invasive mechanical ventilation, respiratory suppression from etomidate is not a significant concern in the RSI trial.

4) Anaphylaxis: Allergic reactions to etomidate are extremely rare and limited to one case of severe hypotension and tachycardia. Patients with known allergy to etomidate are excluded from the RSI trial.

Minor potential risks of receiving etomidate include: transient venous pain on injection (20% of the patients) and transient skeletal muscle movements (32% of patients) including myoclonus, nausea, or vomiting.

12.3 Potential Risk of Participation in the RSI Trial

The RSI trial will enroll critically ill adults whose treating clinicians have determined that (1) tracheal intubation is clinically required and (2) use of either ketamine or etomidate is consistent with optimal care for the patient. Both ketamine and etomidate are FDA-approved medications being used within their FDA approved indications, and the only prior randomized trial reported no significant difference in outcome between the two medications. More than 95% of patients undergoing tracheal intubation in the study sites receive either ketamine or etomidate as a part of routine clinical care. All patients eligible for the RSI trial will experience the risks of emergency tracheal intubation and the risks of receipt of an induction medication such as ketamine or etomidate as a part of their routine clinical care, whether or not they are enrolled in the RSI trial. The incremental risks of participation in the RSI trial are (1) the risk associated with collection of PHI and (2) the risk associated with allowing the choice between ketamine and etomidate to be made by trial group assignment rather than by the treating clinician. Because the only patients eligible are those whose treating clinicians feel use of either ketamine or etomidate is

consistent with optimal care, the incremental risk of participation in the RSI trial, compared to routine clinical care outside the trial, is minimal.

12.4 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 subject protection requirement by incorporating numerous design elements to minimize risk to patients.

Both therapies used in the RSI trial, ketamine and etomidate, are approved by the Food and Drug Administration and have been used in clinical practice for decades with an established safety profile in the same populations included in the RSI trial. Both medications will be administered at the recommended dose and route.

To further mitigate risk, we will exclude patients with specific risk factors for adverse events from ketamine or etomidate including patients with known allergies to ketamine or etomidate, patients with a primary diagnosis of trauma, and any patient for whom treating clinicians believe that ketamine or etomidate is required or contraindicated for the optimal care of the patient. Finally, 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.

12.5 Potential Benefit

Participation in the RSI trial holds the prospect of direct benefit to the subjects. Previous animal and clinical studies have established several mechanisms by which either ketamine or etomidate might provide a direct benefit to individual critically ill subjects undergoing tracheal intubation via improved hemodynamics and survival.

Determining whether ketamine or etomidate improves clinical outcomes among critically ill patients undergoing tracheal intubation in the ED or ICU will also benefit RSI trial patients who go on to require emergency tracheal intubation again in the future, as well as the millions of critically ill adults who undergo tracheal intubation each year.

12.6 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." The incremental risks of participation in the RSI trial, compared to routine clinical care outside the trial for eligible patients, are minimal as all patients enrolled in the RSI trial would have received a sedative as part of emergency tracheal intubation in routine clinical care, regardless of participation in the RSI trial. Understanding the effect of these two commonly used medications on clinical outcomes will benefit RSI trial patients who go on to require emergency tracheal intubation again in the future, as well as the millions of critically ill adults who undergo tracheal intubation each year. Thus, the risks to subjects are reasonable in relation to the anticipated benefits and importance of the knowledge to be gained.

13. HUMAN SUBJECTS PROTECTIONS

Emergency tracheal intubation of critically ill adults is a time-sensitive procedure with a brief therapeutic window between the decision to perform intubation and the completion of the procedure. Critically ill patients requiring tracheal intubation are nearly uniformly unconscious, delirious, or in states of distress for which it would be unsafe to delay intubation for an informed consent discussion with the patient or a surrogate. Legally authorized representatives are rarely available during the narrow therapeutic window. Even in the rare cases where the patient retains decisional capacity or the patient's legally authorized representative (LAR) is present at the bedside at the moment the decision is made to intubate a critically ill patient, the urgency of the intubation procedure would preclude the detailed discussion of risks and benefits required for informed consent.

Therefore, it is expected that all patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC). Additional details regarding how the RSI trial will comply with each of the requirements of EFIC are provided in Appendix B.

13.1 Length of Therapeutic Window

For an induction medication used for emergency tracheal intubation, the therapeutic window begins at the time treating clinicians decide to perform emergency tracheal intubation with sedation and ends at the time an induction medication is administered for emergency tracheal intubation. To our knowledge, no published literature has quantified this therapeutic window among critically ill adults. Among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the ED or ICU in the planned study sites of the RSI trial, the median time from treating clinicians verbalizing the decision to intubate with sedation (or placing a written order for an induction medication) to the administration of an induction medication was 5 minutes [interquartile range, 1 minute to 10 minutes]. For no patient was this window longer than 30 minutes. 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. For most patients in the RSI trial, completion of the trial intervention (a one-time injection at the start of the emergency tracheal intubation procedure) is anticipated to occur less than 5 minutes after meeting trial eligibility criteria. Thus, in the RSI trial, we anticipate that the therapeutic window for most patients will be less than 5 minutes.

13.2 Inability to Conduct Trial without EFIC

Most patients eligible for the RSI trial will be experiencing unconsciousness or delirium due to critical illness. More than half of critically ill adults undergoing tracheal intubation in the ED or ICU have a Glasgow Coma Scale score less than 12 (equivalent to moderate brain injury) and among those whose level of consciousness is not impaired, most experience acute delirium. Even in instances in which a patient retains capacity, or an LAR is immediately available, the rapidity with which emergency tracheal intubation is clinically required, and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation, precludes a meaningful informed consent process.

Delaying emergency tracheal intubation for a critically ill adults to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

One approach for obtaining prospective consent for interventions with short therapeutic window is to consent patients at high risk of requiring the intervention in the future. Unfortunately, there is no reasonable method for prospectively identifying individuals who will develop a need for emergency tracheal intubation. Many different acute illnesses lead to emergency tracheal intubation in the ED or ICU including stroke, spontaneous intracranial hemorrhage, seizure, sepsis, drug overdose, acute coronary syndrome, aspiration pneumonitis, acute bacterial pneumonia, pneumothorax, and others. Any patient in the community or in the hospital may unexpectedly develop a need for emergency tracheal intubation within a period of minutes with no warning.

For these reasons, the RSI trial could not be conducted without EFIC, and it is expected that all patients will be enrolled through EFIC.

13.3 Opportunity to Decline Participation

Although it is expected that in most, if not all cases, the urgency of the procedure and the nature of the patient's critical illness will preclude a detailed informed consent discussion between the trained research staff and the patient or LAR during the brief therapeutic window, a consent form will be available and the RSI trial will provide two mechanisms to opt-out of participation.

First, medical alert bracelets will be made available prior to and throughout the trial for any community members who become aware of the trial and desire to express their preference against participation should they become critically ill and require tracheal intubation (details of public notification plan and process of requesting opt-out bracelets are provided in the Community Consultation and Public Disclosure Plan).

Second, when feasible, the RSI trial will provide an opportunity for patients, LARs, or family members to express their objection immediately prior to research enrollment. While the nature of emergency tracheal intubation precludes a full, written, informed consent process in most, if not all, cases, the RSI trial will provide an opportunity for patients, LARs, or family members to object to participation based on more limited information whenever feasible using a pre-enrollment opt-out script. Because patient enrollment and delivery of the trial intervention are performed by treating clinicians (not research staff) and occur within a period of minutes after meeting eligibility, this opt-out script will be read by treating clinicians using a script approved by the IRB to describe the study and provide an opportunity for patients, LARs, or family members to decline participation before enrollment (Appendix C). The decisional capacity of the patient and the safety and feasibility of reading the script during the brief therapeutic window will be determined by the treating clinicians. Allowing a mechanism, whenever feasible, for patients to opt out of participation is consistent with the respect for autonomy emphasized in the EFIC guidelines.

13.4 Notification of Enrollment

At the soonest feasible opportunity after study enrollment, the patient or the patient's LAR or family member will be notified of the study enrollment. Details of the investigation will be provided, all questions will be answered, and the patient or patient's LAR or family member will be informed of their right to discontinue study participation. The patient or LAR or family member will be provided with a

patient notification form (Appendix D) which contains study details and contact information for study personnel and the IRB.

Because the study intervention is a one-time injection occurring within minutes of enrollment, all patients will have completed the study intervention and experienced the risks and benefits of the study intervention by the time notification of participation occurs. The only remaining study activity is review of the patient's medical record by study personnel until the end of the patient's hospitalization. For those who wish to discontinue participation, no further data will be collected. Data collected prior to withdrawal will remain in the study database as per FDA requirements and guidance.

A minimum of three attempts will be made to discuss the study with the patient or the patient's LAR. Whenever feasible, this will occur in a face-to-face discussion in the hospital between trained study personnel and the patient or LAR. If the patient is discharged before a face-to-face discussion occurs, these attempts will be made by phone, and a notification sheet will be mailed to the patient's address (Appendix E).

If a patient is enrolled in the RSI trial and dies before a face-to-face discussion with the patient or LAR, a reliable mailing address for the patient's family or LAR will be obtained. After allowing a two to four-week period of grieving, study personnel will send a letter (Appendix F) with basic information about the clinical investigation, the patient's inclusion, and contact information so that families can call or write to obtain more information or to get questions answered if desired.

If the patient regains decision-making capacity prior to hospital discharge, study personnel will notify the patient of the study and ask if the patient wants to continue participation.

13.5 Documentation and Tracking of Notification Process

Notification logs will be incorporated into the study case report forms and will allow tracking and reporting of the timeliness of these processes. This log will include the types of attempts made, the number and timing of those attempts, and the outcome of each attempt. Notification logs will be available for IRB review as requested and will be summarized for the IRB at the time of continuing review.

13.6 Selection of Subjects

Federal regulations 45 CFR 46(a)(3) require the equitable selection of subjects. All patients undergoing tracheal intubation in a participating unit who meet inclusion criteria without meeting exclusion criteria will be enrolled. We will not discriminate based on gender, race, or ethnicity. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of patients conforms to the principle of distributive justice.

13.7 Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of ketamine and etomidate during the tracheal intubation of critically ill patients. Due to the nature of this patient population, most patients will have impaired decision-making capabilities. Moreover, those with intact decision-making capacities probably have milder disease than those with impaired capacity. Therefore, the validity of the study and

its generalizability to severely ill patients would be compromised by enrolling only those patients with retained decision-making capacity. Hence, patients recruited for this trial are not being unfairly burdened with involvement in this research.

13.8 Investigational New Drug Application

As required by studies conducted under 21 CFR 50.24, the RSI protocol will be included as part of an Investigational New Drug Application to the United States Food and Drug Administration (FDA). The study will not proceed until the primary investigator has received written authorization from both the FDA and the Vanderbilt Institutional Review Board

13.9 Additional Safeguards for Vulnerable Patients

The present research will involve patients who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these patients. Such safeguards might include but are not limited to: a) assessment of the patient's capacity to understand notification of enrollment and b) the availability of the LAR to monitor the patient's participation and withdrawal from the study. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

13.10 Confidentiality

Federal regulations 45 CFR 46 111 (a) (7) requires that, when appropriate, there are adequate provisions to protect the privacy of patients and to maintain the confidentiality of data. 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. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated. Further, tools within the secure online database will be used so that only the coordinating center and investigators from the enrolling site will have access to data from patients enrolled at that site.

14. ADVERSE EVENTS

Assuring patient safety is an essential component of this protocol. Both ketamine and etomidate have been approved by the Food and Drug Administration and 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 ketamine or etomidate;
2. Systematic collection of safety outcomes relevant to use of ketamine and etomidate in this setting;
3. Structured reporting of adverse events.

14.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a medication or a study procedure, whether or not considered medication related.

Serious Adverse Event: A serious adverse event is any adverse event that results in one of the outcomes listed in section 14.3 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

14.2 Safety Monitoring

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 for 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 as close as feasible to 24 hours after randomization during initial data collection. The second will occur at the first of hospital discharge or 28 days after enrollment during 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.

The following adverse events will be considered reportable and thus collected in the adverse event case report forms:

- Serious adverse events that are considered by the investigator to be related to study procedures, possibly or probably related, or of uncertain relationship (Appendix G)
- Unexpected adverse events that are considered by the investigator to be related to study procedures, possibly or probably related, or of uncertain relationship (Appendix G)

Study-specific clinical outcomes (Primary, Secondary and Safety Outcomes), including serious outcomes such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the adverse event to be serious and definitely related to the administration of study medication or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix G.

Because ketamine and etomidate are 1) FDA-approved, 2) used within their approved indications, and 3) have well-established safety profiles, the RSI trial will not plan to collect non-serious adverse events as suggested in FDA guidelines for Investigator Reporting (21 CFR 312.64(b)) for post-marketing outcome trials conducted with an IND.

Adverse events will be evaluated by the lead investigator at each enrolling site . If an adverse event is judged to be potentially reportable, as outlined above, then the lead investigator at each enrolling site will record the adverse event via electronic data entry for review. The principal investigator will be responsible for making final determinations regarding potential relatedness of adverse events, based on the criteria outlined in Section 14.3 and Appendix G. The principal investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the study protocol or the investigator brochure for Ketamine or Etomidate. In making determinations, the principal investigator will determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

14.3 Serious Adverse Events

The lead investigator at each enrolling site must alert the primary investigator of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix G for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs).

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization
- Persistent or significant disability/incapacity

Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events

- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

The DSMB will consist of members with expertise in bioethics, emergency medicine, pulmonary critical care, 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 Principal Investigator 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 with the assistance of the Principal Investigator. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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17. APPENDICES

Appendix A. Schedule of Events

Study Activity	Pre-Induction	Administration of Sedatives (Induction)	Tracheal Intubation	Day 1	Days 2-27	Day 28
Eligibility assessment	X					
Opt-out conversation (when feasible)	X					
Pre-enrollment time-out	X					
Randomization	X					
Recording of baseline blood pressure and oxygen saturation	X					
Study medication delivery (Ketamine or Etomidate)		X				
Recording of peri-procedural outcomes		X	X	X		
Assessment for study medication adherence		X	X	X		
Safety monitoring for adverse events		X	X	X		X
Notification of Enrollment				X	X	
Mortality assessment			X	X	X	X
28-day in-hospital outcomes (chart review)						X

Appendix B: Compliance with Criteria and Processes Required for EFIC

FDA regulations identify the specific circumstances in which EFIC is appropriate. RSI fulfills these requirements for emergency research. In the following section, the components of the regulations are reproduced, along with an explanation of how RSI will comply with each requirement.

1) Critical illness requiring emergency tracheal intubation is a life-threatening situation and available treatments are unsatisfactory or unproven.

> *21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.*

Each year more than 1.5 million critically ill patients receive mechanical ventilation in the United States.[1–3] Despite adherence to recommended best-practices for tracheal intubation (e.g., preoxygenation,[15,16] optimization of patient positioning,[9] and procedural checklists[8]), one in five critically ill patients experiences hypotension and one-in-forty experiences cardiac arrest during the brief, two-minute procedure to place an endotracheal tube.[6–10] Around 30% of critically ill adults undergoing emergency tracheal intubation die prior to hospital discharge.

Rapid sequence induction and tracheal intubation, the most common method of intubation for critically ill patients, is the nearly simultaneous administration of a sedative medication and neuromuscular blocking medication. The ideal sedative agent for rapid sequence intubation would rapidly provide a deep state of unconsciousness and analgesia without causing hemodynamic side effects, but no available agent meets all criteria.[20] The administration of any available sedative at a dose large enough to rapidly induce unconsciousness contributes to cardiovascular collapse through vasodilation, decreased cardiac filling pressures from sedation-induced venodilation, and decreased endogenous catecholamines.[21–24] While all sedatives commonly used during emergency tracheal intubation of critically ill patients have been associated with unsatisfactory hypotension (21 CFR 50.24(a)(1)), ketamine and etomidate are the medications used most commonly in clinical practice due to their rapid onset and relatively favorable hemodynamic profiles (as described in section 2.1.2).[25,26] A large multi-center trial is needed to determine the effects on peri-procedural hemodynamics and mortality of the two most commonly used sedatives for the tracheal intubation of critically ill adults.

2) Obtaining prospective informed consent is not feasible during emergency tracheal intubation.

> *21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.*

Most patients eligible for the RSI trial will be experiencing unconsciousness or delirium due to critical illness. More than half of critically ill adults undergoing tracheal intubation in the ED or ICU have a Glasgow Coma Scale score less than 12 (equivalent to moderate brain injury) and among those whose level of consciousness is not impaired, most experience acute delirium. Even in instances in which a patient retains capacity, or an LAR is immediately available, the rapidity with which emergency tracheal intubation is clinically required, and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation, precludes a meaningful informed consent process. Delaying emergency tracheal intubation for a critically ill adults to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

There is no reasonable method for prospectively identifying individuals for informed consent prior to developing a need for emergency tracheal intubation. Many different acute illnesses lead to emergency tracheal intubation in the ED or ICU including stroke, spontaneous intracranial hemorrhage, seizure, sepsis, drug overdose, acute coronary syndrome, aspiration pneumonitis, acute bacterial pneumonia, pneumothorax, and others. Any patient in the community or in the hospital may unexpectedly develop a need for emergency tracheal intubation within a period of minutes with no warning.

For these reasons, the RSI trial could not be conducted without EFIC, and it is expected that most, if not all, patients will be enrolled through EFIC.

3) Participation in RSI holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Participation in RSI holds out the prospect of direct benefit to subjects. Critical illness requiring emergency tracheal intubation is a life-threatening condition with a high incidence of hypotension and cardiac arrest that necessitates immediate intervention. Previous animal and clinical studies have established several mechanisms by which either ketamine or etomidate might provide a direct benefit to individual critically ill subjects undergoing tracheal intubation via improved hemodynamics and survival.

The risks associated with the investigation are reasonable in relation to what is known about tracheal intubation of critically ill patients. All patients enrolled in the RSI trial would have received a sedative as part of emergency tracheal intubation in routine clinical care, regardless of participation in the RSI trial. The treatment groups represent the two most commonly used sedatives, and there is no evidence currently that either medication is superior with regard to peri-procedural hemodynamics or survival. Therefore, there is no reason to believe that participation in this study would expose patients to greater medical risks than those experienced by critically ill patients undergoing tracheal intubation as part of routine clinical care.

4) The RSI trial cannot be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because 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. A meaningful informed consent process requires that the patient or LAR have time to understand the material presented, be able to ask questions and have time to consider their options. This is not possible in the brief therapeutic window between the decision to intubate a critically ill patient and the initiation of the procedure.

5) The need for immediate treatment of critically ill patients requiring emergency tracheal intubation is expected to preclude obtaining informed consent from an LAR in most, if not all cases, during the brief therapeutic window

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.*

For an induction medication used for emergency tracheal intubation, the therapeutic window begins at the time treating clinicians decide to perform emergency tracheal intubation with sedation and ends at the time an induction medication is administered for emergency tracheal intubation. To our knowledge, no published literature has quantified this therapeutic window among critically ill adults. Among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the ED or ICU in the planned study sites of the RSI trial, the median time from treating clinicians verbalizing the decision to intubate with sedation (or placing a written order for an induction medication) to the administration of an induction medication was 1 minute [interquartile range, 1 minute to 10 minutes]. For no patient was this window longer than 30 minutes. 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. For most patients in the RSI trial, completion of the trial intervention (a one-time injection at the start of the emergency tracheal intubation procedure) is anticipated to occur less than 5 minutes after meeting trial eligibility criteria. Thus, in the RSI trial, we anticipate that the therapeutic window for most patients will be less than 5 minutes. While a written informed consent is available and will be used when feasible, it is expected that written consent will be infeasible in most, if not all, cases because delaying the emergency tracheal intubation of critically ill adults would cause irreparable harm to patients. Whenever feasible, however, the RSI trial will provide an opportunity for patients, LARs, or family members to opt-out of trial participation.

Because patient enrollment and delivery of the trial intervention are performed by treating clinicians (not research staff) and occur within a period of minutes after meeting eligibility, treating clinicians will use a brief written script, approved by the IRB, to describe the study and provide an opportunity for the patient, LAR, or family member to opt-out (Appendix D). The decisional capacity of the patient and the safety and feasibility of reading the script during the brief therapeutic window will be determined by the treating clinicians. Allowing a mechanism, whenever feasible, for patients to opt out of participation is consistent with the respect for autonomy emphasized in the EFIC guidelines.

We will make every effort to contact legal representatives after enrollment to notify LARs that the patient was enrolled in a randomized trial and provide an opportunity to withdraw from further participation. If legal representatives are not immediately available, research personnel will attempt to contact the subject's legal representative as soon as feasible and a summary of these efforts will be documented in the patient's study record. If the subject becomes competent during the study period, he/she will be approached by research personnel for notification of enrollment.

Investigators will prospectively record the efforts by treating clinicians to allow patients, LARs, or family members to opt-out of participation and the efforts by study staff to notify patients and LAR of enrollment. These efforts will be summarized and reported to the DSMB at their semi-annual meetings and to the IRB at the initial and continuing reviews.

6) Informed consent procedures and documents in the RSI trial will be reviewed and approved by the IRB

> *21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.*

All consent procedures and documents that will be used in the RSI trial will be approved by the IRB prior to the initiation of enrollment.

7) Additional protections of the rights and welfare of the subjects will be provided in the RSI trial, including:

Community Consultation

i. *21 CFR 50.24(a)(7) Additional: Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;*

A detailed plan for community consultation has been developed for the RSI trial (see Community Consultation and Public Disclosure Plan). The plan included in the initial draft of the RSI protocol was informed by two Community Engagement Studios, organized by the Vanderbilt Community Engagement

Research Core. The first meeting, held on February 2, 2021, included healthcare providers who routinely participated in emergency tracheal intubation in the ED or ICU. The second meeting, held on February 4, 2021, included patients or caretakers of patients who had experienced critical illness with emergency tracheal intubation. Investigators solicited feedback on the design of the RSI trial, potential risks and benefits of participation, the inability to obtain prospective informed consent, the opportunity to opt-out of participation, and the plans for further Community Consultation, Public Disclosure of the conduct and results of the trial. The protocol, the plan for further Community Consultation, and the plan for Public Disclosure were refined based on this feedback to address the concerns of the community. Enrollment in the RSI trial will not begin until 1) the IRB has approved the proposed community consultation plan, 2) study personnel have completed the proposed community consultation plan, and 3) the IRB has reviewed and certified the completion of community consultation and approved enrollment.

Public Disclosure

ii. *21 CFR 50.24(a)(7): Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;*
iii. *Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;*

Public disclosure is a primary element in making certain that RSI is conducted in an entirely transparent manner. A detailed public disclosure plan has been developed for the RSI trial (see Community Consultation and Public Disclosure Plan). The plan included in the initial draft of the RSI protocol was informed by two Community Engagement Studios, organized by the Vanderbilt Community Engagement Research Core. The first meeting, held on February 2, 2021, included healthcare providers who routinely participated in emergency tracheal intubation in the ED or ICU. The second meeting, held on February 4, 2021, included patients or caretakers of patients who had experienced critical illness with emergency tracheal intubation. Investigators solicited feedback on the design of the RSI trial, potential risks and benefits of participation, the inability to obtain prospective consent, the opportunity to opt-out of participation, and the plans for further Community Consultation, Public Disclosure of the conduct and results of the trial. The protocol, the plan for further Community Consultation, and the plan for Public Disclosure were refined based on this feedback to address the concerns of the community. Enrollment in the RSI trial will not begin until 1) the IRB has approved the proposed public disclosure plan, 2) study personnel have completed the proposed public disclosure activities, and 3) the IRB has reviewed and certified the completion of public disclosure and approved enrollment.

Data and Safety Monitoring Committee

iv. *21 CFR 50.24(a)(7): Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

The Data Safety Monitoring Board (DSMB) will function as an independent data monitoring committee who will exercise oversight of the study. The composition and responsibilities of the DSMB are described in protocol section 15.

Contacting Other Family

> *v. 21 CFR 50.24(a)(7) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

It will not be feasible or ethically possible in the RSI trial, for the reasons described above, to delay treatment of a critically ill patient requiring emergency tracheal intubation for long enough to contact either an LAR or other family members who are not present. We will, however, provide patients and LARs or family members who are present with the opportunity to opt-out of enrollment using the recitation of a standardized script by treating clinicians during the brief therapeutic window (Appendix E). Further, we will provide a mechanism whereby community members who would not want to participate if undergoing tracheal intubation in the ED or ICU can communicate that decision to providers without causing any delay in treatment using opt-out bracelets. As part of the primary assessment of a critically ill patient, providers already check for a medical alert bracelet. The study will provide medical alert bracelets with the words "RSI declined" to any community member requesting one. The process by which community members are notified of the study and requests an opt-out bracelet are explained in the Community Consultation and Public Disclosure Plan. Medical alert bracelets are a common and effective means of communicating information to ED and ICU providers while unconscious or in acute distress. Requests for RSI opt-out bracelets and their use in identifying patients for exclusion will be tracked by study investigators and this information can be made available to the IRB at the time of continuing review.

Post Enrollment Notification

> *vi. 21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be*

informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.

Subjects enrolled in RSI or their LAR or family will be informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity as detailed above. It is anticipated that the notification of patients' LAR or family will most usually take place within 24 hours of enrollment. Attempts to notify the subject or an LAR are repeated until successful or at least three attempts have been made. If a patient's LAR or family member is notified of enrollment and the patient subsequently regains decision-making capacity, the patient will be notified of the study and will be asked if he or she wants to continue the study.

All notification attempts will be logged and recorded in the study record. Reports of these logs will be summarized to the DSMB at semi-annual reports and available for inclusion in annual reports to the IRB.

By the time patients, LARs, or family members are notified of participation, the study intervention (a one-time infusion at the time of tracheal intubation) will have been completed and patients will have experienced all of the risks or benefits associated with the study intervention. The only remaining study procedure will be review of the electronic health record by study personnel. Requesting that patients, LARs, or family member provide informed consent for continued participation after completion of the study intervention would not provide any additional patient protections, but would risk diminishing the overall validity and value of the research by biasing estimates of safety and efficacy if consent for continued participation occurred differentially between the trial groups because of the effects of the trial interventions. The RSI trial will, therefore, use public notification, community consultation, a pre-enrollment opt-out conversation (by treating clinicians whenever feasible), medical alert bracelets, patient and LAR notification of enrollment, and a provision of an opportunity to opt out of ongoing participation.

Record Keeping

21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.

Records documenting the enrollment of patients using EFIC, procedures for opt-out prior to enrollment, and attempts to notify patients, LARs, and family members of enrollment will be kept for a minimum of three years after completion of the clinical investigation.

IND Requirement

21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate

IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.

For critically ill adults undergoing emergency tracheal intubation for whom treating clinicians feel either ketamine or etomidate is consistent with optimal care, the incremental risks of participating in the RSI trial, compared to clinical care for the patient outside the trial, are minimal. As such, the RSI trial might be considered to quality for waiver of consent and exemption from IND requirements under 21 CFR 312 because:

- Both ketamine and etomidate are lawfully marketed in the United States for use as sedative agents during tracheal intubation (the indication for which they will be used in the RSI trial)
- The current study is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for either ketamine or etomidate
- The current study is not intended to support a change in advertising for ketamine or etomidate
- The current study does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of ketamine or etomidate. The current study will use ketamine and etomidate at the doses recommended by the FDA-approved package insert and excludes patient populations that would have increased risks of complications and any patients for whom any provider believes ketamine or etomidate is required or contraindicated
- The study will be conducted with the requirements for institutional review set forth in FDA regulations 21 CFR 56.
- The current study will be conducted in compliance with FDA regulations 21 CFR 312.7 regarding promotion and charging for investigational medication

We will, however, conduct the RSI trial under EFIC in order to ensure patients receive the additional protections offered by community consultation and disclosure through EFIC. As required by EFIC regulations 21 CFR 50.24(d), an IND for the RSI trial was obtained from the FDA (IND 141424). The Study Principal Investigator serves as the sponsor of the IND.

Communication of IRB Determinations

21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.

If an application for RSI is disapproved by a local IRB, the Study PI/sponsor will promptly disclose this information to the FDA.

APPENDIX C. Script to Provide an Opportunity to Opt-Out of Participation

The script below will be included in the enrollment materials available to treating clinicians at the time of emergency tracheal intubation.

OPT-OUT SCRIPT

If, **in your clinical judgement**, the patient **lacks capacity** and a family member is not at the bedside, **OR** you believe it would be **unsafe or infeasible** to delay the intubation while you read the script below, enroll the patient (open the envelope) and proceed with intubation without completing the section below.

Otherwise, please read the following section aloud and provide an opportunity for the patient/family to opt-out of participation.

1. You (*your loved one*) need(*s*) to be placed on a breathing machine, which requires a brief procedure to place a breathing tube.

2. There are two medications that we commonly give patients to make them sleepy and relaxed for this procedure. As your medical team, we think either of these medications would be a good and safe choice for you.

3. To help us understand which of the two medications is best, we are conducting a research study that compares the two medications.

4. If you say "Yes" to participation, we will allow the study to choose which of the two medications you will receive and someone from the study will come by later to provide details and answer your questions. If you say "No", we will choose one of the two medications ourselves. Do you agree to participate?

☐ "Yes" - Patient/family agreed to participate (open envelope to enroll patient)

☐ "No" - Patient/family declined participation (place envelope in "used" bin; do not enroll)

Vanderbilt doctors are helping find the best way to place patients on a breathing machine.

1

What is the purpose of the study?

To safely place someone on a breathing machine (**intubation**), doctors use a medication (a **sedative**) to make the patient sleepy.

Ketamine and **Etomidate** are sedative medications used across the country in medical care.

Both medications are approved by the Food and Drug Administration (FDA) and both are considered effective.

The goal of the **"Randomized Trial of Sedative Choice for Intubation (RSI)"** study is to learn if one of these medications is better for preventing low blood pressure, oxygen levels, serious heart problems, and even death for patients being placed on a breathing machine.

What do I need to know?

1. **Placing seriously ill patients on a breathing machine is an emergency procedure.** There is often no time for doctors to discuss the risks and benefits of the procedure with the patient. Doctors typically go ahead with life-saving care without the patient's "okay" (consent). For these same reasons, doctors may not be able to get a patient's okay (consent) to take part in the RSI study.

2. **Your healthcare team felt both medications would be safe while you were being placed on a breathing machine, so the medication was assigned by the RSI study.**

   During the placement of a breathing tube, doctors and nurses are always standing with the patient, closely watching to keep them safe.

3. The study team will confidentially review your medical record for details of your hospitalization. **There are no further treatments or tests for the study and no other part of your care will be affected.**

What if I have questions about the RSI Study?

If you have further questions, do not want the study team to review your medical record going forward, or you want to have your confidential information removed from the study, you may talk to your doctors or nurses or call the Principal Investigator for this study, Dr. Jonathan Casey at (615) 208-6139.

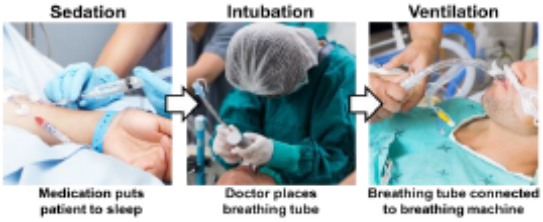
The box is for IRB USE ONLY Do not edit or delete

The following pages have information on the RSI study and each medication.

Study Title: Randomized Trial of Sedative Choice for Intubation ("RSI") Trial
Version Date: January 26, 2022
PI: Jonathan Casey, MD, MSCI

The following is given to provide you with additional information about this research study. Please read this form with care and ask any questions you may have about this study. Your questions will be answered. Also, you will be given a copy of this notification form.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask someone.



Key information about this study:
Each year millions of seriously ill adults need life-saving treatment with a breathing machine. To safely place someone on a breathing machine (a procedure known as "intubation"), doctors give a drug to make the patient sleepy (known as a "sedative"). The two "sedative" drugs most often given to seriously ill patients receiving a breathing tube in the United States are ketamine and etomidate. Both drugs are approved by the United States Food and Drug Administration (FDA). Both are given by doctors all the time. But it is not known which drug is *best*. Early studies suggest that patients do equally well with the two drugs. Knowing for certain whether the two drugs really are the same for patients, or if one is better, could improve care for many patients in the future.

To understand whether ketamine or etomidate is a better medication for placing a breathing tube, doctors and nurses in this unit are comparing the two medications. For a patient being placed on a breathing machine in an emergency department or intensive care unit that is part of the RSI study:

- When the doctors feel ketamine would be best, the doctors use ketamine.
- When the doctors feel that etomidate would be best, the doctors use etomidate.
- When the doctors do not have a preference, the patient takes part in the RSI study and is assigned either ketamine or etomidate randomly, meaning every patient has a fair and equal chance of getting either drug.

Detailed Information:
The rest of this document includes detailed information about this study (in addition to the information listed above).

Your doctors felt your medical condition required the placement of a breathing tube. Your doctors felt that both ketamine and etomidate would be effective for you and did not have a preference between the two. Therefore, the choice between ketamine or etomidate was made by the study in a way that will help your doctors understand which medication is best.

Risks of breathing tube placement using ketamine or etomidate:
Both ketamine and etomidate have been approved by the Food and Drug Administration (FDA) for use during breathing tube placement. Both are commonly used as a part of routine medical care (without participation in a study). Neither medication is known to increase the risk of serious problems with low oxygen levels, low blood pressure, cardiac arrest, brain injury, or death, but these are all potential risks of receiving a breathing tube with ketamine, etomidate, or a different sedative medication as a part of routine medical care (without participation in a study).

Possible Risks of Ketamine:
When ketamine is used to make patients sleepy for the placement of a breathing tube, the most common side effects are:

- Confusion, hallucinations, and irrational behavior (>10%)

Uncommon but more severe potential side effects of ketamine include:

- Low or high blood pressure, low or high heart rate, cardiac arrest, severely slowed breathing, allergic reactions including anaphylaxis, increased intracranial pressure (high pressure in the brain), loss of appetite, nausea and vomiting, spasm of the vocal cords, or double vision

Possible Risks of Etomidate:
When etomidate is used to make patients sleepy for the placement of a breathing tube, the most common side effects are:

- Myoclonus (a sudden spasm of the muscles) or other transient muscle movements (33%), suppression of the adrenal gland (>10%), nausea and vomiting (>10%), hiccups (<10%)

Uncommon but more severe potential side effects of etomidate include:

- Low or high blood pressure, low or high heart rate, cardiac arrest, severely slowed breathing, allergic reactions including anaphylaxis, spasm of the vocal cords

Risks of participation in the study:
Because you needed to receive a breathing tube as part of your clinical care and your doctors felt that both ketamine and etomidate were safe options for you and had no preference between them, participating in this study did not add significant risk compared to your routine medical care (without participation in a study). The study will use information from your medical record to help understand the effects of each medication.

Remember: Both drugs are commonly used to place patients on breathing machines. Both are approved by the FDA for this use. Only when doctors do not have a preference does the RSI study choose the drug – and even then, the doctors can always choose to use another drug to ensure the best care for the patient. During the placement of a breathing tube doctors and nurses are standing with the patient, closely watching to keep them safe, and preventing and treating possible problems.

Good effects that might result from this study:
You may have personally benefitted if the medication used during your breathing tube placement is ultimately found to be best. Your participation will help doctors and nurses everywhere better understand the safest approach to breathing tube placement for future patients like you.

Explanation of Procedures:
The choice between ketamine or etomidate was made by the study in a way that will help your doctors understand which medication is best ("randomization"). During placement of the breathing tube, a doctor or nurse recorded your heart rate, blood pressure, oxygen level, and receipt of medications. This study affected only the choice to use ketamine or etomidate. Every other aspect of your care has been and will be determined by you and your doctors and nurses.

Going forward, the only study procedure will be the collection of details of your hospital stay from your medical record.

Why was I not asked about being in this study before placement of the breathing tube?
Placement of a breathing tube in the emergency department or intensive care unit must occur quickly to keep you safe. Your doctors felt that delaying this procedure to allow a research team to have a detailed discussion of the study with you ("informed consent") was not safe. Permission to include patients in research without written informed consent is only allowed for studies of patients with life-threatening medical conditions that require urgent intervention who, because of their condition, cannot provide consent. The permission was only granted after informing and seeking input from the local community and developing a plan to inform patients that they were included in the study (as we are doing now).

Payments for your time spent taking part in this study or expenses:
You will not receive payment for your participation in this study.

Costs to you if you take part in this study:
There is no cost to you for taking part in this study.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the Investigator that an injury occurred, then you and/or your insurance may be billed for the cost of medical care provided at Vanderbilt to treat the injury. You will be responsible for any copayments or deductibles associated with the treatment of that injury.

There are no plans for Vanderbilt or the National Institute of Health to pay for the costs of any additional care. There are no plans for Vanderbilt or the National Institute of Health to give you money for the injury.

Who to call for any questions or in case you are injured:

Study Title: Randomized Trial of Sedative Choice for Intubation ("RSI") Trial
Version Date: January 26, 2022
PI: Jonathan Casey, MD, MSCI

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please feel free to contact Dr. Jonathan Casey at (615) 208-6139. If you cannot reach the research staff, please page the study doctor at (615) 835-5496.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the VUMC Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way. If you decide to stop being part of this study, we will not collect any additional information from your electronic medical record (the only remaining part of the study). We will, however, keep the data already collected to be able to report on the safety of the study.

Clinical Trials Registry:
A description of this clinical trial will be available on www.clinicaltrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Confidentiality:
Information obtained about you for this study will be kept confidential to the extent allowed by law. Research information that identifies you may be shared with the Institutional Review Board (IRB) and the Office for Human Research Protections (OHRP). There is a risk that if people outside the study get your health data, they could misuse it for purposes other than those outlined in this notification form. The study team has strict privacy and confidentiality protection procedures in place to prevent this from occurring so the chance of this happening to you is extremely small.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means. It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Privacy:
Information about you may be made available to others to use for research. To protect your privacy, we will not release your name.

Study Results:

The results of this study will be made public once the study is completed using methods such as press releases, social media advertisements, and advertisements in local newspapers.

Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information.

Who will see, use or share the information?
The people who may request, receive or use your private health information include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example if needed for your clinical care or study oversight. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let them know by using the contact information provided in this notification form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Appendix E: Letter to be Mailed if Unable to Notify Patient prior to Discharge

VANDERBILT UNIVERSITY MEDICAL CENTER

Date: [Insert date letter is written]

Dear [Patient Name] or family:

This letter is to inform you about a research study at Vanderbilt University Medical Center called the **Randomized Trial of Sedative Choice for Intubation (RSI)**.

What is the RSI study?

Many seriously ill patients receive life-saving support with a breathing machine. When a patient is being placed on a breathing machine, doctors give medication to make the patient sleepy (a "sedative"). The two sedative medications most often given to patients are ketamine and etomidate. Both medications are approved as safe and effective by the United States FDA and are given to patients every day. We are leading the RSI study to determine which of the two medications is *best*.

Who will the RSI study help?

The RSI study will help many seriously ill patients who need a breathing machine in the future.

How does the RSI study involve you?

During your recent hospitalization at Vanderbilt, your medical condition required that you be placed on a breathing machine. When you were being placed on a breathing machine, your doctors felt that both ketamine and etomidate were safe options for you, so, the RSI study selected between the two randomly, meaning that you had a fair and equal chance of getting either medication. The RSI study did not affect any other part of your care. Information was collected from your medical record, which remains confidential.

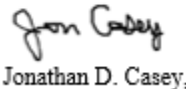
Why are you receiving this information now?

We were unable to talk with you about the RSI study before you were placed on a breathing machine because your medical condition was serious and your doctors needed to place a breathing tube urgently. Although we attempt to talk about the RSI study with all patients while they are in the hospital, you were discharged from the hospital before we spoke with you. We are sending this letter to provide you information and offer an opportunity to answer any questions you may have.

Who can you ask questions about the RSI study?

If you have questions about the RSI study, or would like to request that no additional information be collected from your medical record, please call me (Dr. Jonathan Casey) at 615-208-6139. The Vanderbilt Institutional Review Board (IRB), which oversees the RSI study, can be reached with any questions or concerns at (615)-322-2918 or toll-free at (866)-224-8273.

Thank you for your time and please reach out with any questions,



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Appendix F: Letter to Mailed if Patient Dies before Notification

VANDERBILT UNIVERSITY MEDICAL CENTER

[*date letter is written*]

To the family of [*patient's name*],

We understand that this letter may come at a difficult time, and we are sorry for your loss. If you, or your family members, need help or support with your grief, please reach out to Vanderbilt's grief support team through the office of Spiritual and Pastoral Care at 615-343-3535.

The purpose of this letter is to let you know about a research study at Vanderbilt University Medical Center focused on improving care for seriously ill patients to which [*insert patient's name*] contributed.

What is the Randomized Trial of Sedative Choice for Intubation (RSI) study?

Many seriously ill patients receive life-saving support with a breathing machine. When a patient is being placed on a breathing machine, doctors give a medication to make the patient sleepy (a "sedative"). The two sedative medications most often given to patients are ketamine and etomidate. Both medications are approved by the United States FDA and are given to patients every day. The goal of the RSI study to determine which of the two medications is *best*.

Who will the RSI study help?

The RSI study will help many seriously ill patients who need a breathing machine in the future.

How did [*insert patient's name*] contribute to the RSI study?

During [*patient's name*]'s recent hospitalization at Vanderbilt, [*his/her*] medical condition required that [*he/she*] be placed on a breathing machine. When [*he/she*] was being placed on a breathing machine, [*his/her*] doctors felt that both ketamine and etomidate were safe options for [*him/her*], so, the RSI study selected between the two randomly, meaning that [*he/she*] had a fair and equal chance of getting either medication. The RSI study did not affect any other part of [*his/her*] care. Information was collected from [*his/her*] medical record, which remains confidential.

Why are you receiving this information now?

We were unable to talk with [*patient's name*] or you about the RSI study before [*he/she*] was placed on a breathing machine because [*his/her*] medical condition was serious and [*his/her*] doctors needed to place a breathing tube urgently. Although we attempt to talk about the RSI study with all patients while they are in the hospital, [*he/she*] passed away before we spoke with [*him/her*] or you. We are sending this letter to provide you information and offer an opportunity to answer any questions you may have.

Who can you ask questions about the RSI study?

If you have questions about the RSI study, please call me (Dr. Jonathan Casey) at 615-208-6139. The Vanderbilt Institutional Review Board (IRB), which oversees the RSI study, can be reached with any questions or concerns at (615)-322-2918 or toll-free at (866)-224-8273.

Again, we apologize for this intrusion. Please accept our sincere condolences to you and your family.

Kindest regards,

Jonathan D. Casey, MD, MSc
Assistant Professor of Allergy, Pulmonary, and Critical Care Medicine
Vanderbilt University Medical Center

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As noted in section 14, the lead investigator at each enrolling site is required to report all potentially reportable adverse events to the principal investigator within 24 hours of becoming aware of the event. Reportable events in the RSI trial are defined as adverse events that are unexpected and serious have a reasonable possibility that the event was due to a study medication or procedure (or of uncertain relatedness)

The primary investigator will work collaboratively with the lead investigator at each enrolling site to determine if a serious adverse event has a reasonable possibility of having been caused by the study medication or study procedure, as outlined in 21 CFR 312.32(a)(1), and below. In this unblinded trial, both the investigator and primary investigator will be aware of group assignment and the receipt of either ketamine or etomidate. An adverse is considered "unexpected" if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study medication, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

H.1. Expedited Adverse Event Review and DSMB Notification Process

The principal investigator will be responsible for notifying the NHLBI, the IRB, and the FDA and will follow NHLBI guidelines for reporting of adverse events, https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy

The principal investigator will report, at a minimum:

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

H.2. Unanticipated Problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and patient notification document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- 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.

In accordance with NHLBI policy, an unanticipated problem that is not an SAE will be reported within 14 days to the DSMB, IRB, and NHLBI.

H.3. Determining Relationship of Adverse Events to Study Medication or Study Procedures

Site investigators will be asked to grade the strength of the relationship of an adverse event to study medication or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) 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 event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "Probably or Possibly" associated should be selected.
- Probably Not Related: The 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 event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

The principal investigator will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study medication or study procedure. The principal investigator will be responsible for the final adjudication of relatedness that will be used to determine if an adverse event is reportable.

H.4. Clinical Outcomes that may be Exempt from Adverse Event 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 a reportable adverse event. For example, a cardiac arrest that the investigator considers Definitely Related to ketamine would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

Randomized Trial of Sedative Choice for Intubation ("RSI") Trial Protocol

The Pragmatic Critical Care Research Group Investigators

Title:	**R**andomized Trial of **S**edative Choice for **I**ntubation
Acronym:	RSI
Funders:	The National Heart, Lung, and Blood Institute (NHLBI) & Patient-Centered Outcomes Research Institute (PCORI)
Network:	Pragmatic Critical Care Research Group
Protocol:	Version 2.2
Date:	March 7, 2025
Study Chairs:	Jonathan Casey MD, MSc, Vanderbilt University Medical Center Matthew Semler MD, MSc, Vanderbilt University Medical Center Jin Han MD, MSc, Vanderbilt University Medical Center

Table of Contents

REVISIONS TO THE PROTOCOL

Protocol Version 1.0
Date: March 9, 2022
Initial protocol

Protocol Version 1.1
Date: May 23, 2022
Purpose: This amendment is to add additional details regarding the approach to notifying, at the earliest feasible opportunity, each patient, or if the patient remains incapacitated, a legally authorized representative of the patient, or if such a representative is not reasonably available, a family member, of the patient's inclusion in the study. This amendment also describes the approach to obtaining prospective informed consent to be contacted for potential participation in ancillary trials.

Protocol Version 2.0
Date: October 18, 2023
Description: This amendment triggers Stage 2 (multi-center) of the RSI trial, following the receipt of funding for Stage 2 of the RSI trial from PCORI, and includes revisions to the protocol to align with the grant approved by PCORI. Major changes made in version 2.0 of the grant include:

- Activation of Stage 2 with pre-planned prioritization of Stage 2 outcomes (primary outcome: mortality at 1 month [28 days]) and removal of stage 1 analyses that will not be conducted with the activation of stage 2.
- Increased sample size of 2,364 patients based on updated power calculation and input from stakeholders regarding the minimum clinically important difference. Sample size at which single pre-specified interim analysis would occur was updated to remain at 50% of total enrollment (1,182 patients).
- The process for pre-enrollment opt-out was updated for operationalization at additional sites in Stage 2 (multi-center stage) of RSI.
- Primary outcome changed to a generalized linear mixed effects model with a random effect for study site (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and a fixed effect for group assignment (ketamine group vs etomidate group) and subgroup analysis updated to include a random effect for study site to match the primary analysis.
- Addition of a plan to approach intubation survivors for consent to collect long-term outcomes.
- Removal of example notification forms (following review and approval by IRB).
- Replacement of the section "Consent to be Contacted for Ancillary Studies" by Appendix E describing the plan for collection of long-term outcomes.

Protocol Version 2.1
Date: April 30, 2024
Description: This amendment is to make minor revisions to secondary analyses to match the research plan approved by the funder, clarify plans regarding enrollment of ineligible patients, add definitions for protocol deviations and protocol violations, and add detail regarding the provision of resources to patients participating with RSI-LTO who are found to have non-life-threatening psychiatric issues such as severe PTSD or depression. These changes include:

- Revising the covariates that will be included in the adjusted analysis of the primary outcome (a secondary analysis).
- Adding details of a planned analysis of Heterogeneity of Treatment Effect ("Individualized Treatment Effect") for the short- and long-term outcomes as a new appendix (Appendix F).
- Adding definitions and reporting plans for protocol deviations and violations and details of the plan for communication to the funder to Appendix D.
- Adding details regarding how patients who are found to be prisoners will be identified and withdrawn from the study.
- Describing what information will be collected during follow-up phone calls about patients with a new diagnosis of PTSD, depression, or anxiety, and the resources that will be provided to them.

Protocol Version 2.2
Date: March 7, 2025
Description: This amendment is (i) to make minor revisions to secondary analyses to match the final trial statistical analysis plan at the time of its submission for publication and (ii) to revise the trial protocol to permit Waiver of Documentation of informed consent for patients discharged from the hospital who have completed an informed consent discussion and consent to participate but for whom receiving, signing, and returning by mail the informed consent document would be logistically burdensome and increase the risk of disclosure of PHI.

ABBREVIATIONS

AE	Adverse event
APACHE	Acute Physiology and Chronic Health Evaluation
DSMB	Data safety monitoring board
ED	Emergency department
EFIC	Exception from Informed Consent (21 CFR 50.24.7)
ICU	Intensive care unit
IV	Intravenous
LAR	Legally authorized representative
PI	Principal investigator (the clinician leading the study across all sites)
PTSD	Post-traumatic stress disorder
RCT	Randomized control trial
SAE	Serious adverse events
S/F	SpO_2/FiO_2 ratio
SOP	Standard operating procedure

1. STUDY SUMMARY

Title	Randomized Trial of Sedative Choice for Intubation (RSI)
Background	Among critically ill adults undergoing emergency tracheal intubation, one in five experience hypotension, cardiac arrest, or death. The sedatives used to rapidly induce anesthesia for emergency tracheal intubation have been hypothesized to effect cardiovascular complications and patient outcomes, but the optimal sedative medication for intubation of critically ill adults remains unknown. Ketamine and etomidate are the two most commonly used sedatives during intubation of critically ill adults. Data from a randomized clinical trial are urgently needed to determine the effect of ketamine versus etomidate on cardiovascular complications and clinical outcomes of emergency tracheal intubation.
Study Design	Multi-center non-blinded, parallel-group, randomized clinical trial
Treatment Groups	Ketamine group: Patients will receive intravenous ketamine at a recommended dose of 2 mg/kg for induction of anesthesia for emergency tracheal intubation. Etomidate group: Patients will receive intravenous etomidate at a recommended dose of 0.3 mg/kg for the induction of anesthesia for emergency tracheal intubation. In this investigator-initiated, multi-center, non-blinded, randomized trial comparing two commonly used medications within their approved indications, the assigned sedative medication will be dispensed from the clinical pharmacy and administered by clinical personnel as would occur in clinical care.
Sample Size	Stage 1 (feasibility): 464 patients Stage 2 (effectiveness): 1,900 patients Total Sample Size: 2,364 patients
Inclusion Criteria	4. Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit 5. Planned procedure is orotracheal intubation using a laryngoscope 6. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
Exclusion Criteria	11. Patient is known to be less than 18 years old 12. Patient is known to be pregnant 13. Patient is known to be a prisoner 14. Patient is known to have an allergy to ketamine or etomidate 15. Patient is presenting to the emergency department with a primary diagnosis of trauma 16. Patient or LAR declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI trial

	17. Clinician feels ketamine is required or contraindicated for the optimal care of the patient 18. Clinician feels etomidate is required or contraindicated for the optimal care of the patient 19. Clinician feels an induction medication other than ketamine or etomidate is required for the optimal care of the patient 20. Immediate need for tracheal intubation precludes safe performance of study procedures
Consent	Emergency tracheal intubation of critically ill patients is a time-sensitive procedure with a brief therapeutic window between the decision to perform intubation and the completion of the procedure. A written informed consent is available and will be used when feasible in RSI. However, it is expected that written consent will be infeasible in most, if not all, cases because delaying the emergency tracheal intubation of critically ill adults would cause irreparable harm to patients. Therefore, it is expected that most, if not all, patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC). In conformance with EFIC requirements, measures to protect the rights and welfare of subjects will include: a) community consultation, b) public disclosure of plans to conduct the trial, c) public disclosure of trial results, d) independent data monitoring, and e) opportunity for pre-randomization opt-out (when feasible) and notification of the patient, legally authorized representative, or a family member at the soonest feasible opportunity of a patient's enrollment in the trial with an opportunity to discontinue trial participation. For patients who are enrolled under EFIC and survive the intubation, the research team will approach the patient or legally authorized representative to obtain consent for the collection of long-term outcomes.
Randomization	Eligible patients will be randomized 1:1 to ketamine versus etomidate. 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 operators until after the decision has been made to enroll the patient in the study. Following enrollment, the trial will not blind patients or treating clinicians to study group assignment.
Primary Outcome of RSI trial	All-cause, 28-day in-hospital mortality
Secondary Outcome of RSI trial	Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation: o Systolic blood pressure < 65 mmHg o New or increased vasopressors o Cardiac arrest not resulting in death within 1 hour of induction o Cardiac arrest resulting in death within 1 hour of induction

Exploratory Outcomes of RSI trial	• Procedural Characteristics & Complications
	  ○ Cormack-Lehane Grade of glottic view
	  ○ Successful intubation on the first attempt, defined as placement of an endotracheal tube in the trachea with a single insertion of a laryngoscope blade into the mouth and EITHER a single insertion of an endotracheal tube into the mouth OR a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube over the bougie into the mouth.
	  ○ Time from induction to successful tracheal intubation
	  ○ Lowest oxygen saturation between induction and two minutes after intubation
	  ○ Lowest oxygen saturation < 80% between induction to two minutes after intubation
	  ○ Highest and lowest systolic blood pressure from induction to two minutes after intubation
	  ○ Systolic blood pressure > 180 between induction and two minutes after intubation
	  ○ Systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
	  ○ New or increased vasopressor between induction and 2 minutes after intubation
	  ○ Cardiac arrest within 2 minutes of intubation not resulting in death
	  ○ Cardiac arrest within 2 minutes of intubation resulting in death
	• Short-term Clinical Outcomes
	  ○ Ventilator-free days to study day 28
	  ○ Vasopressor-free days to study day 28
	  ○ ICU-free days to study day 28

Safety Outcomes of RSI trial	• Systolic blood pressure at 24 hours after induction • Receipt of vasopressors at 24 hours after induction • Cardiac arrest receiving cardiopulmonary resuscitation between induction and hospital discharge
Long-term Outcomes (RSI-LTO)	For patients who provide consent for collection of long-term outcomes, the outcomes listed in Appendix E will be collected by phone at 3 and 12 months. The main long-term outcome will be symptoms of post-traumatic stress disorder (PTSD) at 12 months.
Analysis	The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to ketamine versus patients randomized to etomidate with regard to the primary outcome.

2. TRIAL DESCRIPTION

2.1 Background

Each year more than 1.5 million critically ill adults receive invasive mechanical ventilation in the United States,[1–3] at a cost of nearly $30 billion dollars annually.[1,2] Recent research has dramatically improved patient safety during the maintenance, weaning, and liberation stages of invasive mechanical ventilation.[4,5] In contrast, the optimal approach to the initiation of mechanical ventilation remains an important knowledge gap in the care of adults with respiratory failure. Among critically ill adults, life-threatening complications during tracheal intubation and initiation of invasive mechanical ventilation remain common. One in five patients experiences hypotension and one-in-forty experiences cardiac arrest during the two-minute tracheal intubation procedure.[6–10]

2.1.1 Cardiovascular Collapse during Intubation

Cardiovascular collapse is a peri-procedural outcome defined as severe hypotension, new or increased vasopressors, cardiac arrest or death. The occurrence of cardiovascular collapse during tracheal intubation of critically ill adults increases patients' risk of in-hospital mortality.[11] Randomized trials examining intubation technique commonly target cardiovascular collapse as an outcome.[12–14] Adherence to recommended best-practices for tracheal intubation (e.g., preoxygenation,[15,16] optimization of patient positioning,[9] and procedural checklists[8]) are insufficient to prevent 20-40% of critically ill adults from experiencing cardiovascular collapse during tracheal intubation.[12,14,17–19]

2.1.2 Sedative Medications Contribute to the Risk of Cardiovascular Collapse

Rapid sequence induction and tracheal intubation, the most common method of intubation for critically ill patients, is the nearly simultaneous administration of a sedative medication and neuromuscular blocking medication. The ideal sedative agent for rapid sequence intubation would rapidly provide a deep state of unconsciousness and analgesia without causing hemodynamic side effects. No available agent meets all of these criteria.[20] The administration of any of the available sedative agents at a dose large enough to rapidly induce unconsciousness contributes to cardiovascular collapse through vasodilation, decreased cardiac filling pressures from sedation-induced venodilation, and decreased endogenous catecholamines.[21–24] While all sedatives commonly used during emergency tracheal intubation of critically ill patients have been associated with unsatisfactory hypotension (21 CFR 50.24(a)(1)), ketamine and etomidate are the medications used most commonly in clinical practice due to their rapid onset and favorable hemodynamic profiles relative to the other available sedatives.[25,26] Other sedatives that have been used in some settings during rapid sequence intubation include benzodiazepines, propofol, and barbiturates. Benzodiazepines do not provide any analgesia and are associated with an unsatisfactory degree of hypotension, with a drop in mean arterial blood pressure of 10 to 25 percent, even among healthy patients.[27–29] At present, barbiturates are rarely used for tracheal intubation in the US because of unsatisfactorily high rates of post-intubation hypotension and evidence of negative cardiac ionotropy.[30] While propofol is commonly used to induce anesthesia among healthy patients, and is commonly administered as a continuous infusion to maintain sedation for critically ill patients, it is used less commonly as a bolus during tracheal intubation of critically ill patients because it has been suggested to cause unsatisfactorily high rates of hypotension and cardiac depression, compared to ketamine or etomidate.[31,32]

2.1.3 Ketamine as a Sedative during Tracheal Intubation.

Ketamine is a phencyclidine derivative that provides anesthesia via its effect at the NMDA receptors. Ketamine has been approved by the United States Food and Drug Administration (FDA) with approved indications including "use as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation" and "induction of anesthesia prior to the administration of other general anesthetic agents." In addition to sedation, ketamine provides significant amnesia and analgesia via action at the opioid receptors, and is commonly used for procedural sedation and as a continuous infusion to control pain.[33]

Ketamine activates the sympathetic nervous system, stimulating the release of catecholamines,[34] which may increase heart rate and blood pressure during intubation and prevent peri-procedural cardiovascular collapse.[33] Conversely ketamine has direct negative ionotropic effects, leading to myocardial depression.[30,35,36] While the myocardial depression may be counteracted by increased catecholamine release, ketamine could cause cardiovascular collapse among patients with depleted catecholamine stores, and case reports of unexpected cardiac arrest during intubations with ketamine have been published.[37] Despite stimulating the release of catecholamines, using ketamine as the induction agent during emergency tracheal intubation does not appear to frequently cause or worsen hypertensive urgency or emergency; however, the literature on this topic is limited to case reports.[38]

Historically, concerns have been raised that ketamine might increase intracranial pressure and cause deleterious decreases in cranial perfusion pressure. Recent studies have suggested, however, that ketamine may be associated with a beneficial increase in cranial perfusion pressure as a result of increased mean arterial pressure,[39,40] and a recent, large before-after study showed no significant differences in clinical outcomes for trauma patients intubated with ketamine versus etomidate.[41]

2.1.4 Etomidate as a Sedative during Tracheal Intubation.

Etomidate is an imidazole derivative that acts at gamma-aminobutyric acid "A" (GABA) receptors. Etomidate has been approved by the FDA with an indication for "induction of general anesthesia." In a recent review of more than 19,000 intubations by a large, multicenter emergency medicine registry, etomidate was the most commonly used sedative during emergency tracheal intubation.[26]

Etomidate causes less hemodynamic instability than propofol[42] and midazolam,[27] but the data regarding the relative risk of hemodynamical instability with etomidate, compared to ketamine, is unclear. It was initially suggested that ketamine might cause less hypotension than etomidate, given ketamine's ability to stimulate the release of catecholamines,[43,44] but a recent observational study comparing ketamine and etomidate among nearly 7,000 critically ill adults undergoing tracheal intubation in emergency departments suggested that ketamine was independently associated with an increased risk of peri-intubation hypotension.[26]

Etomidate was initially used both for induction of anesthesia and as a continuous drip for maintenance of anesthesia. Its use as a continuous drip for maintenance of anesthesia was halted after it was discovered that prolonged use of etomidate causes inhibition of adrenal cortisol production by blockade of 11-β-hydroxylase, leading to adrenal insufficiency, and increased mortality.[45–47] Etomidate use as a single bolus for induction of anesthesia has continued, but numerous studies have demonstrated that even a single dose of etomidate can cause transient adrenal insufficiency.[48–53] The clinical significance of this relative

adrenal insufficiency, however, remains unclear. Contrasting observational studies have suggested that etomidate may have positive,[41,54] negative [47,52,55–57] or neutral impacts[41,48,49,51,58,59] on mortality.

2.1.5 Prior Evidence from Clinical Trials.

Two randomized trials have directly compared ketamine to etomidate for RSI among critically ill adults.[60,61]

The Ketased trial, published in 2009, was a 469-patient trial conducted across 12 emergency medical services and emergency departments in France.[60] Because many patients were enrolled in the pre-hospital setting without continuous blood pressure monitoring, peri-procedural outcomes such as cardiovascular collapse were not collected, and the results were indeterminate, in regards to the primary outcome, average Sequential Organ Failure Assessment (SOFA) scores in the 72 hours after intubation. The results, however, demonstrated significant heterogeneity. Patients with trauma (for whom increased intracranial pressure from ketamine may be important) experienced a non-significant 4% absolute increase in mortality when intubated with ketamine compared to etomidate. All other patients experienced a non-significantly lower mortality when intubated with ketamine, particularly patients with sepsis who experienced a non-significant 7% absolute mortality benefit (and in whom adrenal insufficiency from etomidate may be particularly important).

The EvK trial, published in January 2022, was a single-center, 801-patient trial conducted among hospitalized patients at a single hospital in Texas.[61] Survival at 7 days, the primary outcome of the EvK trial, was higher in the ketamine group, compared to the etomidate group (85.1% vs 77.3%; p=0.005), but this difference was attenuated by day 28, at which point it was no longer significant (66.8% vs 64.1%, p=0.294). The conclusion of this single-center trial was that "there was no significant difference in survival by Day 28", however it was noted that this "could represent a small but durable long-term survival effect, one which our trial was under-powered to detect."[61]

2.1.6 Rationale for a Trial of Ketamine vs Etomidate in Non-Traumatic Critical Illness.

Experts have pointed out that the currently available data on sedative choice during tracheal intubation of critically ill patients are inadequate and have called for additional randomized clinical trials.[48,49,62] Because (1) cardiovascular collapse is common during tracheal intubation of critically ill adults (2) sedatives are a driver of cardiovascular collapse, (3) use of ketamine or etomidate varies between centers, specialties, and operators, and (4) prior data suggests the potential for ketamine to significantly decrease mortality for patients without trauma, a large, multicenter trial is needed to determine the effects of ketamine and etomidate on mortality in non-traumatic critical illness.

2.1.7 Rationale for Two Stages of the RSI trial.

Stage 1 of the RSI trial will focus on feasibility and short-term, peri-procedural outcomes. This stage is required to demonstrate the feasibility of performing a pragmatic trial comparing ketamine to etomidate during emergency tracheal intubation of critically ill adults under exception from informed-consent (EFIC) requirements for emergency research (under FDA code of regulations 21 CFR 50.24.7).[99,100] Stage 1 of the RSI trial (funded by the National Heart, Lung, and Blood Institute; grant number, K23HL153584) is designed to be of sufficient size to inform the effects of ketamine and etomidate on the short-term, peri-procedural outcome of cardiovascular collapse.

Stage 2 of the RSI trial will focus on the effect of ketamine vs etomidate on in-hospital mortality. Data on the effects of ketamine and etomidate on the short-term, peri-procedural outcome of cardiovascular collapse (the primary outcome of stage 1) could make an immediate impact on the use of these medications in clinical practice. However, the effects of ketamine and etomidate on in-hospital mortality may be mediated by mechanisms presenting after the peri-procedural period (e.g. adrenal insufficiency or increased intracranial pressure), and the effects of ketamine and etomidate on cardiovascular collapse may, therefore, be discordant with their effects on in-hospital mortality. A finding in stage 1 of the RSI trial that ketamine decreases, increases, or has no impact on cardiovascular collapse would in no way detract from the need for definitive data on the effect of ketamine and etomidate on in-hospital mortality.

Completing a feasibility trial, closing enrollment, and subsequently initiating a separate, new, definitive trial using the same study design is inefficient. Such an approach introduces delays in enrollment between the stages and fails to make use of data on clinical outcomes from patients enrolled during the feasibility stage. This increases the total number of patients who must experience the potential risks of trial participation to obtain a definitive answer to the research question. The RSI trial is, therefore, planned as a single, adaptive trial with two stages.

To increase efficiency and minimize the number of patients exposed to the potential risks of trial participation, the RSI trial is designed to allow progress from the stage assessing feasibility (Stage 1) to the stage assessing effectiveness (Stage 2) if the following criteria are met: (1) the data and safety monitoring board (DSMB) determines that the feasibility and safety of conducting the trial have been demonstrated; (2) the investigators determine that the observed enrollment rate, protocol compliance, separation between groups in receipt of the assigned therapy, and data completeness and quality permit progression to Stage 2; and (3) funding for a multicenter trial is available. Additional details regarding the progression from Stage 1 to Stage 2 are providing in section 10.3 of the protocol.

2.2 Study Aims and Hypotheses

2.2.1 Study aims

Stage 1: To compare the effects of ketamine versus etomidate on cardiovascular collapse during tracheal intubation of critically ill adults. To evaluate the feasibility of conducting a pragmatic trial of ketamine versus etomidate during tracheal intubation of critically ill adults in the ED or ICU using EFIC.

Stage 2: To compare the effects of ketamine versus etomidate on in-hospital mortality among non-traumatic critically ill adults undergoing tracheal intubation in the ED or ICU

2.2.2 Study hypothesis

Stage 1: Conducting a pragmatic trial comparing ketamine versus etomidate during tracheal intubation of non-traumatic critically ill adults in the ED or ICU using EFIC will be feasible. Ketamine will decrease the incidence of cardiovascular collapse.

Stage 2: Ketamine will decrease the incidence of in-hospital mortality among non-traumatic critically ill adults undergoing intubation in the ED or ICU.

2.3 Study Design

We will conduct an investigator-initiated non-blinded, pragmatic, parallel-group, randomized clinical trial evaluating the effect of ketamine versus etomidate on clinical outcomes of non-traumatic critically ill adults undergoing tracheal intubation in the ED and ICU.

3. STUDY POPULATION AND ENROLLMENT

3.1 Inclusion Criteria

4. Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit
5. Planned procedure is orotracheal intubation using a laryngoscope
6. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit

3.2 Exclusion Criteria

11. Patient is known to be less than 18 years old
12. Patient is known to be pregnant
13. Patient is known to be a prisoner
14. Patient is known to have an allergy to ketamine or etomidate
15. Patient is presenting to the emergency department with a primary diagnosis of trauma
16. Patient or LAR declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI trial
17. Clinician feels ketamine is required or contraindicated for the optimal care of the patient
18. Clinician feels etomidate is required or contraindicated for the optimal care of the patient
19. Clinician feels an induction medication other than ketamine or etomidate is required for the optimal care of the patient
20. Immediate need for intubation precludes safe performance of study procedures

3.3 Justification of Exclusion Criteria

The RSI trial is intended to be broadly inclusive of critically ill patients who would receive ketamine or etomidate during intubation in usual care. The purpose of the exclusion criteria is to prevent the enrollment of patients who should not be enrolled under EFIC, patients who have a contraindication to study medications, or patients who have an indication for an alternative treatment. Pregnant women and prisoners are explicitly excluded from studies performed under EFIC. Patients with trauma are excluded from the RSI trial given the concern that ketamine may cause increased intracranial pressure among patients with head trauma. No patients will be excluded on the basis of race, ethnicity, or sex.

4. Process of Obtaining Informed Consent

Respect for human subjects and their safety is paramount in clinical research. Clinical research aiming to evaluate optimal care for critically ill adults during an emergency procedure presents unique ethical challenges. Protecting patient autonomy through the informed consent process is an ethical cornerstone of human subjects research.

An informed consent document is available and will be used to obtain written informed consent from the patient or legally authorized representative for participation in the trial, when feasible. However, it is expected that obtaining written informed consent will be infeasible in most, if not all, cases due to:

3. **The expected medical condition of the patient.** Based on prior trials in the same patient population and setting, approximately 70% of patients eligible for the trial will be experiencing encephalopathy (altered mental status) and the median Glasgow coma scale score will be 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 the trial will not have the capacity to provide informed consent.
4. **Sufficient time for the patient or legally authorized representative to consider participation & circumstances for consent that minimize the possibility of undue influence.** Even in instances in which a patient retains decisional capacity, or a legally authorized representative (LAR) is immediately available, the rapidity with which emergency tracheal intubation is clinically required (and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation) precludes execution of a meaningful informed consent process. Although no published literature quantifies the time from the decision to perform emergency tracheal intubation (the inclusion criteria for the trial) until the initiation of intubation (the trial intervention), among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the VUMC ED or ICU, approximately 50% of intubations occurred within 5 minutes, 75% of intubations occurred within 10 minutes, and no intubations occurred longer than 30 minutes after treating clinicians verbalized the decision to intubate (or placed a written order for an induction medication). Obtaining informed consent for research requires research personnel to assess decisional capacity, identify an 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 therefore cannot be executed in the 5 minutes before emergency tracheal intubation of a critically ill adult or their LAR in the ED or ICU. Moreover, obtaining informed consent for participation in research in the minutes before emergency tracheal intubation from a distressed patient or LAR places the informed consent process for research adjacent to the receipt of life-saving care and risks blurring the distinction between treatment and research. Emergency tracheal intubation of critically ill adults is, definitionally, 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.

The RSI trial comparing ketamine versus etomidate during tracheal intubation of critically ill adults can, therefore, only be conducted with exception from informed consent (EFIC) for emergency research, and it is expected that most, if not all, patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC).

Complete details of the plan for conducting the RSI trial in compliance with FDA regulation for EFIC are provided in Appendix B. In coordination with the IRB, investigators for the RSI trial will conduct community consultation and public disclosure prior to beginning enrollment (see Community Consultation and Public Disclosure Plan). The trial will be overseen by the IRB and an independent data and safety monitoring board.

While the nature of emergency tracheal intubation precludes a full, written, informed consent process in most, if not all, cases, the RSI trial will provide an opportunity for patients, LARs, or family members to object to participation based on more limited information whenever feasible using a pre-enrollment opt-out script (details in section 13.3).

4.1 Post-Enrollment Notification

After enrollment of each patient, study personnel will attempt to notify the patients, LAR, or family members of enrollment in the trial in person at the soonest feasible opportunity. Notification of enrollment will be performed by research team members trained in informed consent processes, HIPAA laws, and the trial protocol. Patients or family members will be provided with a notification document approved by the Institutional Review Board (IRB). In the event that the patient, LAR, or family member cannot be contacted in person (for example, if they are outside of the state), study personnel will notify by telephone or by registered mail. There is no single timeline that is appropriate for all patients or families who are dealing with issues surrounding emergency tracheal intubation in the setting of critical illness. Study personnel will coordinate with treating clinicians to incorporate the judgement of treating clinicians as to the appropriate timing of notification for a given patient. For cases in which a LAR or family member cannot be reached and the patient does not survive their critical illness, study personnel will send a letter approved by the IRB. Study personnel will keep a log that reflects the required steps for contacting the LAR or family member. The notification tracking log will be completed for each patient enrolled and included in the patient's research records.

Patients, families, or LARs may decline follow-up or access to medical record review, as stated in the notification document. If a patient, family or LAR declines follow up or access to medical record review, this information will be documented in the patient's research record, along with the date and reason. As suggested in federal regulations for EFIC, the study investigators may examine data collected prior to patient withdrawal as this is necessary to maximize understanding of the safety of the study intervention, but the study team will not access the subject's medical records after the date of discontinuation (even if the subject has not been discharged from the hospital). As suggested in federal regulations the study team may access data about the patient's death from public vital statistics records and other public records not subject to restriction under 21 CFR 50.24 or other FDA regulations.

4.2 Consent for Long-Term Follow-Up

For patients enrolled and notified under EFIC, the research team will continue to follow for an opportunity to consent the patient or LAR for collection of long-term outcomes at 3 and 12 months (additional details in Appendix E).

In some cases, consent for long-term outcomes may occur at the same time as post-enrollment notification, shortly after intubation. However, because federal regulations for EFIC require that post-enrollment notification occur at the soonest feasible opportunity, even if the only person available to be notified is a family member who is not a LAR for the patient, consent for long-term outcome collection may occur days after post-enrollment notification. In some cases (e.g., where a LAR is not available and the patient does not regain decisional capacity before hospital discharge), written informed consent for long-term outcome collection may occur by phone following hospital discharge.

5.0 Enrollment and Randomization

Patients will be enrolled at the time that treating clinicians have decided to pursue tracheal intubation and confirmed that the patient meets eligibility criteria. The enrollment materials for the RSI trial will include instructions for a pre-procedural timeout to review the inclusion and exclusion criteria prior to enrollment. This process requires less than 10 seconds and can be easily completed during the 2-minute preoxygenation period. This approach has been successfully used in multiple prior trials.[7–10]

Patients who are enrolled will be randomized 1:1 to ketamine or etomidate using random permuted blocks of two, four, and six. Study group assignment will be stored and concealed prior to enrollment using opaque envelopes or the Randomization Module in the online database REDCap.

5.1 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, site investigators will report it to the trial primary investigators and coordinating center **within 24 hours** of becoming aware of the occurrence. If the enrollment meets criteria for a protocol violation (section 12.6), it will be to the DSMB and IRB **within 7 days** of the site becoming aware of the occurrence.

5.2 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 have been a prisoner, 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 except the anonymous study ID, study site, and the randomized group assignment. If a patient is not

a prisoner at the time of enrollment and becomes a prisoner between enrollment and the end of study follow up, all study procedures will stop immediately, the patient will be withdrawn from further participation the study, and no additional information will be entered into the study record. 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.

6.0 Blinding

The trial will not blind patients or treating clinicians to study group assignment. Obscuring treatment assignment in a controlled trial is particularly important when the outcomes are subjective, such as alleviation of pain, but less important for objective criteria, such as hypotension, cardiac arrest, or death.[63] Treating clinician's awareness of study group assignment in the current trial may predispose to differential administration of co-interventions. For example, patients in the etomidate group may be more likely to be treated by clinicians with corticosteroid replacement therapy. In an explanatory trial focused on the mechanistic effects of a medication, such a difference in co-intervention could be viewed as confounding. In a pragmatic trial, the intent is to compare the manner in which the two interventions of interest would be administered as a part of routine clinical practice. Therefore, if patients in the etomidate group are administered corticosteroids at a higher rate than in the ketamine group, but the clinical outcomes in such circumstances are not different between groups, this provides the most robust answer to the question of the comparative effectiveness of ketamine versus etomidate for RSI as a part of routine clinical care.

7. STUDY INTERVENTIONS

7.1 Treatment of Study Patients

Timing of study procedures is based on the time of the administration of sedative medication (e.g., ketamine or etomidate), which is the first step of rapid sequence induction and tracheal intubation and will be defined as "Time 0.".

Study medications will be administered by the same treating clinicians (e.g., registered nurse, physician, pharmacist) who would administer those medications as part of routine clinical care.

7.2 Ketamine Group

Patients in the ketamine group will be assigned to receive intravenous ketamine for induction of anesthesia during tracheal intubation. A dose of 2 mg/kg will be recommended, and the group assignment sheet will contain a nomogram providing the recommended dose for a range of patient weights (in pounds and kg). In this pragmatic trial, treating clinicians will be able elect to give a lesser or greater dose of ketamine than recommended if felt to be required for optimal patient care.

7.3 Etomidate Group

Patients in the etomidate group will be assigned to receive intravenous etomidate for induction of anesthesia during tracheal intubation. A dose of 0.3 mg/kg will be recommended, and the group assignment sheet will contain a nomogram providing the recommended dose for a range of patient weights (in pounds and kg). In this pragmatic trial, treating clinicians will be able elect to give a lesser or greater dose of etomidate than recommended if felt to be required for optimal patient care.

7.4 Co-Interventions

The RSI trial will control only the first sedative medication administered during the intubation procedure. Subsequent sedative boluses or drips will be determined by treating clinicians. Other aspects of tracheal intubation (e.g., pre-intubation fluid management, pre-oxygenation, choice of neuromuscular blocking medication, choice of laryngoscopy device) will be performed by treating clinicians according to standardized clinical protocols already in place in the study units. Co-interventions that could modify the effect of ketamine or etomidate on cardiovascular collapse or clinical outcomes (e.g., vasopressors, corticosteroids) will be prospectively recorded.

7.5 Packaging and Labeling

Ketamine and etomidate will be packaged and labeled by the manufacturers of the medications. The labeling will not be altered. As the study is unblinded, concealment of the study medication after randomization is not necessary.

Ketamine has been approved by the United States Food and Drug Administration (FDA) and is commercially available with approved indications including “use as the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation” and “induction of anesthesia prior to the administration of other general anesthetic agents.” Etomidate has been approved by the FDA and is commercially available with an indication for “induction of general anesthesia.”

Because both agents are FDA-approved and will be used in a manner consistent with FDA-labeling and standard of care for tracheal intubation in the ED and ICU, labeling ketamine and etomidate as investigational drugs is unnecessary. At all times and all study sites, study medications will already include standard labeling applied by the manufacturer.

The IND application for the RSI trial will, therefore, request a waiver of 21 CFR 312.6, which requires labeling of investigational new drugs with the statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use.” Given ED and ICU staff familiarity with the current labeling applied by the manufacturer, lack of investigational labeling will not pose a significant or unreasonable risk for any patient. In fact, investigational labeling could introduce increased risk to patients by introducing a new and unfamiliar label to a commonly used medication during a high-risk, time-sensitive procedure.

7.6 Storage and Accountability

The medications administered in this investigation will be stored and handled as they are in routine clinical care in the study units, in accordance with institutional policies for each medication. This will

include secure storage in pharmacy and in study units with the use of a password-protected secure medication storage devices (e.g. Omnicell machine). When treatment allocation is revealed at the time of enrollment, the assigned medication will be ordered, procured, prepared, and administered by clinical pharmacists, registered nurses, or physicians as it would be as part of routine clinical care.

7.7 On-Study Monitoring

This study will take place in high-acuity clinical care environments (EDs and ICUs) at the time of a procedure routinely performed as part of usual care. Thus, at the time of the study intervention, the patient will have in the room: a physician trained in the care of critically ill adults, a critical care or emergency medicine nurse, and usually a respiratory therapist and pharmacist. The patient will be receiving continuous invasive or non-invasive monitoring.

The intravenous injection of either ketamine or etomidate produces anesthetic effects that last for less than 10 minutes. Therefore, patients will be intensely monitored, with treating clinicians at the bedside for the duration of the primary effects of the study agents. Following intubation, no additional monitoring is planned beyond what occurs in the usual care of critically ill patients who have received these medications.

8. OUTCOMES

8.1 Primary Outcome

- All-cause, 28-day, in-hospital mortality

8.2 Secondary Outcome

- Cardiovascular Collapse, a composite of any of the following between induction and 2 minutes after intubation:
    - Systolic blood pressure < 65 mmHg
    - New or increased vasopressors
    - Cardiac arrest not resulting in death within 1 hour of induction
    - Cardiac arrest resulting in death within 1 hour of induction

8.3 Exploratory Outcomes

- Procedural Characteristics & Complications
    - Cormack-Lehane Grade of glottic view
    - Successful intubation on the first attempt, defined as placement of an endotracheal tube in the trachea with a single insertion of a laryngoscope blade into the mouth and EITHER a single insertion of an endotracheal tube into the mouth OR a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube over the bougie into the mouth.
    - Time from induction to successful tracheal intubation
    - Lowest oxygen saturation between induction and two minutes after intubation
    - Lowest oxygen saturation < 80% between induction to two minutes after intubation

    - Highest and lowest systolic blood pressure from induction to two minutes after intubation
    - Systolic blood pressure > 180 between induction and two minutes after intubation
    - Systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
    - New or increased vasopressor between induction and 2 minutes after intubation
    - Cardiac arrest within 2 minutes of intubation not resulting in death within 1 hour of induction
    - Cardiac arrest within 2 minutes of intubation resulting in death within 1 hour of induction
- Short-term Clinical Outcomes
    - Ventilator-free days to study day 28
    - Vasopressor-free days to study day 28
    - ICU-free days to study day 28

8.4 Safety outcomes

- Systolic blood pressure at 24 hours after induction
- Receipt of vasopressors at 24 hours after induction
- Cardiac arrest receiving cardiopulmonary resuscitation between induction and hospital discharge

8.5 Long-term outcomes

- Long-term outcomes for RSI (RSI-LTO) are described in Appendix E

9. DATA COLLECTION

Data will be stored in the secure, online database REDCap. A trained independent observer, not involved in the performance of the procedure, will collect peri-procedural outcomes, including oxygen saturation and systolic blood pressure at the time of induction, lowest oxygen saturation and lowest systolic blood pressure between induction and two minutes after tracheal intubation, peri-procedural cardiac arrest, and time from induction to intubation. This process for outcome collection has been used by the primary investigator during multiple prior trials with nearly perfect agreement with the reference standard of direct observation by research staff (Spearman's rho rank correlation coefficient = 0.998).[9] Immediately after each intubation, the operator will report approach to preoxygenation, pre-intubation vasopressors, Cormack-Lehane grade of glottic view,[64] airway complications during the procedure, and the level of operator experience. Study personnel will manually collect data from the medical record on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes.

9.1 Baseline Variable Collection

- Presence or absence of inclusion and exclusion criteria
- Date and time of induction
- Admission data: date and time of presentation, location at enrollment (ED, hospital ward, ICU)
- Demographics (age, sex, race, ethnicity, height, weight)
- Severity of illness score prior to induction

- Active medical problems at the time of induction
- Active comorbidities complicating induction
- Vasopressor use in the hour prior to induction
- Noninvasive ventilator use in the 1 hour prior to induction
- High flow nasal cannula use in the 1 hour prior to induction
- Highest FiO2 delivered in the 1 hour prior to induction
- Indication for intubation
- Preoxygenation technique
- Operator experience (number of prior intubations performed)
- Receipt of corticosteroids in the 48 hours prior to induction
- Vasopressor administration prior to or with induction
- Oxygen saturation by pulse oximetry at time of induction
- Systolic blood pressure at time of induction

9.2 Peri-Procedural Variables

- Lowest arterial oxygen saturation from induction to two minutes after intubation
- Lowest systolic blood pressure from induction to two minutes after intubation
- Highest systolic blood pressure from induction to two minutes after intubation
- Vasopressor administration from induction to two minutes after intubation
- Cardiac arrest from induction to one hour after intubation
- Time from induction to tracheal intubation
- Total number of attempts at intubation
- Sedative agent and dose
- Neuromuscular blocking agent and dose
- Use of nasal cannula, high flow nasal cannula, oxygen by bag-valve-mask, ventilation by bag mask, non-invasive ventilation, or ventilation by laryngeal mask airway between sedative administration and intubation
- Laryngoscope type
- Use of a bougie
- Presence of aspiration between induction and intubation
- Cormack-Lehane grade of glottic view
- Rescue device use
- Need for additional operators
- Mechanical complications (esophageal intubation)
- Self-reported difficulty of the intubation

9.3 Assessments between Hospital Presentation and Hospital Discharge

- Cardiac arrest between one hour after intubation and hospital discharge
- Oxygen saturation at 24 hours after intubation
- FiO2 at 24 hours after intubation
- PEEP at 24 hours after intubation

- Vital signs (e.g., heart rate, blood pressure, respiratory rate) and hemodynamic support (e.g., dose of vasopressors) during the hospitalization
- Receipt of corticosteroids between induction and hospital discharge
- Clinically recorded Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) scores on days 1-7
- Clinically recorded Glasgow Coma Scale on days 1-7
- Date and time of final receipt of invasive mechanical ventilation
- Date and time of first and final receipt of vasopressors following sedative administration (if applicable)
- Date and time of final ICU discharge (if applicable)
- Date and time of hospital discharge (if applicable)
- Date of death (if applicable)

9.4 REDCap Clinical Data Interoperability Services

This project will utilize the REDCap platform for data collection and management. Project team members listed as Key Study Personnel with existing electronic health record (EHR) system access rights may also be granted use of REDCap Clinical Data Interoperability Services (CDIS) tools. These tools are designed to enable transfer of relevant study-related data from the Vanderbilt Research Derivative (or local equivalents) and/or directly from the EHR into REDCap.

10. STATISTICAL CONSIDERATIONS

10.1 Stage 1 Sample Size Calculation

Stage 1 of the RSI trial is primarily focused on feasibility. However, stage 1 will be of sufficient size to provide critical data on the short-term periprocedural outcome of cardiovascular collapse. Assuming that cardiovascular collapse will occur in 19% of patients in the etomidate group (a similar incidence as observed in a prior trial of airway management in which etomidate was the primary sedative),[12] we calculate that enrolling 464 patients will provide 80% statistical power (at a two-sided alpha of 0.05) to demonstrate a relative risk reduction of 50% in the primary outcome of cardiovascular collapse in the ketamine group, compared to the etomidate group.

10.2 Stage 2 Sample Size Calculation

To estimate the incidence of in-hospital mortality in the etomidate group of stage 2 of the RSI trial, we used data from 656 adults undergoing tracheal intubation for non-traumatic critical illness who were recently enrolled from EDs and ICUs in two recent randomized trials in the ED and ICU. Among these patients, the incidence of 28-day in-hospital mortality was 31%. The minimum clinically important difference (MCID) in mortality used in the design of prior critical care RCTs has been an absolute risk reduction of a median of 8 percent (IQR, 6-10).[65] We powered the RSI trial to detect a more conservative absolute risk reduction of 6 percent. This equates to an incidence of the primary outcome of 25% in the ketamine group and a relative risk of mortality with ketamine compared to etomidate of 0.81 –

comparable to the relative risk of 0.827 among adults with non-traumatic critical illness observed in the only prior RCT comparing ketamine vs etomidate.[60] Achieving 80% statistical power at a two-sided alpha of 0.05 to detect a 6 percent absolute difference between groups in the primary outcome would require enrolling 911 patients per group (1,822 overall). Anticipating that, like prior EFIC trials, less than 5% of patients will discontinue participation after enrollment, we aim to enroll a total of 1,900 patients.

10.2 Stage 2 Sample Size Re-Estimation

At the time of progression from Stage 1 to Stage 2, the sample size estimate was updated. Using newly accrued data from clinical trials, the incidence of mortality by 1 month in the etomidate group was updated to 30%.[66] Given the absolute difference in mortality between ketamine and etomidate in two small prior trials of 6-7%,[67,68] patient and clinician stakeholders suggested that, for two common and inexpensive interventions, the trial should have adequate statistical power to detect an absolute difference between groups in mortality of approximately 5%. Thus, we used the *bsamsize* R function to calculate that achieving 80% statistical power at a two-sided alpha of 0.05 to detect a difference in mortality of 5.2% (30.0% in the etomidate group vs 24.8% in the ketamine group) would require 2,308 patients. Anticipating that, like prior EFIC trials, less than 3% of participants will drop out before 1 month, we will enroll a total of **2,364 patients (1,182 per group)**.

10.3 Progression from Stage 1 to Stage 2 of RSI

At the time of initial trial planning, it was determined that if, between initiation of enrollment in Stage 1 and enrollment of 464 patients in Stage 1, funding became available for Stage 2, the DSMB would perform a formal assessment of feasibility and issue a recommendation of whether the trial should progress from Stage 1 to Stage 2.

To perform this assessment of feasibility, the DSMB reviewed data from at least 100 patients enrolled in Stage 1 regarding: 1) the rate of enrollment, 2) the number, proportion, and reasons for exclusion, 3) protocol adherence, 4) data quality, 5) compliance with the requirements of EFIC (under FDA code of regulations 21 CFR 50.24.7) including a review of the timeliness and success of patient or LAR notification,[99,100] and 6) adverse events. Metrics upon which the DSMB could base their recommendation to progress to Stage 2 included:

6. Enrollment of at least 16 patients per month.
7. Appropriate documentation of patient eligibility and adherence to EFIC requirements for notification of enrollment for **all** patients.
8. Greater than 95% of enrolled patients receiving the induction medication assigned by the trial
9. Appropriate mechanisms for ongoing monitoring of EFIC compliance, tracking of excluded patients, and protocol adherence.
10. Adequate completeness and timeliness of data entry.

The initial trial protocol specified that if the DSMB recommended trial progress to Stage 2 and the investigators accept the DSMB's recommendation, no analysis of Stage 1 outcomes (primary outcome of cardiovascular collapse) would be performed. At the end of enrollment in Stage 2, all 2,364 patients enrolled in the trial (Stage 1 plus Stage 2) will be included in a single planned analysis of the Stage 2 outcomes (primary outcome of 28-day in-hospital mortality).

On July 18, 2023, the investigators were notified that Stage 2 of the RSI trial had been funded by the Patient-Centered Outcomes Research Institute. The DSMB was provided with feasibility data from Stage 1 and on August 1, 2023, recommended that the RSI trial advance to Stage 2. No outcome analyses were performed.

10.4 Primary Analysis

The primary analysis will be an intention-to-treat comparison of patients randomized to ketamine versus patients randomized to etomidate with regard to the primary outcome. The difference between the two study groups will be compared using a generalized linear mixed effects model with a random effect for study site (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and a fixed effect for group assignment (ketamine group vs etomidate group).

10.5 Secondary Analyses

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 (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and fixed effects for group assignment and the following pre-specified baseline variables: age; sex; race; ethnicity; area deprivation index (a proxy for socioeconomic status and an indicator of neighborhood disadvantage); rurality; number of comorbidities; and pre-enrollment severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation II score.

10.6 Subgroup Analyses

To evaluate whether pre-specified baseline subgrouping variables modify the effect of study group assignment on the primary outcome, we will perform a generalized linear mixed effects model with a random effect for study site (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) with the primary outcome as the dependent variable and independent variables of study group, the proposed subgrouping variabke, and the interaction between the two. 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. The subgrouping variables will be pre-specified in a statistical analysis plan that will be published before enrollment in the trial concludes. These variables will include:

1. Sepsis or septic shock (Yes / No)
2. Vasopressor receipt (Yes / No)
3. Patient location (ED / ICU)
4. Adrenal insufficiency or chronic receipt of corticosteroids (Yes / No)
5. Acute neurologic condition (Yes / No)
6. Active cardiac condition (Yes /No)

7. Baseline risk of the primary outcome (continuous)

In addition to traditional one-variable-at-a-time subgroup analyses, we analyze heterogeneity of treatment effect using both a risk-modeling approach and an effect-modeling approach (see Appendix F), the details of which will be described in the statistical analysis plan published before the conclusion of enrollment.

10.7 Interim Analysis

The DSMB will review an interim analysis performed after the enrollment of 1,182 patients (50% of the anticipated trial enrollment). 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 generalized linear mixed effects model with a random effect for study site (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and a fixed effect for group assignment (ketamine group vs etomidate group). 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).

10.8 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[69] and the European Medicines Association,[70] each will be tested using a two-sided P value with a significance level of 0.05. For all other 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*,[71] and no corrections for multiple comparisons will be performed.

10.9 Handling of Missing Data

No patients will be lost to follow up before the measurement of the primary outcome, except those that choose to withdraw from the study. 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.

11. DATA QUALITY MONITORING AND STORAGE

11.1 Data Quality Monitoring

Data quality will be reviewed using front-end range and logic checks at the time of data entry and back-end monitoring of data using application programming interface tools connecting the online database to statistical software to generate data reports. The coordinating center will perform remote monitoring of documentation of eligibility criteria, completion of EFIC requirements, and the completeness of study outcome collection.

11.2 Data Storage

Data will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

12. RISK ASSESSMENT

12.1 Potential Risks of Receiving Ketamine

Ketamine is a rapid-acting general anesthetic producing an anesthetic state characterized by profound analgesia, normal pharyngeal-laryngeal reflexes, normal or slightly enhanced skeletal muscle tone, cardiovascular and respiratory stimulation, and occasionally a transient and minimal respiratory depression. At an intravenous dose of 2 mg/kg of body weight, the onset of ketamine is rapid, usually producing surgical anesthesia within 30 seconds after injection. The anesthetic effect usually lasts five to ten minutes and the duration of action of the medication is less than fifteen minutes.

Potential risks of receiving ketamine can be classified based on their severity as major or minor. Major potential risks of receiving ketamine include:

6) Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of ketamine alone. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred. Elevation of blood pressure begins shortly after injection, reaches a maximum within a few minutes, and usually returns to preanesthetic values within 15 minutes after injection. In the majority of cases, the systolic and diastolic blood pressure peaks from 10% to 50% above preanesthetic levels shortly after induction of anesthesia. Regardless of which sedative is used, cardiovascular complications including hypotension and cardiac arrest are common during the tracheal intubation of critically ill adults. Determining whether or not use of ketamine for induction of anesthesia during intubation of critically ill adults effects the risk of cardiovascular events compared to etomidate is a key objective of the RSI trial.

7) Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of ketamine. Laryngospasm has also been reported. Given that ketamine will be used in this trial only as part of the process of tracheal intubation and initiation of invasive mechanical ventilation, respiratory suppression from ketamine is not a significant concern in the RSI trial.

8) Anaphylaxis: Allergic reactions to ketamine are extremely rare and only a few cases of anaphylaxis have been reported. Patients with known allergy to ketamine are excluded from the RSI trial.[72,73]

9) Psychological: According to the FDA package insert for ketamine, adverse psychological manifestations with ketamine are common, reportedly occurring in up to 12% of patients. The

psychological manifestations vary in severity from pleasant dream-like states to hallucinations and emergence delirium. The duration is reported to be no more than several hours for most patients with rare occurrences up to 24 hours post postoperatively. Because patients in the RSI trial are critically ill and will receive ketamine at the time of tracheal intubation with a median duration of invasive mechanical ventilation and accompanying sedation and analgesia of 2-3 days,[10,12] psychological manifestations are unlikely to represent significant risk to patients in the RSI trial.

10) Increased intracranial pressure: An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride and caution is recommended for patients with preanesthetic elevated cerebrospinal fluid pressure. However, the original evidence supporting this assertion is anecdotal and recent studies have contraindicated these findings, suggesting that ketamine may be associated with a beneficial increase in cranial perfusion pressure as a result of increased mean arterial pressure.[39,40] Ketamine is routinely administered to patients with head trauma in routine clinical care in the study settings. However, to maximize patient safety, patients presenting with a primary diagnosis of trauma are excluded from the RSI trial.

Minor potential risks of receiving ketamine include: diplopia, nystagmus, temporary increase in intraocular pressure, anorexia, nausea, and vomiting. Lower urinary tract and bladder symptoms have also been reported with chronic use.

12.2 Potential Risks of Receiving Etomidate

Etomidate is a rapidly acting general anesthetic without analgesic activity. At a dose of 0.3 mg/kg body weight, onset of action is usually within one minute with a duration of action of three to five minutes.

Potential risks of receiving etomidate can be classified based on their severity as major or minor. Major potential risks of receiving etomidate include:

5) Endocrine: Reduced plasma cortisol and aldosterone levels have been reported following the induction doses of etomidate that will be recommended in the RSI trial. These reductions in plasma cortisol and aldosterone persist for approximately 6-8 hours and appear to be unresponsive to ACTH stimulation. They are likely related to blockage of 11 beta-hydroxylation within the adrenal cortex. Determining whether or not these transient reduction in cortisol and aldosterone levels influence clinical outcomes for patients is a key objective of the RSI trial.

6) Circulatory: Hypertension, hypotension, tachycardia, bradycardia, and other arrhythmias have occasionally been observed during induction with etomidate. Geriatric patients, particularly those with hypertension, may be at increased risk for the development of cardiac depression following etomidate administration. Regardless of which sedative is used, cardiovascular complications including hypotension and cardiac arrest are common during the tracheal intubation of critically ill adults. Determining whether or not use of etomidate for induction of anesthesia during intubation of critically ill adults effects the risk of cardiovascular events compared to ketamine is a key objective of the RSI trial.

7) Respiration: Hyperventilation, hypoventilation, apnea of short duration (5 to 90 seconds with spontaneous recovery), laryngospasm, hiccup and snoring suggestive of partial upper airway obstruction have been observed in some patients. Given that etomidate will be used in this trial only as part of the process of tracheal intubation and initiation of invasive mechanical ventilation, respiratory suppression from etomidate is not a significant concern in the RSI trial.

8) Anaphylaxis: Allergic reactions to etomidate are extremely rare and limited to one case of severe hypotension and tachycardia. Patients with known allergy to etomidate are excluded from the RSI trial.

Minor potential risks of receiving etomidate include: transient venous pain on injection (20% of the patients) and transient skeletal muscle movements (32% of patients) including myoclonus, nausea, or vomiting.

12.3 Potential Risk of Participation in the RSI Trial

The RSI trial will enroll critically ill adults whose treating clinicians have determined that (1) tracheal intubation is clinically required and (2) use of either ketamine or etomidate is consistent with optimal care for the patient. Both ketamine and etomidate are FDA-approved medications being used within their FDA approved indications, and the only prior randomized trial reported no significant difference in outcome between the two medications. More than 95% of patients undergoing tracheal intubation in the study sites receive either ketamine or etomidate as a part of routine clinical care. All patients eligible for the RSI trial will experience the risks of emergency tracheal intubation and the risks of receipt of an induction medication such as ketamine or etomidate as a part of their routine clinical care, whether or not they are enrolled in the RSI trial. The incremental risks of participation in the RSI trial are (1) the risk associated with collection of PHI and (2) the risk associated with allowing the choice between ketamine and etomidate to be made by trial group assignment rather than by the treating clinician. Because the only patients eligible are those whose treating clinicians feel use of either ketamine or etomidate is consistent with optimal care, the incremental risk of participation in the RSI trial, compared to routine clinical care outside the trial, is minimal.

12.4 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 subject protection requirement by incorporating numerous design elements to minimize risk to patients.

Both therapies used in the RSI trial, ketamine and etomidate, are approved by the Food and Drug Administration and have been used in clinical practice for decades with an established safety profile in the same populations included in the RSI trial. Both medications will be administered at the recommended dose and route.

To further mitigate risk, we will exclude patients with specific risk factors for adverse events from ketamine or etomidate including patients with known allergies to ketamine or etomidate, patients with a primary diagnosis of trauma, and any patient for whom treating clinicians believe that ketamine or

etomidate is required or contraindicated for the optimal care of the patient. Finally, 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.

12.5 Potential Benefit

Participation in the RSI trial holds the prospect of direct benefit to the subjects. Previous animal and clinical studies have established several mechanisms by which either ketamine or etomidate might provide a direct benefit to individual critically ill subjects undergoing tracheal intubation via improved hemodynamics and survival.

Determining whether ketamine or etomidate improves clinical outcomes among critically ill patients undergoing tracheal intubation in the ED or ICU will also benefit RSI trial patients who go on to require emergency tracheal intubation again in the future, as well as the millions of critically ill adults who undergo tracheal intubation each year.

12.6 Risk in Relation to Anticipated Benefit

Federal regulations at 45 CFR 46.111 (a)(2) require that "the risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result." The incremental risks of participation in the RSI trial, compared to routine clinical care outside the trial for eligible patients, are minimal as all patients enrolled in the RSI trial would have received a sedative as part of emergency tracheal intubation in routine clinical care, regardless of participation in the RSI trial. Understanding the effect of these two commonly used medications on clinical outcomes will benefit RSI trial patients who go on to require emergency tracheal intubation again in the future, as well as the millions of critically ill adults who undergo tracheal intubation each year. Thus, the risks to subjects are reasonable in relation to the anticipated benefits and importance of the knowledge to be gained.

13. HUMAN SUBJECTS PROTECTIONS

Emergency tracheal intubation of critically ill adults is a time-sensitive procedure with a brief therapeutic window between the decision to perform intubation and the completion of the procedure. Critically ill patients requiring tracheal intubation are nearly uniformly unconscious, delirious, or in states of distress for which it would be unsafe to delay intubation for an informed consent discussion with the patient or a surrogate. Legally authorized representatives are rarely available during the narrow therapeutic window. Even in the rare cases where the patient retains decisional capacity or the patient's legally authorized representative (LAR) is present at the bedside at the moment the decision is made to intubate a critically ill patient, the urgency of the intubation procedure would preclude the detailed discussion of risks and benefits required for informed consent in most, if not all, cases.

Therefore, it is expected that all patients will be enrolled under "Exception from informed consent required for emergency research" (EFIC). Additional details regarding how the RSI trial will comply with each of the requirements of EFIC are provided in Appendix B.

13.1 Length of Therapeutic Window

For an induction medication used for emergency tracheal intubation, the therapeutic window begins at the time treating clinicians decide to perform emergency tracheal intubation with sedation and ends at the time an induction medication is administered for emergency tracheal intubation. To our knowledge, no published literature has quantified this therapeutic window among critically ill adults. Among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the ED or ICU in the planned study sites of the RSI trial, the median time from treating clinicians verbalizing the decision to intubate with sedation (or placing a written order for an induction medication) to the administration of an induction medication was 5 minutes [interquartile range, 1 minute to 10 minutes]. For no patient was this window longer than 30 minutes. 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. For most patients in the RSI trial, completion of the trial intervention (a one-time injection at the start of the emergency tracheal intubation procedure) is anticipated to occur less than 5 minutes after meeting trial eligibility criteria. Thus, in the RSI trial, we anticipate that the therapeutic window for most patients will be less than 5 minutes.

13.2 Inability to Conduct Trial without EFIC

Most patients eligible for the RSI trial will be experiencing unconsciousness or delirium due to critical illness. More than half of critically ill adults undergoing tracheal intubation in the ED or ICU have a Glasgow Coma Scale score less than 12 (equivalent to moderate brain injury) and among those whose level of consciousness is not impaired, most experience acute delirium. Even in instances in which a patient retains capacity, or an LAR is immediately available, the rapidity with which emergency tracheal intubation is clinically required, and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation, precludes a meaningful informed consent process in most, if not all, cases. Delaying emergency tracheal intubation for a critically ill adults to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

One approach for obtaining prospective consent for interventions with short therapeutic window is to consent patients at high risk of requiring the intervention in the future. Unfortunately, there is no reasonable method for prospectively identifying individuals who will develop a need for emergency tracheal intubation. Many different acute illnesses lead to emergency tracheal intubation in the ED or ICU including stroke, spontaneous intracranial hemorrhage, seizure, sepsis, drug overdose, acute coronary syndrome, aspiration pneumonitis, acute bacterial pneumonia, pneumothorax, and others. Any patient in the community or in the hospital may unexpectedly develop a need for emergency tracheal intubation within a period of minutes with no warning.

For these reasons, the RSI trial could not be conducted without EFIC, and it is expected that all patients will be enrolled through EFIC.

13.3 Opportunity to Decline Participation

Although it is expected that in most, if not all cases, the urgency of the procedure and the nature of the patient's critical illness will preclude a detailed informed consent discussion between the trained research staff and the patient or LAR during the brief therapeutic window, a consent form will be available and the RSI trial will provide two mechanisms to opt-out of participation.

First, medical alert bracelets will be made available prior to and throughout the trial for any community members who become aware of the trial and desire to express their preference against participation should they become critically ill and require tracheal intubation (details of public notification plan and process of requesting opt-out bracelets are provided in the Community Consultation and Public Disclosure Plan).

Second, when feasible, the RSI trial will provide an opportunity for patients, LARs, or family members to express their objection immediately prior to research enrollment. While the nature of emergency tracheal intubation precludes a full, written, informed consent process in most, if not all, cases, the RSI trial will provide an opportunity for patients, LARs, or family members to object to participation based on more limited information whenever feasible using a pre-enrollment opt-out script. This will occur in cases in which the patient retains decisional capacity or a family member or LAR is available, research staff are able to reach the patient or LAR before intubation, and treating clinicians have determined that based on the clinical status of the patient there is insufficient time to complete a formal informed consent process. The IRB-approved opt-out script will describe the study and provide an opportunity for patients, LARs, or family members to decline participation before enrollment (Appendix C). The decisional capacity of the patient and the safety and feasibility of reading the script during the brief therapeutic window will be determined by the treating clinicians. Allowing a mechanism, whenever feasible, for patients to opt out of participation is consistent with the respect for autonomy emphasized in the EFIC guidelines.

13.4 Notification of Enrollment

At the earliest feasible opportunity, each patient, or if the patient remains incapacitated, a legally authorized representative of the patient, or if such a representative is not reasonably available, a family member, will be notified of the patient's inclusion in the study. Details of the study will be provided, all questions will be answered, and the patient or patient's LAR or family member will be informed of their right to discontinue study participation at any time without penalty or loss of benefits of which the patient is otherwise entitled. The patient or LAR or family member will be provided with a patient notification form which contains study details and contact information for study personnel and the IRB.

Because the study intervention is a one-time injection occurring within minutes of enrollment, all patients will have completed the study intervention and experienced the risks and benefits of the study intervention by the time notification of participation occurs so written informed consent will not be obtained. The only remaining study activity is review of the patient's medical record by study personnel until the end of the patient's hospitalization. For those who wish to discontinue participation, no further data will be collected. Data collected prior to withdrawal will remain in the study database as per FDA requirements and guidance.

A minimum of three attempts will be made to discuss the study with the patient or the patient's LAR. Whenever feasible, this will occur in a face-to-face discussion in the hospital between trained study

personnel and the patient or LAR. If the patient is discharged before a face-to-face discussion occurs, these attempts will be made by phone, and a notification sheet will be mailed to the patient's address.

If a patient is enrolled in the RSI trial and dies before a face-to-face discussion with the patient or LAR, a reliable mailing address for the patient's family or LAR will be obtained. After allowing a two to four-week period of grieving, study personnel will send a letter with basic information about the clinical investigation, the patient's inclusion, and contact information so that families can call or write to obtain more information or to get questions answered if desired.

If the patient regains decision-making capacity prior to hospital discharge, study personnel will notify the patient of the study and ask if the patient wants to continue participation.

13.5 Documentation and Tracking of Notification Process

Notification logs will be incorporated into the study case report forms and will allow tracking and reporting of the timeliness of these processes. This log will include the types of attempts made, the number and timing of those attempts, and the outcome of each attempt. Notification logs will be available for IRB review as requested and will be summarized for the IRB at the time of continuing review.

13.6 Selection of Subjects

Federal regulations 45 CFR 46(a)(3) require the equitable selection of subjects. All patients undergoing tracheal intubation in a participating unit who meet inclusion criteria without meeting exclusion criteria will be enrolled. We will not discriminate based on gender, race, or ethnicity. Study exclusion criteria neither unjustly exclude classes of individuals from participation in the research nor unjustly include classes of individuals for participation in the research. Hence, the recruitment of patients conforms to the principle of distributive justice.

13.7 Justification of Including Vulnerable Subjects

The present research aims to investigate the safety and efficacy of ketamine and etomidate during the tracheal intubation of critically ill patients. Due to the nature of this patient population, most patients will have impaired decision-making capabilities. Moreover, those with intact decision-making capacities probably have milder disease than those with impaired capacity. Therefore, the validity of the study and its generalizability to severely ill patients would be compromised by enrolling only those patients with retained decision-making capacity. Hence, patients recruited for this trial are not being unfairly burdened with involvement in this research.

13.8 Investigational New Drug Application

As required by studies conducted under 21 CFR 50.24, the RSI protocol will be included as part of an Investigational New Drug Application to the United States Food and Drug Administration (FDA). The study will not proceed until the primary investigator has received written authorization from both the FDA and the Vanderbilt Institutional Review Board

13.9 Additional Safeguards for Vulnerable Patients

The present research will involve patients who might be vulnerable to coercion or undue influence. As required in 45CFR46.111(b), we recommend that sites utilize additional safeguards to protect the rights and welfare of these patients. Such safeguards might include but are not limited to: a) assessment of the patient's capacity to understand notification of enrollment and b) the availability of the LAR to monitor the patient's participation and withdrawal from the study. The specific nature of the additional safeguards will be left to the discretion of the central IRB, in conjunction with the sites.

13.10 Confidentiality

Federal regulations 45 CFR 46 111 (a) (7) requires that, when appropriate, there are adequate provisions to protect the privacy of patients and to maintain the confidentiality of data. 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. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered into a secure online database. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated. Further, tools within the secure online database will be used so that only the coordinating center and investigators from the enrolling site will have access to data from patients enrolled at that site.

14. ADVERSE EVENTS

Assuring patient safety is an essential component of this protocol. Both ketamine and etomidate have been approved by the Food and Drug Administration and 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:

4. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from ketamine or etomidate;
5. Systematic collection of safety outcomes relevant to use of ketamine and etomidate in this setting;
6. Structured reporting of adverse events.

14.1 Adverse Event Definitions

Adverse Event: Any untoward medical occurrence associated with the use of a medication or a study procedure, whether or not considered medication related.

Serious Adverse Event: A serious adverse event is any adverse event that results in one of the outcomes listed in section 14.3 below.

Adverse Reaction: An adverse reaction means any adverse event caused by a study intervention. An adverse reaction is a subset of all suspected adverse events where there is a reason to conclude that the study intervention caused the event.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the study procedures caused the adverse event. Reasonable possibility means there is evidence to suggest a causal relationship between the study procedures and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction.

Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse reaction that is both unexpected (not consistent with risks outlined in the study protocol or investigator brochure), serious, and meets the definition of a suspected adverse reaction.

14.2 Safety Monitoring

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 for 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 as close as feasible to 24 hours after randomization during initial data collection. The second will occur at the first of hospital discharge or 28 days after enrollment during 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.

The following adverse events will be considered reportable and thus collected in the adverse event case report forms:

- Serious adverse events that are considered by the investigator to be related to study procedures, possibly or probably related, or of uncertain relationship (Appendix D)
- Unexpected adverse events that are considered by the investigator to be related to study procedures, possibly or probably related, or of uncertain relationship (Appendix D)

Study-specific clinical outcomes (Primary, Secondary and Safety Outcomes), including serious outcomes such as organ failures and death, are systematically recorded in the case report forms and are exempt from adverse event reporting unless the investigator deems the adverse event to be serious and definitely related to the administration of study medication or the conduct of study procedures (or of uncertain relationship) as outlined in Appendix D.

Because ketamine and etomidate are 1) FDA-approved, 2) used within their approved indications, and 3) have well-established safety profiles, the RSI trial will not plan to collect non-serious

adverse events as suggested in FDA guidelines for Investigator Reporting (21 CFR 312.64(b)) for post-marketing outcome trials conducted with an IND.

Adverse events will be evaluated by the lead investigator at each enrolling site. If an adverse event is judged to be potentially reportable, as outlined above, then the lead investigator at each enrolling site will record the adverse event via electronic data entry for review. The principal investigator will be responsible for making final determinations regarding potential relatedness of adverse events, based on the criteria outlined in Section 14.3 and Appendix D. The principal investigators will also consider if the event is unexpected. Unexpected adverse events are events not listed in the study protocol or the investigator brochure for Ketamine or Etomidate. In making determinations, the principal investigator will determine if adverse events are unanticipated given the patient's clinical course, previous medical conditions, and concomitant medications.

14.3 Serious Adverse Events

The lead investigator at each enrolling site must alert the primary investigator of any **serious and study procedure related** adverse event within 24 hours of investigator awareness of the event. Alerts issued via telephone are to be immediately followed with official notification on the adverse event case report form. See Appendix D for reporting timelines for serious, unexpected, study related events (SAEs) and serious, unexpected suspected adverse reactions (SUSARs).

As per the FDA and NIH definitions, a serious adverse event is any adverse event that results in one of the following outcomes:

- Death
- A life-threatening experience (that is, immediate risk of dying)
- Prolonged inpatient hospitalization or re-hospitalization
- Persistent or significant disability/incapacity

Reportable serious adverse events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse events when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

The DSMB will consist of members with expertise in bioethics, emergency medicine, pulmonary critical care, 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 Principal Investigator 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 with the assistance of the Principal Investigator. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

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17. APPENDICES

Appendix A. Schedule of Events

Study Activity	Pre-Induction	Administration of Sedatives (Induction)	Tracheal Intubation	Day 1	Days 2-27	Day 28
Eligibility assessment	X					
Opt-out conversation (when feasible)	X					
Pre-enrollment time-out	X					
Randomization	X					
Recording of baseline blood pressure and oxygen saturation	X					
Study medication delivery (Ketamine or Etomidate)		X				
Recording of peri-procedural outcomes		X	X	X		
Assessment for study medication adherence		X	X	X		
Safety monitoring for adverse events		X	X	X		X
Notification of Enrollment				X	X	
Mortality assessment			X	X	X	X
28-day in-hospital outcomes (chart review)						X

1) Critical illness requiring emergency tracheal intubation is a life-threatening situation and available treatments are unsatisfactory or unproven.

> *21 CFR 50.24(a)(1) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.*

Each year more than 1.5 million critically ill patients receive mechanical ventilation in the United States.[1–3] Despite adherence to recommended best-practices for tracheal intubation (e.g., preoxygenation,[15,16] optimization of patient positioning,[9] and procedural checklists[8]), one in five critically ill patients experiences hypotension and one-in-forty experiences cardiac arrest during the brief, two-minute procedure to place an endotracheal tube.[6–10] Around 30% of critically ill adults undergoing emergency tracheal intubation die prior to hospital discharge.

Rapid sequence induction and tracheal intubation, the most common method of intubation for critically ill patients, is the nearly simultaneous administration of a sedative medication and neuromuscular blocking medication. The ideal sedative agent for rapid sequence intubation would rapidly provide a deep state of unconsciousness and analgesia without causing hemodynamic side effects, but no available agent meets all criteria.[20] The administration of any available sedative at a dose large enough to rapidly induce unconsciousness contributes to cardiovascular collapse through vasodilation, decreased cardiac filling pressures from sedation-induced venodilation, and decreased endogenous catecholamines.[21–24] While all sedatives commonly used during emergency tracheal intubation of critically ill patients have been associated with unsatisfactory hypotension (21 CFR 50.24(a)(1)), ketamine and etomidate are the medications used most commonly in clinical practice due to their rapid onset and relatively favorable hemodynamic profiles (as described in section 2.1.2).[25,26] A large multi-center trial is needed to determine the effects on peri-procedural hemodynamics and mortality of the two most commonly used sedatives for the tracheal intubation of critically ill adults.

2) Obtaining prospective informed consent is not feasible during emergency tracheal intubation.

> *21 CFR 50.24(a)(2) Obtaining informed consent is not feasible because: (i) the subjects will not be able to give their informed consent as a result of their medical condition; (ii) the intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and (iii) There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.*

Most patients eligible for the RSI trial will be experiencing unconsciousness or delirium due to critical illness. More than half of critically ill adults undergoing tracheal intubation in the ED or ICU have a Glasgow Coma Scale score less than 12 (equivalent to moderate brain injury) and among those whose level of consciousness is not impaired, most experience acute delirium. Even in instances in which a

patient retains capacity, or an LAR is immediately available, the rapidity with which emergency tracheal intubation is clinically required, and the accompanying distress of the patient or LAR from the critical illness and need for emergency tracheal intubation, precludes a meaningful informed consent process. Delaying emergency tracheal intubation for a critically ill adults to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

There is no reasonable method for prospectively identifying individuals for informed consent prior to developing a need for emergency tracheal intubation. Many different acute illnesses lead to emergency tracheal intubation in the ED or ICU including stroke, spontaneous intracranial hemorrhage, seizure, sepsis, drug overdose, acute coronary syndrome, aspiration pneumonitis, acute bacterial pneumonia, pneumothorax, and others. Any patient in the community or in the hospital may unexpectedly develop a need for emergency tracheal intubation within a period of minutes with no warning.

For these reasons, the RSI trial could not be conducted without EFIC, and it is expected that most, if not all, patients will be enrolled through EFIC.

3) Participation in RSI holds prospect of direct benefit to subjects

> *21 CFR 50.24(a)(3) Participation in the research holds out the prospect of direct benefit to the subjects because: (i) subjects are facing a life-threatening situation that necessitates intervention; (ii) appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and (iii) risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.*

Participation in RSI holds out the prospect of direct benefit to subjects. Critical illness requiring emergency tracheal intubation is a life-threatening condition with a high incidence of hypotension and cardiac arrest that necessitates immediate intervention. Previous animal and clinical studies have established several mechanisms by which either ketamine or etomidate might provide a direct benefit to individual critically ill subjects undergoing tracheal intubation via improved hemodynamics and survival.

The risks associated with the investigation are reasonable in relation to what is known about tracheal intubation of critically ill patients. All patients enrolled in the RSI trial would have received a sedative as part of emergency tracheal intubation in routine clinical care, regardless of participation in the RSI trial. The treatment groups represent the two most commonly used sedatives, and there is no evidence currently that either medication is superior with regard to peri-procedural hemodynamics or survival. Therefore, there is no reason to believe that participation in this study would expose patients to greater medical risks than those experienced by critically ill patients undergoing tracheal intubation as part of routine clinical care.

4) The RSI trial cannot be practicably carried out without exception from informed consent

> *21 CFR 50.24(a)(4) The clinical investigation could not practicably be carried out without the waiver.*

This research could not be carried out without EFIC because 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. A meaningful informed consent process requires that the patient or LAR have time to understand the material presented, be able to ask questions and have time to consider their options. This is not possible in the brief therapeutic window between the decision to intubate a critically ill patient and the initiation of the procedure.

5) The need for immediate treatment of critically ill patients requiring emergency tracheal intubation is expected to preclude obtaining informed consent from an LAR in most, if not all cases, during the brief therapeutic window

> *21 CFR 50.24 (a)(5) The proposed investigational plan defines the length of the potential therapeutic window based on scientific evidence, and the investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent. The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.*

For an induction medication used for emergency tracheal intubation, the therapeutic window begins at the time treating clinicians decide to perform emergency tracheal intubation with sedation and ends at the time an induction medication is administered for emergency tracheal intubation. To our knowledge, no published literature has quantified this therapeutic window among critically ill adults. Among a convenience sample of 25 consecutive critically ill adults undergoing emergency tracheal intubation in the ED or ICU in the planned study sites of the RSI trial, the median time from treating clinicians verbalizing the decision to intubate with sedation (or placing a written order for an induction medication) to the administration of an induction medication was 1 minute [interquartile range, 1 minute to 10 minutes]. For no patient was this window longer than 30 minutes. 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. For most patients in the RSI trial, completion of the trial intervention (a one-time injection at the start of the emergency tracheal intubation procedure) is anticipated to occur less than 5 minutes after meeting trial eligibility criteria. Thus, in the RSI trial, we anticipate that the therapeutic window for most patients will be less than 5 minutes. While a written informed consent is available and will be used when feasible, it is expected that written consent will be infeasible in most, if not all, cases because delaying the emergency tracheal intubation of critically ill adults would cause irreparable harm to patients. Whenever feasible, however, the RSI trial will provide an opportunity for patients, LARs, or family members to opt-out of trial participation.

This will occur in cases in which the patient retains decisional capacity or a family member or LAR is available, research staff are able to reach the patient or LAR before intubation, and treating clinicians have determined that based on the clinical status of the patient there is insufficient time to complete a formal informed consent process (Appendix C). The decisional capacity of the patient and the safety and feasibility of reading the script during the brief therapeutic window will be determined by the treating

clinicians. Allowing a mechanism, whenever feasible, for patients to opt out of participation is consistent with the respect for autonomy emphasized in the EFIC guidelines.

We will make every effort to contact legal representatives after enrollment to notify LARs that the patient was enrolled in a randomized trial and provide an opportunity to withdraw from further participation. If legal representatives are not immediately available, research personnel will attempt to contact the subject's legal representative as soon as feasible and a summary of these efforts will be documented in the patient's study record. If the subject becomes competent during the study period, he/she will be approached by research personnel for notification of enrollment.

Investigators will prospectively record cases when patients, LARs, or family members opt-out of participation and the efforts by study staff to notify patients and LAR of enrollment. These efforts will be summarized and reported to the DSMB at their semi-annual meetings and to the IRB at the initial and continuing reviews.

6) Informed consent procedures and documents in the RSI trial will be reviewed and approved by the IRB

> *21 CFR 50.24(a)(6) The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with Sec. 50.25. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible. The IRB has reviewed and approved procedures and information to be used when providing an opportunity for a family member to object to a subject's participation in the clinical investigation consistent with paragraph (a)(7)(v) of this section.*

All consent procedures and documents that will be used in the RSI trial will be approved by the IRB prior to the initiation of enrollment.

7) Additional protections of the rights and welfare of the subjects will be provided in the RSI trial, including:

Community Consultation

> *vii. 21 CFR 50.24(a)(7) Additional: Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn;*

A detailed plan for community consultation has been developed for the RSI trial (see Community Consultation and Public Disclosure Plan). The plan included in the initial draft of the RSI protocol was informed by two Community Engagement Studios, organized by the Vanderbilt Community Engagement Research Core. The first meeting, held on February 2, 2021, included healthcare providers who routinely participated in emergency tracheal intubation in the ED or ICU. The second meeting, held on February 4, 2021, included patients or caretakers of patients who had experienced critical illness with emergency tracheal intubation. Investigators solicited feedback on the design of the RSI trial, potential risks and benefits of participation, the inability to obtain prospective informed consent, the opportunity to opt-out

of participation, and the plans for further Community Consultation, Public Disclosure of the conduct and results of the trial. The protocol, the plan for further Community Consultation, and the plan for Public Disclosure were refined based on this feedback to address the concerns of the community. Enrollment in the RSI trial will not begin until 1) the IRB has approved the proposed community consultation plan, 2) study personnel have completed the proposed community consultation plan, and 3) the IRB has reviewed and certified the completion of community consultation and approved enrollment.

Public Disclosure

viii. *21 CFR 50.24(a)(7): Public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits;*

ix. *Public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;*

Public disclosure is a primary element in making certain that RSI is conducted in an entirely transparent manner. A detailed public disclosure plan has been developed for the RSI trial (see Community Consultation and Public Disclosure Plan). The plan included in the initial draft of the RSI protocol was informed by two Community Engagement Studios, organized by the Vanderbilt Community Engagement Research Core. The first meeting, held on February 2, 2021, included healthcare providers who routinely participated in emergency tracheal intubation in the ED or ICU. The second meeting, held on February 4, 2021, included patients or caretakers of patients who had experienced critical illness with emergency tracheal intubation. Investigators solicited feedback on the design of the RSI trial, potential risks and benefits of participation, the inability to obtain prospective consent, the opportunity to opt-out of participation, and the plans for further Community Consultation, Public Disclosure of the conduct and results of the trial. The protocol, the plan for further Community Consultation, and the plan for Public Disclosure were refined based on this feedback to address the concerns of the community. Enrollment in the RSI trial will not begin until 1) the IRB has approved the proposed public disclosure plan, 2) study personnel have completed the proposed public disclosure activities, and 3) the IRB has reviewed and certified the completion of public disclosure and approved enrollment.

Data and Safety Monitoring Committee

x. *21 CFR 50.24(a)(7): Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation;*

The Data Safety Monitoring Board (DSMB) will function as an independent data monitoring committee who will exercise oversight of the study. The composition and responsibilities of the DSMB are described in protocol section 15.

Contacting Other Family

xi. *21 CFR 50.24(a)(7) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the clinical investigation. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.*

It will not be feasible or ethically possible in the RSI trial, for the reasons described above, to delay treatment of a critically ill patient requiring emergency tracheal intubation for long enough to contact either an LAR or other family members who are not present. We will, however, provide patients and LARs or family members who are present with the opportunity to opt-out of enrollment using the recitation of a standardized script by research staff during the brief therapeutic window (Appendix C). Further, we will provide a mechanism whereby community members who would not want to participate if undergoing tracheal intubation in the ED or ICU can communicate that decision to providers without causing any delay in treatment using opt-out bracelets. As part of the primary assessment of a critically ill patient, providers already check for a medical alert bracelet. The study will provide medical alert bracelets with the words "RSI declined" to any community member requesting one. The process by which community members are notified of the study and requests an opt-out bracelet are explained in the Community Consultation and Public Disclosure Plan. Medical alert bracelets are a common and effective means of communicating information to ED and ICU providers while unconscious or in acute distress. Requests for RSI opt-out bracelets and their use in identifying patients for exclusion will be tracked by study investigators and this information can be made available to the IRB at the time of continuing review.

Post Enrollment Notification

xii. *21 CFR 50.24(b) The IRB is responsible for ensuring that procedures are in place to inform, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, of the subject's inclusion in the clinical investigation, the details of the investigation and other information contained in the informed consent document. The IRB shall also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the clinical investigation and the subject's condition improves, the subject is also to be informed as soon as feasible. If a subject is entered into a clinical investigation with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the clinical investigation is to be provided to the subject's legally authorized representative or family member, if feasible.*

Subjects enrolled in RSI or their LAR or family will be informed of the subject's inclusion in the clinical investigation at the earliest possible opportunity as detailed above. It is anticipated that the notification of patients' LAR or family will most usually take place within 24 hours of enrollment. Attempts to notify the subject or an LAR are repeated until successful or at least three attempts have been made. If a patient's LAR or family member is notified of enrollment and the patient subsequently regains decision-making capacity, the patient will be notified of the study and will be asked if he or she wants to continue the study.

All notification attempts will be logged and recorded in the study record. Reports of these logs will be summarized to the DSMB at semi-annual reports and available for inclusion in annual reports to the IRB.

By the time patients, LARs, or family members are notified of participation, the study intervention (a one-time infusion at the time of tracheal intubation) will have been completed and patients will have experienced all of the risks or benefits associated with the study intervention. The only remaining study procedure will be review of the electronic health record by study personnel. Requesting that patients, LARs, or family member provide informed consent for continued participation after completion of the study intervention would not provide any additional patient protections, but would risk diminishing the overall validity and value of the research by biasing estimates of safety and efficacy if consent for continued participation occurred differentially between the trial groups because of the effects of the trial interventions. The RSI trial will, therefore, use public notification, community consultation, a pre-enrollment opt-out conversation (by research staff), medical alert bracelets, patient and LAR notification of enrollment, and a provision of an opportunity to opt out of ongoing participation.

Record Keeping

> *21 CFR 50.24(c) Like other IRB records, records of the determinations above must be kept for a minimum of three years after the completion of the clinical investigation. Again, like other IRB records, these are subject to inspection and copying by FDA.*

Records documenting the enrollment of patients using EFIC, procedures for opt-out prior to enrollment, and attempts to notify patients, LARs, and family members of enrollment will be kept for a minimum of three years after completion of the clinical investigation.

IND Requirement

> *21 CFR 50.24(d) Protocols involving an exception to the informed consent requirement under this section must be performed under a separate investigational new drug application (IND) or investigational device exemption (IDE) that clearly identifies such protocols as protocols that may include subjects who are unable to consent. The submission of those protocols in a separate IND/IDE is required even if an IND for the same drug product or an IDE for the same device already exists. Applications for investigations under this section may not be submitted as amendments under Secs. 312.30 or 812.35 of this chapter.*

For critically ill adults undergoing emergency tracheal intubation for whom treating clinicians feel either ketamine or etomidate is consistent with optimal care, the incremental risks of participating in the RSI trial, compared to clinical care for the patient outside the trial, are minimal. As such, the RSI trial might be considered to quality for waiver of consent and exemption from IND requirements under 21 CFR 312 because:

- Both ketamine and etomidate are lawfully marketed in the United States for use as sedative agents during tracheal intubation (the indication for which they will be used in the RSI trial)
- The current study is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for either ketamine or etomidate
- The current study is not intended to support a change in advertising for ketamine or etomidate
- The current study does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of ketamine or etomidate. The current study will use ketamine and etomidate at the doses recommended by the FDA-approved package insert and excludes patient populations that would have increased risks of complications and any patients for whom any provider believes ketamine or etomidate is required or contraindicated
- The study will be conducted with the requirements for institutional review set forth in FDA regulations 21 CFR 56.
- The current study will be conducted in compliance with FDA regulations 21 CFR 312.7 regarding promotion and charging for investigational medication

We will, however, conduct the RSI trial under EFIC in order to ensure patients receive the additional protections offered by community consultation and disclosure through EFIC. As required by EFIC regulations 21 CFR 50.24(d), an IND for the RSI trial was obtained from the FDA (IND 141424). The Study Principal Investigator serves as the sponsor of the IND.

Communication of IRB Determinations

> *21 CFR 50.24(e) If an IRB determines that it cannot approve a clinical investigation because the investigation does not meet the criteria in the exception provided under paragraph (a) of this section or because of other relevant ethical concerns, the IRB must document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the clinical investigation. The sponsor of the clinical investigation must promptly disclose this information to FDA and to the sponsor's clinical investigators who are participating or are asked to participate in this or a substantially equivalent clinical investigation of the sponsor, and to other IRBs that have been, or are, asked to review this or a substantially equivalent investigation by that sponsor.*

If an application for RSI is disapproved by a local IRB, the Study PI/sponsor will promptly disclose this information to the FDA.

Appendix C. Script to Provide an Opportunity to Opt-Out of Participation

The script below will be used by research staff in cases in which the patient retains decisional capacity or a family member or LAR is available, the research team reaches the patient or LAR before intubation and based on the clinical status of the patient there is insufficient time to complete the intubation process prior to intubation.

OPT-OUT SCRIPT

1. You (*your loved one*) need(*s*) to be placed on a breathing machine, which requires a brief procedure to place a breathing tube.

2. There are two medications that we commonly give patients to make them sleepy and relaxed for this procedure. As your medical team, we think either of these medications would be a good and safe choice for you.

3. To help us understand which of the two medications is best, we are conducting a research study that compares the two medications.

4. If you say "Yes" to participation, we will allow the study to choose which of the two medications you will receive and someone from the study will come by later to provide details and answer your questions. If you say "No", we will choose one of the two medications ourselves. Do you agree to participate?

☐ "Yes" - Patient/family agreed to participate (open envelope to enroll patient)

☐ "No" - Patient/family declined participation (place envelope in "used" bin; do not enroll)

Appendix D: Adverse Event Reporting and Unanticipated Events

As noted in section 14, the lead investigator at each enrolling site is required to report all potentially reportable adverse events to the principal investigator within 24 hours of becoming aware of the event. Reportable events in the RSI trial are defined as adverse events that are unexpected and serious have a reasonable possibility that the event was due to a study medication or procedure (or of uncertain relatedness)

The primary investigator will work collaboratively with the lead investigator at each enrolling site to determine if a serious adverse event has a reasonable possibility of having been caused by the study medication or study procedure, as outlined in 21 CFR 312.32(a)(1), and below. In this unblinded trial, both the investigator and primary investigator will be aware of group assignment and the receipt of either ketamine or etomidate. An adverse is considered "unexpected" if it is not listed in the investigator brochure or the study protocol (21 CFR 312.32(a)). If a determination is made that a serious adverse event has a reasonable possibility of having been caused by a study procedure or the study medication, it will be classified as a suspected adverse reaction. If the suspected adverse reaction is unexpected, it will be classified as a serious unexpected suspected adverse reaction (SUSAR).

D.1. Expedited Adverse Event Review and DSMB Notification Process

The principal investigator will be responsible for notifying the funder, the IRB, and the FDA and will follow NHLBI guidelines for reporting of adverse events, https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/nhlbi-adverse-event-and-unanticipated-problem-reporting-policy

The principal investigator will report, at a minimum:

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

D.2. Unanticipated Problems (UP)

Investigators must also report Unanticipated Problems, regardless of severity, associated with study procedures within 24 hours. An unanticipated problem is defined as follows: any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and patient notification document; and the characteristics of the subject population being studied;
- Related or possibly related to participation in the research, in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research;
- 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.

In accordance with NHLBI policy, an unanticipated problem that is not an SAE will be reported within 14 days to the DSMB, IRB, and NHLBI.

D.3. Determining Relationship of Adverse Events to Study Medication or Study Procedures

Site investigators will be asked to grade the strength of the relationship of an adverse event to study medication or study procedures as follows:

- Definitely Related: The event follows: a) A reasonable, temporal sequence from a study procedure; and b) Cannot be explained by the known characteristics of the patient's clinical state or other therapies; and c) 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 event should be assessed following the same criteria for "Definitely Associated". If in the investigator's opinion at least one or more of the criteria are not present, then "Probably or Possibly" associated should be selected.
- Probably Not Related: The 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 event is definitely produced by the patient's clinical state or by other modes of therapy administered to the patient.
- Uncertain Relationship: The event does not meet any of the criteria previously outlined.

The principal investigator will work collaboratively with the reporting investigator to determine if a serious adverse event has a reasonable possibility of having been caused by the study medication or study procedure. The principal investigator will be responsible for the final adjudication of relatedness that will be used to determine if an adverse event is reportable.

D.4. Clinical Outcomes that may be Exempt from Adverse Event 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 a reportable adverse event. For example, a cardiac arrest that the investigator considers Definitely Related to ketamine would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

D.5 Protocol Deviations and Violations

Investigators will also monitor for Protocol Deviations and Protocol Violations. Protocol Deviations and Protocol Violations are defined as follows:

- Protocol Deviation: An incident involving noncompliance with the trial protocol that typically does not have a significant effect on the subject's rights, safety, welfare, and/or the integrity of the resultant data. Deviations may result from the action of the participant, investigator, or staff.
- Protocol Violation: Accidental or unintentional changes to the IRB approved protocol procedures that affect the subject's rights, safety, welfare, and/or the integrity of the resultant data.

Protocol violations will be reported to the DSMB and IRB within 7 days of becoming aware of the event. Protocol deviations will be tracked and reported to the DSMB at the time of semi-annual meetings and to the IRB through continuing reviews.

D.6 Communication with the Funder(s)

With the support of personnel at the Coordinating Center, the investigators leading the trial will ensure that the funder(s) of the research study is/are informed in a timely manner of reporting relating to and recommendations, decisions, findings, actions, and steps taken emanating from activities relevant to the DSMP, including those from the DSMP, sIRB, FDA, and any other relevant regulatory bodies. This will include providing documentation of:

- New and continuing IRB approvals
- Approval of a DSMB charter by IRB or DSMB

- Copies of documents or materials relating to the DSMP, such as minutes of open sessions of the DSMB (upon request by the funder)
- Summary of any significant data and safety monitoring issues, including
    - Summary of reports submitted to DSMB, IRB, FDA, or other regulatory body about unanticipated problems involving risks to patients (e.g., adverse events, deviation from approved protocol that places patients at increased risk of harm, data breach, procedural or medication error)
    - Summary of any significant decisions, findings, recommendations, actions, and directions of a DSMB, IRB, FDA or other regulatory body relating to the research

With the support of personnel at the Coordinating Center, the investigators leading the trial will fulfill all reporting obligations relating to any serious unanticipated problems (e.g., serious adverse events, serious safety issues, or other serious problems) relating to the research study that are required by the funder, DSMB, IRB, FDA, or other regulatory body. The investigators and awardee institution will notify the funder within 10 days after:

- Reporting any serious unanticipated problem (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study to the DSMB, IRB, FDA, or other regulatory body
- Any decision, finding, recommendation, action, or direction of a DSMB, IRB, FDA, or other regulatory body relating to any serious unanticipated problem (e.g., serious adverse event, serious safety issue, or other serious problem) relating to the research study.

Appendix E: Long-Term Outcomes in RSI

1. Title: Effect of Ketamine and Etomidate during **RSI** on **L**ong-**T**erm **O**utcomes (**RSI-LTO**)

2. Background: One-third of adults who are intubated in the ED or ICU experience symptoms of post-traumatic stress disorder (PTSD). PTSD is a psychiatric disorder triggered by a "shocking, scary, or dangerous event."[1–4] Critical illness, tracheal intubation, and mechanical ventilation can be traumatic and distressing events. Patients may recall the intubation procedure, the feeling of the breathing tube in their throat, or being unable to move ("paralyzed"). While on the breathing machine, patients may experience delirium, frightening hallucinations, and delusions. Patients with PTSD after critical illness can be hypervigilant, anxious, and troubled by intrusive thoughts, nightmares, and flashbacks that last months to years after critical illness[5–10] and that PTSD negatively impacts patients' marriages, work, and quality of life and increases patients' risk of depression, anxiety, substance use disorder, and suicide.[2,6,10–16] Ketamine may prevent PTSD symptoms by blocking the pathways in the brain's glutaminergic system that are responsible for the formation of traumatic memories.[17–20] In outpatients with chronic PTSD, a single dose of ketamine has been shown to reduce PTSD symptoms for up to 2 weeks.[21,22] Even a modest reduction in PTSD would translate into tens of thousands of fewer cases of PTSD each year, more cases of PTSD each year than any other medical intervention evaluated to date.

3. Objective of RSI-LTO: To compare the effectiveness of ketamine vs etomidate as sedatives during tracheal intubation of critically ill adults with regard to survival and PTSD symptoms at 12-months.

4. Hypothesis of RSI-LTO: The primary hypothesis of this proposal is that patients who receive ketamine will have fewer PTSD symptoms at 12-months than patients who receive etomidate.

5. Inclusion/Exclusion Criteria for RSI-LTO:

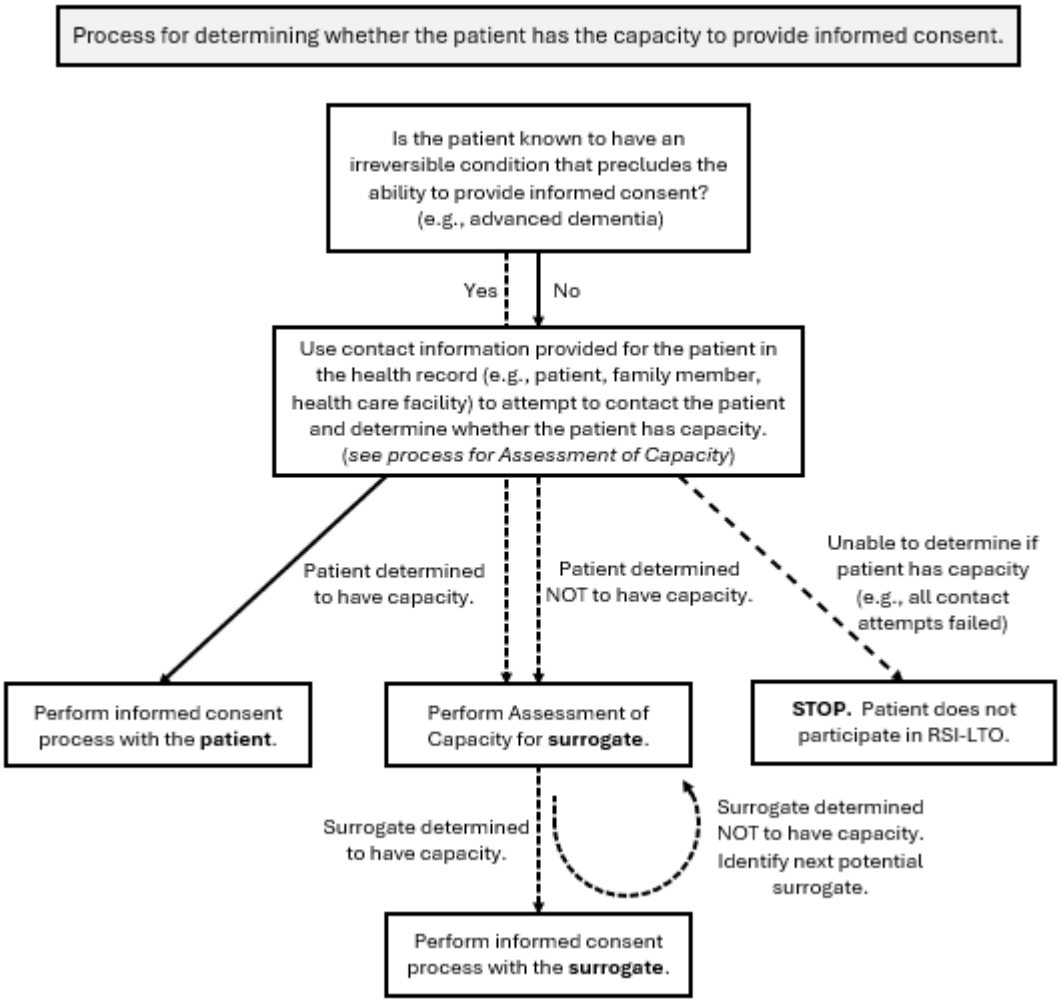
   5.1 Inclusion Criteria for RSI-LTO:
   - Enrolled in RSI trial

   5.2 Exclusion Criteria for RSI-LTO
   - Aphasic or non-verbal prior to tracheal intubation
   - Cannot follow commands prior to tracheal intubation
   - Non-English speaking
   - Deaf

6. Informed Consent for RSI-LTO: For patients who survive intubation, the research team will approach the patient or LAR for consent for collection of long-term outcomes. The research staff will review the study in lay terms and, if the patient/LAR is interested in participating in the collection of long-term outcomes, the research staff will review the informed consent document for RSI-LTO. The patient/LAR will be provided an opportunity to ask any questions.

   Patients in the hospital. Research staff will approach the patient/LAR after extubation from mechanical ventilation or shortly before hospital discharge, whichever occurs first. For patients located in the hospital at the time that the patient/LAR agrees to participate in RSI-LTO, the patient/LAR will sign the informed consent document. A copy of the informed consent document will be provided to the patient/LAR.

Patients not in the hospital. For eligible patients discharged from the hospital without an opportunity to complete an informed consent discussion for RSI-LTO (e.g., a patient discharged to post-acute care or skilled nursing facility without regaining decisional capacity and no available LAR), the patient or legally authorized representative will be contacted by phone, e-mail, or text by research staff from the site where the patient was enrolled, using a script approved by the sIRB. The script will review the details of the RSI trial and offer the opportunity to participate in the collection of long-term outcomes as part of RSI-LTO. For patients or legally authorized representatives who are potentially interested, research staff will assess decisional capacity and initiate the informed consent process. The flow diagram and figure below describe the process by which study personnel will identify who will be contacted for consent in RSI-LTO (patient or LAR) and the process by which that person will be assessed for decisional capacity.



Assessment of Capacity for a Patient or Surrogate.

To be considered to have the capacity to provide informed consent for the RSI-LTO ancillary study, we require that an individual be able to understand the basic information presented about the study, appreciate the potential risks involved, and effectively communicate this information.

After reviewing information on the RSI trial and receiving potential interest in the RSI-LTO ancillary study, study personnel will assess the capacity of the individual to provide informed consent for the RSI-LTO ancillary study by reading the IRB-approved script, reviewing the informed consent document with the individual, and then asking the following two questions:

1) "Can you tell me what the purpose of the study is?"

Correct Answer: To examine how the medicine used for placing a breathing tube affects long-term symptoms of post-traumatic stress disorder or similar outcomes.

2) "Can you tell me one risk of the study?"

Correct Answer: There is risk of loss of privacy or confidentiality.

To be considered to have the capacity to provide informed consent for the RSI-LTO ancillary study, an individual must be able to listen to the information provided about the study and communicate the correct answers to BOTH questions. Individuals who cannot achieve this will be considered not to have the capacity to provide informed consent.

Trained study personnel from the site where the patient was enrolled will complete each aspect of the informed consent process with the patient or LAR by phone, including going over the risks and benefits of participation and answering any questions. Study personnel will obtain consent from the patient or the legally authorized representative for the patient to participate in the collection of long-term outcomes. Research staff will document the informed consent process in the research record including confirmation that a reminder of the details of the RSI trial was provided, and the date, time, and identity of the person who provided the information for informed consent. A waiver of documentation of informed consent will be used and a written signature will not be obtained from the patient or legally authorized representative because:

- The long-term follow-up surveys involve no procedures for which written consent is normally required outside of the research context and pose no more than minimal risk of harm to the patient.
- Many survivors of critical illness and their surrogates are of advanced age, spend months in a long-term acute care hospital or skilled nursing facility following discharge, or have executive dysfunction and physical disability. All of these make the process of returning a written consent document to the local site by mail or eConsent challenging and even distressing to patients. In prior studies of survivors of critical illness, many patients and surrogates have reported frustration that the process of mailing the physical consent form required more time and effort than the remainder of the study, combined.

- The informed consent document contains PHI and returning a signed informed consent document by mail would increase the risk of disclosures of PHI without adding significant additional protections over an informed consent process with a waiver of documentation.

Patient compensation for RSI-LTO: Patients will be provided financial compensation for time spent participating in the collection of long-term outcomes. They will receive $80 when the 3-month follow-up visit has been completed and $100 when the 12-month follow-up has been complete.

7. Study Procedures for RSI-LTO:

7.1 Baseline Patient Interview: (In-hospital or immediately following remote consent)

7.1.1 *Demographics and Patient Characteristics.* Research staff will collect patient demographics, past psychiatric history, psychiatric medications, years of education, employment status, where they grew up, marital status, place of residence, zip code, and highest occupation from the patient or LAR. It is estimated that it will take 8 minutes to collect this data.

7.1.2 *Resiliency.* Because coping skills may be an important determinant of PTSD development, we will also collect the Brief Resilient Coping Scale (BRCS, 4 items, 2 minutes). The BRCS is a 4-item survey that asks patients questions about their ability to cope with stress.

7.1.3 *Prior traumatic experiences and psychological flexibility*. We will collect the Life Events Checklist for DSM-5 (LEC-5), a self-reported measure for potentially traumatic events in a respondent's lifetime and the Acceptance and Action Questionnaire (AAQ-2) to characterize psychological flexibility.

7.1.4 *Social Determinants of Health.* The research staff will collect social determinants of health including financial strain, social support, and social network. It is estimated that these questions will take 10 minutes to collect.

7.2 Electronic Health Record Review:

7.2.1 Baseline: Zip code, psychiatric history including PTSD, depression, bipolar disease, anxiety, and dementia; Elixhauser Comorbidity Index; psychiatric medications such as anti-depressants, mood stabilizers, and sedative hypnotics; height; weight; APACHE II score.

7.2.2 *On-study:* Electronic health record review will be conducted throughout the follow-up period to evaluate for the occurrence of delirium or coma between randomization and 14 days after randomization and to monitor for death or hospital readmissions to help coordinate follow-up phone calls. Medical record review may continue after the follow-up is completed for data cleaning and additional analyses.

7.2.3 Electronic health record review will also be conducted to obtain the patient's Social Security Number for disbursal of the compensation from the Coordinating Center, as well as evaluation of vital status using national death indices if the patient is lost to follow-up.

7.2.4 Contact information (e.g., phone number, address) by which to reach patients for the RSI-LTO surveys will be collected from the patient, LAR, family members, electronic

health record, and other publicly available data sources (e.g., internet search, intelius.com).

7.3 Outcomes for RSI-LTO (Obtained by Follow-Up Phone Interviews at 3 and 12 months):

7.3.1 Main Outcome of RSI-LTO:

- *PTSD symptoms at 12 months*: We will measure PTSD symptoms at 3 and 12 months using the Checklist for Diagnostic and Statistical Manual of Mental Disorders (DSM–5) (PCL-5). The PCL-5 is a widely used 5-10 minute patient survey validated to characterize severity of symptoms of PTSD. Patients rate 20 items corresponding to the DSM-5 criteria for PTSD on a 5-point Likert scale ranging from 0 (not bothersome) to 4 (extremely bothersome). Total scores range from 0 to 80, with higher scores indicating more severe symptoms of PTSD. We chose the PCL-5 over the Clinician Assessment of Post-Traumatic Stress Symptoms for the DSM-5 (CAPS-5) which is the "reference standard" tool for PTSD diagnosis. The CAPS-5 takes 45- to 60-minutes to complete and places significant burden on the patients who can be easily fatigued due to concurrent psychiatric comorbidities, physical disability, and cognitive impairment.

7.3.2 Additional Outcomes of RSI-LTO:

- *Awareness of paralysis, recollection of experiences, and psychological distress*: These will be determined by the modified Brice questionnaire[25–27] and ICU Memory Tool[1,2,28] (15-20 minutes). These semi-structured interviews ask subjects about their recollection of the ICU experience, including emotions, delusional memories, the worst thing experienced during mechanical ventilation, and awareness of being paralyzed. Possible awareness with paralysis event will be defined as: (1) reporting memories of the period between losing consciousness and waking up and (2) a sensation/feeling of wakeful paralysis.[29]
- *Anxiety and depression*: Generalized Anxiety Disorder-7 and Patient Health Questionnaire-9 – Multiple-choice inventories used for measuring the severity of anxiety and depression.
- *Quality of life*: EQ-5D-5L[156,157] – Quantifies quality of life by characterizing mobility, self-care, usual activities, pain/discomfort, anxiety/depression, and global health status.
- *Cognition*: MOCA-Blind[159] – Assess naming, immediate recall, attention, language, abstraction, delayed recall, and orientation. The Vigilance A task asks the patient to tap on the table when they hear the letter "A" while being given a series of letters. Because the MOCA-Blind is administered by phone, study participants will say "yes" when they hear the letter "A." Participants are told that if they hear a different letter, they will not say "yes".
- *Executive function*: Oral Trailmaking Test – Patient counts from 1 to 25 and then alternates between numbers and letters (i.e., 1-A-2-B-3-C, etc.,)
- *Employment*: Employment Questionnaire – A 15-item survey characterizing current level of employment (full, partial, or not employed).
- *Physical disability (collected at 12 months only):* Duke Activity Status Index (DASI) – An 11-item survey that assesses the patient's current ability to perform various physical activities.

- *Vital Status*: Date and location of death will be assessed from enrollment until 12 months after enrollment by trial personnel using review of electronic health records, phone calls with families, and national death indices.

8. Risks: The collection of long-term outcomes represents minimal risk to patients. However, there are some risks to the data collection. There is a small risk that a patient enrolled in may become fatigued or distressed during the study assessments. In these cases, we will immediately stop the assessment and give the patient an opportunity to rest. Afterwards, we will ask the patient if we can continue with the assessments or if we should reschedule the phone-call. Occasionally, patients or families may get frustrated and distressed if the patient is unable to perform the cognitive tasks. We will reassure them that these tasks can be difficult to perform, and that such difficulties are common. If the patient or his or her family continue to be distressed after this reassurance, we will skip that particular task or stop the assessment altogether.

Patients will be asked to recall their memories of the traumatic experiences during their lifetime and the ICU experience. Some of these memories may be distressful and cause patients to become tearful, angry, frightened, or agitated. In these cases, we will immediately stop the assessment and give the patient an opportunity to collect themselves. If necessary, we will stop the interview and contact them at a later time.

Because patient identifiers are accessed throughout all phases of the study, there is a small risk of loss of patient confidentiality. Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all paper-based evaluation forms and reports will be identified only by a coded number. All paper case report forms will be maintained inside a locked office. All related participant study records will be kept in a locked, password protected computer. Only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All statistical analyses will use de-identified data only. Patient name, address, phone number and medical record number will be collected from the electronic medical record to facilitate follow-up and patient re-imbursement. These data will be stored in a secure, password-protected database only accessible to the study team. These patient identifiers will be deleted once all study assessments has been completed and subject has been financially reimbursed.

9. Safety of Participants with Suicidal Ideation: During follow-up phone call, patients will be asked questions about their psychological being. In the very rare event that patients express thoughts about suicide (e.g., suicidal ideation), the research team will instruct the patient to do the following:

- For patients who are expressing active suicidal ideation and are at highest risk for causing imminent harm requiring immediate assistance, patients will be instructed to call 911 or drive to the nearest ED. The local police may be called, especially if the patient refuses to seek help.
- For those who have a mental health provider, they will be instructed to contact them by phone immediately.
- If the patient does not have a mental health provider and does not require immediate assistance, they will be instructed to call one of the following 24/7 resources:

- National Suicide Prevention Lifeline:
  - Phone: 800-273-8255 or 988
  - Website: https://suicidepreventionlifeline.org
- SAMHSA National Helpline
  - Phone: 800-662-HELP (800-662-4357)
  - Website: https://www.samhsa.gov/find-help/national-helpline
- Local mobile crisis

For all high-risk patients, one of the members from the Critical Illness, Brain Dysfunction, and Survivorship Center (CIBS) neuropsychology core, Dr. Han (PI) or a delegate will contact the patient within one day to do a "well check" and ensure that the patient received the appropriate resources. If the patient cannot be reached for this "well check," the local police may be called.

To ensure appropriate resources are provided for patients found to have severe PTSD or depression, we will do the following:

- We will collect information on whether patients received a new diagnosis or treatment of PTSD, depression, or anxiety or saw a therapist, social worker, psychologist, or psychiatrist since they were placed on the breathing machine.
- For patients with severe PTSD or depression, a CIBS social worker, neuropsychologist, or investigator (Drs. Jackson or Han) will call the patient. He/she will instruct the patient to make an appointment with their psychiatrist. If they do not have a psychiatrist, then they will be instructed to see their primary care provider. They will be directed to www.icudelirium.org that has resources for ICU survivors who are suffering from PTSD and depression. If requested, the CIBS social worker will help connect them to a local resource to assist them with their PTSD or depression symptoms. If needed, a CIBS neuropsychologist may offer a one-time consultation.

10. Communication of Participant Results: The cognitive and psychological tests conducted in RSI-LTO are screening tests and not diagnostic tests. Further, the results of screening tests suggesting possible cognitive impairments or psychiatric disease may in themselves be distressing to patients and families, particularly given the absence of available treatments for many of the conditions being evaluated (e.g., cognitive impairments and dementia). We, therefore, do not plan to routinely provide the results of screening tests to patients. However, if patients request the results of testing, they will be provided, and investigators will emphasize that the study measures are screening tests and patients should follow up with their medical providers for a more detailed evaluation.

11. Study Withdrawal/Discontinuation: If the patients does not meet eligibility criteria for RSI-LTO or the patient or caregiver declines participation in RSI-LTO, they will not be included in RSI-LTO. If a patient who has agreed to participate in RSI-LTO elects to discontinue taking part in the RSI-LTO, they can inform the research staff of their wish to withdraw. At that time, no further data will be collected on the patient. All health data previously collected before they withdraw their consent will still be used for reporting and research quality. As suggested in federal regulations, the study team may access data about the patient's death from public vital statistics records and other public records not subject to restriction under 21 CFR 50.24 or other FDA regulations.

Participants who become incarcerated during the follow-up period: As required by the U.S. Department of Health and Human Services, study staff will cease all research interactions and interventions, including collection of identifiable private information, if informed that a study participant has become incarcerated during the 12-month follow-up period. The patient will also be withdrawn from the RSI-LTO study.

12. Statistical Considerations:

12.1 PTSD symptoms (Main Outcome of RSI-LTO): We will compare PTSD symptoms at 12 months between groups using participants' scores on the PCL-5 as an ordinal variable from 0 (no symptoms) to 80 (most severe symptoms). Because a value for the PCL-5 score will not exist for patients who die prior to assessment, our main analysis will use a composite endpoint approach where we will assign patients whose PCL-5 could not be assessed because they died a value of 81 (higher than the worst value on the PTSD symptom scale). We will consider death a worse outcome than being alive with severe PTSD because: [1] 60-80% of patients with PTSD eventually experience full recovery[30] and [2] our stakeholders with PTSD unanimously felt that, despite their symptoms, it was still better to have survived. Our main analysis will compare the PCL-5 at 12 months between patients randomized to ketamine vs patients randomized to etomidate using a partial proportional odds model to permit separate estimates of the effect of ketamine vs etomidate on (1) death and (2) symptoms of PTSD. The partial proportional odds model is a flexible regression model that estimates the treatment effect separately for each of the ordinal outcome categories (i.e., relaxes the proportional odds assumption). For the partial proportional odds model, the PCL-5 scores will be categorized to create the ordinal outcome variables as in the following groupings of values: 0, 1-5, 6-10, 11-15, 16-20, 21-25, 26-30, 31-35, 36-40, 41-45, 46-50, and ≥50 (and death). The reason for groupings of 5 values is that serial changes in individuals of ≥5 on the PCL-5 total score are considered reliable.[31] The reason for grouping all values of 50 or greater is that less that too few patients (<5%) have values in this range to allow smaller groupings. We will perform additional sensitivity analyses. First, we will compare the outcome between trial groups using an unadjusted Wilcoxon Rank Sum Test. Second, we will perform a proportional odds mixed effects model with a random effect for site and fixed effects for trial group and pre-specified covariates: age; sex; race; ethnicity; neighborhood disadvantage;[32] rurality;[33] Elixhauser comorbidity index;[34] pre-enrollment PTSD; pre-enrollment depression, anxiety or bipolar disorder; and APACHE II score. We will also compare PTSD symptoms between groups in survivors-only analysis both unadjusted and adjusting for the above variables plus baseline measures of traumatic experiences (LEC-5), resilience (Brief Resilient Coping Scale), and the social determinants of health in Figure 9. Finally, we will perform Survivor Average Causal Effect analysis[35] and compare PTSD diagnosis using generalized linear models.

12.2 Additional RSI-LTO Outcomes: We will perform intention-to-treat comparisons of additional RSI-LTO 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.

13. Communication with Patients in RSI-LTO: Patients who consent to participate in RSI-LTO will receive an IRB-approved post-card with general information about the RSI-LTO study at the time of

consent to participate in RSI-LTO and by mail one month prior to the 12-month follow up assessment.

14. Return of Aggregate Results in RSI-LTO: We will keep participants informed of any preliminary results through an newsletter, distributed electronically or in paper format, depending on the participant's stated communication preferences. We will continue to distribute the newsletter to all participants (except those who opt not to receive it) until final results are available, at which point, we will provide a lay-person summary of results to that will be made available to participants via the final newsletter, by email or text, by mail, and through the study's website and twitter account.

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Appendix F: Analyses of Heterogeneity of Treatment Effect.

Our analyses of heterogeneity of treatment effect ("individualized treatment effect") will adhere to published standards[1] and the Predictive Approaches to Treatment Effect Heterogeneity (PATH) guidelines.[2] The goal of our analyses will be to provide estimates of the effect of ketamine vs etomidate on [1] "mortality by 1 month (28 days)" and [2] "PTSD symptoms at 12 months" for an individual patient, considering all of the patient's characteristics simultaneously.[2,3] Our analyses will use a computational pipeline that incorporates careful cross-validation to prevent overfitting and optimizes information content. First, in a derivation cohort of the first 1,700 patients enrolled in the RSI trial, we will compare the performance of candidate effect models using 5-fold cross-validation. Specifically, we will consider X-learners with elastic net and random forest base-learners, S-learners with random forest and conditional random forest (cforest) base-learners, T-learner with Bayesian Adaptive Regression Trees (BART) as the base-learner, R-learner with Extreme Gradient Boosting (Xgboost) as the base-learner, and causal forest. The algorithm and base-learner combination resulting in the highest qini coefficient in the out-of-sample predictions from the 5-fold cross-validation will then be fit using all the derivation data to create a final effect model. Second, in a validation cohort of the final 664 patients enrolled, we will validate the performance of the individualized treatment effect model. To do this, we will use the model to predict the effect of ketamine vs etomidate on 28-day in-hospital mortality for each of the 664 patients in the validation cohort (the patient's predicted individualized treatment effect at the time of enrollment). We will compare the treatment effect predicted by the model to the treatment effect observed in the validation cohort, using the adjusted Qini coefficient,[4] the C statistic for benefit,[5] and measures of clinical utility, in alignment with the PATH guidelines (examining characteristics by quartile of predicted benefit). We will evaluate the credibility of any effect modification using rigorous, multidimensional criteria,[6] including examination of alignment with the hypothesis, prior evidence, and the number of tests being performed. Third, once models for estimating the effect of ketamine vs etomidate on "mortality by 1 month" and "PTSD symptoms at 12 months" for individual patients based on their unique characteristics have been derived and validated, we will disseminate the full models and make available a simplified online calculator for the predicted treatment effect for a future patient. We also will disseminate a simplified tree diagram that clinicians can print and use at the bedside to rapidly select the best sedative medication for a future patient based on his or her characteristics. We will report all prespecified and post hoc analyses. The effect-modeling analyses may be presented separately from the other trial results if the time required to conduct them or the space required to present them requires doing so.

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Summary of changes to the RSI trial protocol

Protocol Version 1.0
Date: March 9, 2022
Initial protocol

Protocol Version 1.1
Date: May 23, 2022
Purpose: This amendment is to add additional details regarding the approach to notifying, at the earliest feasible opportunity, each patient, or if the patient remains incapacitated, a legally authorized representative of the patient, or if such a representative is not reasonably available, a family member, of the patient's inclusion in the study. This amendment also describes the approach to obtaining prospective informed consent to be contacted for potential participation in ancillary trials.

Protocol Version 2.0
Date: October 18, 2023
Description: This amendment triggers Stage 2 (multi-center) of the RSI trial, following the receipt of funding for Stage 2 of the RSI trial from PCORI, and includes revisions to the protocol to align with the grant approved by PCORI. Major changes made in version 2.0 of the grant include:

- Activation of Stage 2 with pre-planned prioritization of Stage 2 outcomes (primary outcome: mortality at 1 month [28 days]) and removal of stage 1 analyses that will not be conducted with the activation of stage 2.
- Increased sample size of 2,364 patients based on updated power calculation and input from stakeholders regarding the minimum clinically important difference. Sample size at which single pre-specified interim analysis would occur was updated to remain at 50% of total enrollment (1,182 patients).
- The process for pre-enrollment opt-out was updated for operationalization at additional sites in Stage 2 (multi-center stage) of RSI.
- Primary outcome changed to a generalized linear mixed effects model with a random effect for study site (e.g., Vanderbilt University ED, Vanderbilt University Medical ICU) and a fixed effect for group assignment (ketamine group vs etomidate group) and subgroup analysis updated to include a random effect for study site to match the primary analysis.
- Addition of a plan to approach intubation survivors for consent to collect long-term outcomes.
- Removal of example notification forms (following review and approval by IRB).
- Replacement of the section "Consent to be Contacted for Ancillary Studies" by Appendix E describing the plan for collection of long-term outcomes.

Protocol Version 2.1
Date: April 30, 2024
Description: This amendment is to make minor revisions to secondary analyses to match the research plan approved by the funder, clarify plans regarding enrollment of ineligible patients, add definitions for protocol deviations and protocol violations, and add detail regarding the provision of resources to patients participating with RSI-LTO who are found to have non-life-threatening psychiatric issues such as severe PTSD or depression. These changes include:

- Revising the covariates that will be included in the adjusted analysis of the primary outcome (a secondary analysis).
- Adding details of a planned analysis of Heterogeneity of Treatment Effect ("Individualized Treatment Effect") for the short- and long-term outcomes as a new appendix (Appendix F).
- Adding definitions and reporting plans for protocol deviations and violations and details of the plan for communication to the funder to Appendix D.
- Adding details regarding how patients who are found to be prisoners will be identified and withdrawn from the study.
- Describing what information will be collected during follow-up phone calls about patients with a new diagnosis of PTSD, depression, or anxiety, and the resources that will be provided to them.

Protocol Version 2.2
Date: March 7, 2025
Description: This amendment is (i) to make minor revisions to secondary analyses to match the final trial statistical analysis plan at the time of its submission for publication and (ii) to revise the trial protocol to permit Waiver of Documentation of informed consent for patients discharged from the hospital who have completed an informed consent discussion and consent to participate but for whom receiving, signing, and returning by mail the informed consent document would be logistically burdensome and increase the risk of disclosure of PHI.

Protocol and Statistical Analysis Plan for the Randomized Trial of Sedative Choice for Intubation (RSI)

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Take-Home Points

Study Question: Does use of ketamine for induction of anesthesia during emergency tracheal intubation decrease the incidence of death, compared with use of etomidate?

Results: This manuscript describes the protocol and statistical analysis plan for the Randomized trial of Sedative choice for Intubation (RSI) comparing ketamine vs etomidate for induction of anesthesia for emergency tracheal intubation.

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

ABSTRACT

Background: Emergency tracheal intubation is a common and high-risk procedure. Ketamine and etomidate are sedative medicines commonly used to induce anesthesia for emergency tracheal intubation, but whether the induction medication used affects patient outcomes is uncertain.

Research Question: Does the use of ketamine for induction of anesthesia decrease the incidence of death among adults undergoing emergency tracheal intubation, compared to the use of etomidate?

Study Design and Methods: The Randomized trial of Sedative choice for Intubation (RSI) is a pragmatic, multicenter, unblinded, parallel-group, randomized trial being conducted in 14 sites (6 emergency departments and 8 intensive care units) in the United States. The trial compares ketamine vs etomidate for induction of anesthesia among 2,364 critically ill adults undergoing emergency tracheal intubation. The primary outcome is all-cause, 28-day in-hospital mortality. The secondary outcome is the incidence of cardiovascular collapse during intubation, a composite of hypotension, receipt of vasopressors, and cardiac arrest. Enrollment began on April 6, 2022, and is expected to conclude in 2025.

Interpretation: The RSI trial will provide important data on the effects of ketamine vs etomidate on death and other outcomes for critically ill adults undergoing 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.: NCT05277896; URL: www.clinicaltrials.gov

INTRODUCTION

Millions of critically ill adults undergo emergency tracheal intubation every year worldwide,[1] approximately 30% of whom die before hospital discharge.[2,3] Nearly all patients undergoing emergency tracheal intubation in an emergency department (ED) or intensive care unit (ICU) receive a medication to induce anesthesia for the procedure.[4,5] Whether the medication used to induce anesthesia affects patient outcomes is uncertain.

Etomidate, an imidazole-derived, sedative-hypnotic agent that produces anesthesia by acting on gamma-aminobutyric acid (GABA) receptors, is the medication most often used to induce anesthesia during emergency tracheal intubation in some EDs and ICUs.[5–9] Etomidate has been described as an "ideal" medication for induction of anesthesia in critically ill adults because of its rapid onset, short duration of action, and limited effect on blood pressure.[10] However, etomidate inhibits 11-β-hydroxylase in the adrenal glands, which decreases cortisol production and causes adrenal insufficiency for 24 to 72 hours.[11–14] Among critically ill adults, many of whom experience critical illness-related corticosteroid insufficiency from sepsis or other causes,[15–18] etomidate-induced adrenal insufficiency has been hypothesized to be associated with organ dysfunction and death.[6]

Ketamine, a dissociative agent that produces anesthesia by acting on N-methyl-D-aspartate (NMDA) receptors, is the medication most often used to induce anesthesia during emergency tracheal intubation in some EDs and ICUs.[8,19] In contrast to etomidate, ketamine increases cortisol production.[20,21] However, while ketamine generally increases blood pressure by stimulating the release of catecholamines,[22] it is

a direct negative inotrope[23–26] and has been reported to precipitate rare episodes of severe hypotension[8,27–29] or even cardiac arrest, particularly among critically ill patients who have depleted their stores of endogenous catecholamines.[28,30]

Previous small-to-moderate sized randomized trials comparing ketamine and etomidate for emergency tracheal intubation have reported conflicting results, with some finding that use of ketamine decreased short-term mortality[28,31] and others finding no significant differences in outcomes.[32–34] Currently, whether use of ketamine decreases mortality for critically ill adults undergoing emergency tracheal intubation compared to use of etomidate remains uncertain.

To address this uncertainty, we designed the Randomized trial of Sedative Choice for Intubation (RSI), which will compare ketamine vs etomidate for induction of anesthesia among 2,364 adults undergoing emergency tracheal intubation. We hypothesize that use of ketamine will decrease the incidence of death, compared to etomidate.

STUDY DESIGN AND METHODS

This article was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Table 1 and Section 2 of e-Appendix 1).[35]

Engagement of Patients, Families, and Community Members

Detailed information on engagement with survivors of emergency tracheal intubation, family members, and community members in each phase of the design and conduct of the RSI trial are summarized in Section 3 of e-Appendix 1.

Study Design

RSI is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing the use of ketamine versus etomidate for induction of anesthesia in 2,364 critically ill adults undergoing emergency tracheal intubation in 14 sites (6 EDs and 8 ICUs) in the United States. The primary outcome is all-cause, 28-day in-hospital mortality. The trial is being conducted by the Pragmatic Critical Care Research Group (www.pragmaticcriticalcare.org). The trial was registered prior to initiation of enrollment (ClinicalTrials.gov identifier: NCT05277896).

Ethics and Regulatory Approval

The RSI trial protocol was approved by the institutional review board (IRB) at Vanderbilt University Medical Center (IRB number: 210500) and the US Food and Drug Administration (FDA) (IND 141424).

The study is being conducted with Exception from Informed Consent Requirements for Emergency Research (EFIC) (21 CFR 50.24).[36] Plans for community consultation and public disclosure were approved by the single IRB at Vanderbilt University Medical Center. The IRB of each participating site provided local context for the community consultation and public disclosure plan and activities.

Whenever feasible, patients or their legally authorized representatives (LAR) are approached by research personnel to provide prospective, written informed consent to participate in the trial. When prospective, written informed consent is infeasible, patients are enrolled under EFIC and the patient, the patient's LAR, or a family member is notified of enrollment in the trial at the earliest feasible opportunity (additional details in Section 4 of e-Appendix 1).

Study Population

Critically ill adults undergoing emergency tracheal intubation with sedation in a participating unit are potentially 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 ketamine or etomidate 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 clinician performing the tracheal intubation procedure (referred to as 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 and randomized once the operator opens the trial envelope to reveal study group assignment. After

randomization, patients, clinicians, and study personnel are not blinded to trial group assignment.

STUDY INTERVENTIONS

Ketamine group

For patients in the ketamine group, clinicians are instructed to administer ketamine intravenously to induce anesthesia for emergency tracheal intubation. The dose of ketamine is determined by the clinicians based on the clinical condition of the patient. A nomogram on the study group assignment sheet provides clinicians with doses of ketamine (in milligrams) that correspond to a full dose (2.0 mg/kg), an intermediate dose (1.5 mg/kg), and a reduced dose (1.0 mg/kg) for a range of patient weights (see Section 5 of e-Appendix 1).[37]

Etomidate Group

For patients in the etomidate group, clinicians are instructed to administer etomidate intravenously to induce anesthesia for emergency tracheal intubation. The dose of etomidate is determined by the clinicians based on the clinical condition of the patient. A nomogram on the study group assignment sheet provides clinicians with doses of etomidate (in milligrams) that correspond to a full dose (0.3 mg/kg), an intermediate dose (0.25 mg/kg), and a reduced dose (0.2 mg/kg) for a range of patient weights (see Section 6 of e-Appendix 1).

Co-Interventions

The RSI trial determines only the sedative medication administered for induction of anesthesia during the emergency tracheal intubation procedure. Subsequent boluses or infusions of sedative medications are determined by clinicians. Other aspects of emergency tracheal intubation (e.g., pre-intubation fluid and vasopressor management, choice of neuromuscular blocking medication) are determined by treating clinicians according to clinical protocols in the study units. Co-interventions that could potentially modify the effect of ketamine or etomidate on patient outcomes (e.g., administration of corticosteroids after intubation) are prospectively recorded.

Data Collection

An observer not directly involved with the intubation procedure collects data in real time for key periprocedural outcomes, including oxygen saturation and systolic blood pressure at the time of induction and lowest oxygen saturation, lowest systolic blood pressure, and administration of vasopressors between induction and two minutes after intubation. Observers are either research personnel or trained clinical personnel (e.g., physicians or nurses). The accuracy of this method of data collection has been validated previously[38] and used in numerous previous trials of emergency tracheal intubation.[3,5,7]

Immediately after the intubation procedure, the operator completes a paper data collection form to record characteristics of the procedure (e.g., Cormack-Lehane grade of glottic view[39]), complications during intubation (e.g., cardiac arrest), and the operator's prior intubating experience. Study personnel at each site review the

electronic health record to collect data on baseline characteristics, management before and after laryngoscopy, and in-hospital clinical outcomes such as systolic blood pressure at 24 hours after induction, receipt of vasopressors at 24 hours after induction, ventilator duration, and mortality. Study personnel collect information on mortality occurring after hospital discharge from the electronic health record, public vital statistics records and other public records, and phone calls with patients participating in the long-term outcome assessments at 3 and 12 months (the results of the long-term outcome assessments will be reported separately).

Primary Outcome

The primary outcome is all-cause, 28-day, in-hospital mortality, defined as death from any cause occurring between enrollment and 28 days after enrollment with outcome ascertainment ending at hospital discharge.

Secondary Outcome

The sole secondary outcome is cardiovascular collapse, defined as the occurrence of any of the following between induction and 2 minutes after intubation: (1) systolic blood pressure < 65 mmHg; (2) new or increased vasopressors; (3) cardiac arrest not resulting in death within 1 hour of induction; (4) cardiac arrest resulting in death within 1 hour of induction.

Procedural, Clinical, and Safety Outcomes

Table 3 reports the exploratory procedural outcomes, exploratory clinical outcomes, and safety outcomes. Definitions of free-day outcomes are included in Supplemental Section 7 of e-Appendix 1.[5,7]

Long-term Outcomes

The definitions, collection, and analysis of survival and functional outcomes (e.g., symptoms of post-traumatic stress disorder) at 3 months and 12 months will be prespecified in a separate statistical analysis plan. Because these outcomes will not be available for more than a year after completion of enrollment in the trial, these long-term outcomes have been registered separately (NCT06179485) and will be reported separately from the 28-day outcomes described in this statistical analysis plan.

Data and Safety Monitoring Board

The composition and responsibilities of the Data and Safety Monitoring Board (DSMB) are described in Section 8 of e-Appendix 1. 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.

Trial Stages

The RSI trial was funded in two stages. First, the single-center, feasibility stage of the trial was funded by an award from the National Heart Lung and Blood Institute (K23HL153584). Second, the multicenter stage of trial was funded by a contract from

the Patient-Centered Outcomes Research Institute® (BPS-2022C3-30021). The initial trial protocol specified both stages of the trial and the criteria that had to be met to transition from the single-center stage to the multicenter stage. On August 1, 2023, the DSMB (i) reviewed information on funding for the multicenter stage, (ii) reviewed data on enrollment rate, adherence to trial procedures, and completeness and quality of trial data from the single-center stage, and (iii) approved transition to the multicenter stage of the trial. Neither the DSMB nor the investigators reviewed any analysis of trial outcomes as part of the transition between stages.

Interim Analysis

On January 7, 2025, the DSMB reviewed a single interim analysis, prepared by the unblinded study biostatistician at the anticipated halfway point of the trial after enrolment of 1,182 patients. The pre-specified stopping boundary for efficacy was a P value < 0.001 for the difference between trial groups in the primary outcome using a generalized linear mixed effects model with a random effect for study site and a fixed effect for group assignment (ketamine group vs etomidate group). 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). After reviewing the interim analysis, the DSMB recommended continuing the RSI trial without modification.

Sample Size Estimation

The final sample size for the RSI trial was calculated at the time of receipt of funding for the multicenter stage of the trial from PCORI® (details of the initial sample size calculation are provided in Section 9 of e-Appendix 1). Based on prior trials in the same settings,[5,7] we estimated that the incidence of all-cause, 28-day in-hospital mortality (primary outcome) in the etomidate group would be 30%. The patient and clinician partners recommended that the trial should have adequate statistical power to detect an absolute difference between groups in mortality of approximately 5 percentage points. This difference is more conservative than the median of 8 percentage points (interquartile range, 6-10) used as the minimum clinically important difference in the design of prior randomized trials in critical care[40] and is smaller than the observed difference in mortality between ketamine and etomidate of 6-7 percentage points observed in two previous trials.[28,32] We used the *bsamsize* R function to calculate that achieving 80% statistical power at a two-sided alpha of 0.05 to detect a difference in mortality of 5.2 percentage points (30.0% in the etomidate group vs 24.8% in the ketamine group) would require enrollment of 2,308 patients. Anticipating that, like previous EFIC trials,[41] less than 3% of participants would discontinue follow up before ascertainment of the primary outcome, we planned to enroll a total of 2,364 patients (1,182 per group).

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. Continuous variables will be presented as mean ± SD or median (interquartile range). 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 analyses of secondary and exploratory, emphasis will be placed on the magnitude of differences between groups with 95% confidence intervals, rather than statistical significance. Templates for the tables that will be presented in the results manuscript and supplement for baseline, periprocedural, and in-hospital outcome variables are provided in Supplementary Tables 1-3 in e-Appendix 1.

Main Analysis of the Primary Outcome

The primary analysis will be an intention-to-treat comparison of patients randomized to the ketamine group versus patients randomized to the etomidate group with regard to the primary outcome of all-cause, 28-day in-hospital mortality among all patients in the trial population except those who withdrew from follow up prior to ascertainment of the primary outcome. The primary outcome will be compared between the two trials groups using a generalized linear mixed effects model with a random effect for study site and a fixed effect for group assignment (ketamine group vs etomidate group). The absolute difference in percentages, associated 95% confidence intervals, and a P value for the comparison will be presented. A rationale for the primary outcome and its analysis can be found in Section 10 of e-Appendix 1.

Additional Analyses of the Primary Outcome

Sensitivity Analyses

We will assess the robustness of the findings of the primary analysis in a series of sensitivity analyses using different approaches to defining and analyzing the primary outcome. First, we will repeat the primary analysis among all patients in the trial population, with patients who withdrew from follow up prior to outcome ascertainment treated as (i) all having experienced the primary outcome or (ii) all having not experienced the primary outcome. Second, we will repeat the primary analysis using all-cause, all-location mortality at 28 days (i.e., including available information on deaths that occur after hospital discharge). Third, we will repeat the primary analysis using a Chi-square test rather than a generalized linear mixed effects model. Fourth, we will compare survival to day 28 between trial groups using the Kaplan-Meier method. Fifth, we will perform an adjusted analysis comparing the primary outcome between groups using a generalized linear mixed effects model with a random effect for trial site and fixed effects for trial group assignment and the following pre-specified baseline variables: age; sex; race; ethnicity; area deprivation index (a proxy for socioeconomic status and an indicator of neighborhood disadvantage);[42] rurality;[43] number of comorbidities; and pre-enrollment severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation II score.[44] Continuous variables will be modelled assuming a non-linear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Analyses of heterogeneity of treatment effect

Heterogeneity of treatment effect is nonrandom variation in the magnitude or direction of the effect of a treatment on an outcome across levels of a baseline covariate. We will apply the three complementary approaches to analysis of heterogeneity of treatment effect described in the Predictive Approaches to Treatment effect Heterogeneity Statement: (1) traditional one-variable-at-a-time subgroup analyses; (2) a risk-modeling approach; and (3) an effect-modeling approach.[45] Complete details of all three approaches are described in Section 11 of e-Appendix 1.

Our subgroup analyses will examine whether prespecified baseline variables modify the effect of trial group assignment 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, a random effect for trial site, and independent variables of trial group, the proposed effect modifier, and the interaction between the effect modifier and trial group for each of the following prespecified baseline variables:

1. Sepsis or septic shock (Yes / No)
2. Vasopressor receipt (Yes / No)
3. Patient location (ED / ICU)
4. Adrenal insufficiency or chronic receipt of corticosteroids (Yes / No)
5. Acute neurologic condition (Yes / No)
6. Active cardiac condition (Yes /No)
7. Baseline risk of the primary outcome (continuous)

Analysis of the Secondary Outcome

We will perform an unadjusted, intention-to-treat comparison of patients randomized to the ketamine group versus patients randomized to the etomidate group with regard to the secondary outcome of cardiovascular collapse. A Chi-square test will be used to generate between-group differences and the associated 95% confidence intervals.

Analyses of Additional Outcomes:

We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the ketamine group versus patients randomized to the etomidate group with regard to each pre-specified exploratory procedural outcome, exploratory clinical outcome, and safety outcome. Between-group differences and the associated 95% confidence intervals will be generated using a Chi-square test for categorical outcomes and a Wilcoxon rank-sum test for continuous outcomes.

Handling of Missing Data

We anticipate that no data on the primary outcome will be missing except for patients who withdrew from participation prior to the collection of the primary outcome. When data are missing for an outcome, we will perform complete-case analysis, excluding cases where the data for the analyzed outcome are missing. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

Discussion

This article reports the rationale, design, and analysis plan for the RSI trial, a 2,364-patient randomized trial of ketamine vs etomidate for induction of anesthesia among critically ill adults undergoing emergency tracheal intubation. Several elements of the trial's design warrant discussion.

The RSI trial was designed to compare ketamine vs etomidate and does not examine other medications capable of inducing anesthesia for emergency tracheal intubation, such as propofol or benzodiazepines. These comparators were selected for several reasons. First, ketamine and etomidate are the medications most often used for emergency tracheal intubation in many EDs[8] and ICUs[6], particularly in the US.[3,46–51] Second, ketamine and etomidate are the only medications consistently used for emergency tracheal intubation in clinical care at the 14 sites participating in the trial.[5,7,19] Third, although propofol and benzodiazepines are more commonly used by some clinical specialties (e.g., anesthesiologists)[52,53] and in some clinical settings (e.g., some ICUs outside of the US),[4] observational studies have consistently reported these medications to be associated with higher rates of hypotension during intubation, particularly for patients with pre-existing hemodynamic instability.[4,54] We anticipate that approximately 1-in-4 patients in the RSI trial will be receiving vasopressors before enrollment. Thus, we designed the trial to compare two medications with a hemodynamic profile that permits their use for nearly all critically ill adults, including those with hypotension or shock prior to intubation.

In the RSI trial, clinicians determine what dose of the assigned sedative medication each patient receives based on the clinical condition of the patient using a

dosing nomogram provided by the trial. The nomogram specifies 2 mg/kg of ketamine and 0.3 mg/kg of etomidate as a "full dose". These are the doses specified in the US FDA labeling information for the induction of anesthesia.[37,55] These are also the doses used in two of the largest previous randomized trials comparing ketamine vs etomidate among critically ill adults.[28,32] For patients who clinicians determine require a lower dose, the nomogram also provides information on an intermediate dose (1.5 mg/kg of ketamine or 0.25 mg/kg of etomidate) and a reduced dose (1.0 mg/kg of ketamine or 0.2 mg/kg of etomidate) across a range of patient weights.

The design of the RSI trial differs from that of previous trials comparing ketamine vs etomidate in several respects. First, the planned sample size of 2,364 patients is almost three times as large as any prior trial and will permit more precise estimates of treatment effect.[28,32,33,56] Second, unlike prior trials that excluded patients intubated in the ED,[28] excluded patients intubated in the ICU,[33] or enrolled only patients with sepsis,[56] the RSI trial includes a broad range of patients undergoing emergency tracheal intubation in an ED or ICU, which increases generalizability.[56] The only diagnosis excluded from the RSI trial is patients presenting to the emergency department with a primary diagnosis of trauma. Because some prior data suggested that ketamine might increase intracranial pressure[57] and results of one prior trial suggested a potential difference in treatment effect between patients with and without trauma,[32] we determined that the effect of ketamine vs etomidate on outcomes for patients presenting with trauma was best evaluated in a separate trial. Third, unlike prior trials that did not collect procedural outcomes[32] or long-term patient-centered outcomes,[28,32,33,56] the RSI trial collects physiological outcomes during the procedure

(e.g., cardiovascular collapse during intubation), short-term patient-centered outcomes (e.g., death by day 28), and long-term patient-centered outcomes (e.g., survival and symptoms of post-traumatic stress disorder at 12 months).

Interpretation

The RSI trial will provide important evidence regarding the effect of ketamine vs etomidate on death and other clinical outcomes among critically ill adults undergoing emergency tracheal intubation in an ED or ICU. To aid in the transparency and interpretation of trial results, this manuscript detailing the protocol and statistical analysis plan for the RSI trial has been finalized prior to the conclusion of patient enrollment.

Abbreviations

DSMB: Data and Safety Monitoring Board

ED: Emergency Department

EFIC: Exception from Informed Consent Requirements for Emergency Research

FDA: Food and Drug Administration

ICU: Intensive Care Unit

IRB: Institutional Review Board

LAR: Legally Authorized Representative

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Table 1: Schedule of Enrollment, Interventions, and Assessments in the RSI trial. Information on the collection of outcomes at 3 and 12 months will be reported in a separate statistical analysis plan. Table entries without data mean that data elements were not collected at that time. RSI = Randomized trial of Sedative Choice during Intubation.

	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	28 days
Enrollment:							
Eligibility screen	**X**						
Enrollment		**X**					
Allocation		**X**					
Interventions:							
Ketamine			**X**				
Etomidate			**X**				
Screening for contraindications	**X**	**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**	**X**

Table 2: Inclusion and Exclusion Criteria.

Inclusion Criteria
Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit
Planned procedure is orotracheal intubation using a laryngoscope
Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
Exclusion Criteria
Patient is known to be less than 18 years old
Patient is known to be pregnant
Patient is known to be a prisoner
Patient is known to have an allergy to ketamine or etomidate
Patient is presenting to the emergency department with a primary diagnosis of trauma
Patient or LAR declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI trial
Clinician feels ketamine is required or contraindicated for the optimal care of the patient
Clinician feels etomidate is required or contraindicated for the optimal care of the patient
Clinician feels an induction medication other than ketamine or etomidate is required for the optimal care of the patient
Immediate need for intubation precludes safe performance of study procedures

Table 3: Study outcomes

Primary Outcome	All-cause, 28-day, in-hospital mortality
Secondary Outcome	Cardiovascular collapse, a composite of any of the following between induction and 2 minutes after intubation: (1) systolic blood pressure < 65 mmHg; (2) new or increased vasopressors; (3) cardiac arrest not resulting in death within 1 hour of induction; (4) cardiac arrest resulting in death within 1 hour of induction.
Exploratory Procedural Outcomes	Cormack-Lehane Grade of glottic view
	Successful intubation on the first attempt, defined as placement of an endotracheal tube in the trachea with a single insertion of a laryngoscope blade into the mouth and EITHER a single insertion of an endotracheal tube into the mouth OR a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube over the bougie into the mouth.
	Time from induction to successful tracheal intubation
	Lowest oxygen saturation between induction and two minutes after intubation
	Lowest oxygen saturation < 80% between induction to two minutes after intubation
	Highest and lowest systolic blood pressure from induction to two minutes after intubation
	Systolic blood pressure > 180 between induction and two minutes after intubation
	Systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
	New or increased vasopressor between induction and 2 minutes after intubation
	Cardiac arrest within 2 minutes of intubation not resulting in death within 1 hour of induction
	Cardiac arrest within 2 minutes of intubation resulting in death within 1 hour of induction
Exploratory Clinical Outcomes	Ventilator-free days to study day 28
	Vasopressor-free days to study day 28
	ICU-free days to study day 28
Safety Outcomes	Systolic blood pressure at 24 hours after induction
	Receipt of vasopressors at 24 hours after induction
	Cardiac arrest receiving cardiopulmonary resuscitation between induction and hospital discharge

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Protocol and Statistical Analysis Plan for a Multicenter Randomized Trial of Ketamine vs Etomidate for Emergency Tracheal Intubation

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BACKGROUND: Emergency tracheal intubation is a common and high-risk procedure. Ketamine and etomidate are medicines commonly used to induce anesthesia for emergency tracheal intubation, but whether the induction medication used affects patient outcomes is uncertain.

RESEARCH QUESTION: Does the use of ketamine for induction of anesthesia decrease the incidence of death among adults undergoing emergency tracheal intubation compared with the use of etomidate?

STUDY DESIGN AND METHODS: The Randomized Trial of Sedative Choice for Intubation (RSI) is a pragmatic, multicenter, unmasked, parallel-group randomized trial being conducted at 14 sites (6 emergency departments and 8 ICUs) in the United States. The trial compares ketamine vs etomidate for induction of anesthesia among 2,364 critically ill adults undergoing emergency tracheal intubation. The primary outcome is all-cause 28-day in-hospital mortality. The secondary outcome is the incidence of cardiovascular collapse during intubation, a composite of hypotension, receipt of vasopressors, and cardiac arrest.

RESULTS: Enrollment began on April 6, 2022, and is expected to conclude in 2025.

INTERPRETATION: The RSI will provide important data on the effects of ketamine vs etomidate on death and other outcomes for critically ill adults undergoing emergency tracheal intubation. Specifying the protocol and statistical analysis plan before the conclusion of enrollment increases the rigor, reproducibility, and transparency of the trial.

CLINICAL TRIAL REGISTRATION: ClinicalTrials.gov; No.: NCT05277896; URL: www.clinicaltrials.gov

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KEY WORDS: emergency tracheal intubation; etomidate; induction; ketamine

Take-Home Points

Study Question: Does use of ketamine for induction of anesthesia during emergency tracheal intubation decrease the incidence of death compared with use of etomidate?

Results: This article describes the protocol and statistical analysis plan for the Randomized Trial of Sedative Choice for Intubation comparing ketamine vs etomidate for induction of anesthesia for emergency tracheal intubation.

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

Millions of critically ill adults undergo emergency tracheal intubation every year worldwide,[1] approximately 30% of whom die before hospital discharge.[2,3] Nearly all patients undergoing emergency tracheal intubation in an emergency department (ED) or ICU receive a medication to induce anesthesia for the procedure.[2,4] Whether the medication used to induce anesthesia affects patient outcomes is uncertain.

Etomidate, an imidazole-derived sedative-hypnotic agent that produces anesthesia by acting on γ-aminobutyric acid receptors, is the medication most often used to induce anesthesia during emergency tracheal intubation in some EDs and ICUs.[4-6] Etomidate has been described as an "ideal" medication for induction of anesthesia in critically ill adults because of its rapid onset, short duration of action, and limited effect on BP.[7] However, etomidate inhibits 11-β-hydroxylase in the adrenal glands, which decreases cortisol production and causes adrenal insufficiency for 24 to 72 hours.[8,9] Among critically ill adults, many of whom experience critical illness-related corticosteroid insufficiency resulting from sepsis or other causes,[10-12] etomidate-induced adrenal insufficiency has been hypothesized to be associated with organ dysfunction and death.[5] Concern that adrenal insufficiency caused by etomidate may decrease survival has led federal regulatory agencies in some countries not to approve etomidate for clinical use.[13]

Ketamine, a dissociative agent that produces anesthesia by acting on N-methyl-D-aspartate receptors, is the medication most often used to induce anesthesia during emergency tracheal intubation in some EDs and ICUs.[14,15] In contrast to etomidate, ketamine increases cortisol production.[16,17] However, whereas ketamine generally increases BP by stimulating the release of catecholamines,[18] it is a direct negative inotrope[19-22] and has been reported to precipitate rare episodes of severe hypotension[14,23-25] or even cardiac arrest, particularly among critically ill patients with depleted stores of endogenous catecholamines.[24,26]

Previous small to moderate randomized trials comparing ketamine and etomidate for emergency tracheal intubation have reported conflicting results, with some finding that use of ketamine decreased short-term mortality[24,27] and others finding no significant differences in outcomes.[28-30] Currently, whether use of

ABBREVIATIONS: DSMB = data and safety monitoring board; ED = emergency department; PCORI = Patient-Centered Outcomes Research Institute; RSI = Randomized Trial of Sedative Choice for Intubation

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ketamine decreases mortality for critically ill adults undergoing emergency tracheal intubation compared with the use of etomidate remains uncertain.

To address this uncertainty, we designed the Randomized Trial of Sedative Choice for Intubation (RSI), which will compare ketamine vs etomidate for induction of anesthesia among 2,364 adults undergoing emergency tracheal intubation. We hypothesize that use of ketamine will decrease the incidence of death compared with etomidate.

Study Design and Methods

This article was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines (Table 1, section 2 of e-Appendix 1).[31]

Engagement of Patients, Families, and Community Members

Detailed information on engagement with survivors of emergency tracheal intubation, family members, and community members in each phase of the design and conduct of the RSI are summarized in section 3 of e-Appendix 1.

Study Design

The RSI is a pragmatic, multicenter, unmasked, parallel-group randomized trial comparing the use of ketamine vs etomidate for induction of anesthesia in 2,364 critically ill adults undergoing emergency tracheal intubation in 14 sites (6 EDs and 8 ICUs) in the United States. The primary outcome is all-cause 28-day in-hospital mortality. The trial is being conducted by the Pragmatic Critical Care Research Group (www.pragmaticcriticalcare.org). The trial was registered before initiation of enrollment (ClinicalTrials.gov Identifier: NCT05277896).

Ethics and Regulatory Approval

The RSI protocol was approved by the institutional review board at Vanderbilt University Medical Center (Identifier: 210500) and the US Food and Drug Administration (Investigational New Drug Identifier: 141424). The study is being conducted with Exception From Informed Consent Requirements for Emergency Research (21 CFR 50.24).[32] Whenever feasible, patients or their legally authorized representatives are approached by research personnel to provide prospective, written informed consent to participate in the trial. When prospective, written informed consent is infeasible, patients are enrolled under Exception From

TABLE 1] Schedule of Enrollment, Interventions, and Assessments in the RSI

Time Point	Eligibility Screening: Decision to Perform Tracheal Intubation	Randomization and Allocation: Before Tracheal Intubation	During the Procedure				Final Outcome Assessment at 28 d
			Induction	Tracheal Intubation	0-2 min After Tracheal Intubation	0-24 h After Tracheal Intubation	
Enrollment							
Eligibility screen	X						
Enrollment		X					
Allocation		X					
Interventions							
Ketamine			X				
Etomidate			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	X

Information on the collection of outcomes at 3 and 12 months will be reported in a separate statistical analysis plan. Table entries without data mean that data elements were not collected at that time. RSI = Randomized Trial of Sedative Choice During intubation.

TABLE 2] Inclusion and Exclusion Criteria

Inclusion criteria
Patient is critically ill and undergoing emergency tracheal intubation with sedation in an enrolling unit
Planned procedure is orotracheal intubation using a laryngoscope
Planned operator is a clinician expected to perform tracheal intubation in the participating unit routinely
Exclusion criteria
Patient is known to be younger than 18 y
Patient is known to be pregnant
Patient is known to be incarcerated
Patient is known to have an allergy to ketamine or etomidate
Patient is seeking treatment at the emergency department with a primary diagnosis of trauma
Patient or legally authorized representative declines participation during pre-enrollment opt-out conversation or by wearing opt-out bracelet for the RSI
Clinician believes that ketamine is required or contraindicated for the optimal care of the patient
Clinician believes that etomidate is required or contraindicated for the optimal care of the patient
Clinician believes that an induction medication other than ketamine or etomidate is required for the optimal care of the patient
Immediate need for intubation precludes safe performance of study procedures

RSI = Randomized Trial of Sedative Choice for Intubation.

Informed Consent Requirements for Emergency Research and the patient, the patient's legally authorized representative, or a family member is notified of enrollment in the trial at the earliest feasible opportunity (additional details in section 4 of e-Appendix 1). Plans for community consultation and public disclosure were approved by the single institutional review board at Vanderbilt University Medical Center. The institutional review board of each participating site provided local context for the community consultation and public disclosure plan and activities.

Study Population

Critically ill adults undergoing emergency tracheal intubation with sedation in a participating unit are potentially eligible. The trial excludes patients who are pregnant, incarcerated, or younger than 18 years. 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 ketamine or etomidate 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 clinician performing the tracheal intubation procedure (referred to as 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 and randomized 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 trial group assignment.

Study Interventions

Ketamine Group: For patients in the ketamine group, clinicians are instructed to administer IV ketamine to induce anesthesia for emergency tracheal intubation. The dose of ketamine is determined by the clinicians based on the clinical condition of the patient. A nomogram on the study group assignment sheet provides clinicians with doses of ketamine (in milligrams) that correspond to a full dose (2.0 mg/kg), an intermediate dose (1.5 mg/kg), and a reduced dose (1.0 mg/kg) for a range of patient weights (section 5 of e-Appendix 1).[33]

Etomidate Group: For patients in the etomidate group, clinicians are instructed to administer IV etomidate to induce anesthesia for emergency tracheal intubation. The dose of etomidate is determined by the clinicians based on the clinical condition of the patient. A nomogram on the study group assignment sheet provides clinicians with doses of etomidate (in milligrams) that correspond to a full dose (0.3 mg/kg), an intermediate dose (0.25 mg/kg), and a reduced dose (0.2 mg/kg) for a range of patient weights (section 6 of e-Appendix 1).

Cointerventions: The RSI determines the initial primary medication administered for induction of anesthesia during the emergency tracheal intubation procedure. Subsequent boluses or infusions of sedative medications are determined by clinicians. Other aspects of emergency tracheal intubation (eg, fluid and vasopressor management before intubation, choice of neuromuscular blocking medication) are determined by treating clinicians according to clinical protocols in the study units. Cointerventions that potentially could modify the effect of ketamine or etomidate on patient outcomes (eg, administration of corticosteroids after intubation) are recorded prospectively.

Data Collection

An observer not directly involved with the intubation procedure collects data in real time for key periprocedural outcomes, including oxygen saturation and systolic BP at the time of induction and lowest oxygen saturation, lowest systolic BP, and administration of vasopressors between induction and 2 minutes after intubation. Observers are either research personnel or trained clinical personnel (eg, physicians or nurses). The accuracy of this method of data collection has been validated previously[34] and has been used in numerous previous trials of emergency tracheal intubation.[3,4,6]

Immediately after the intubation procedure, the operator completes a paper data collection form to record characteristics of the procedure (eg, Cormack-Lehane grade of glottic view[35]), complications during intubation (eg, cardiac arrest), and the operator's prior intubating experience. Study personnel at each site review the electronic health record to collect data on baseline characteristics, management before and after laryngoscopy, and in-hospital clinical outcomes such as systolic BP at 24 hours after induction, receipt of vasopressors at 24 hours after induction, ventilator duration, and mortality. Study personnel collect information on mortality occurring after hospital discharge from the electronic health record, public vital statistics records and other public records, and phone calls with patients participating in the long-term outcome assessments at 3 and 12 months (the results of the long-term outcome assessments will be reported separately).

Primary Outcome

The primary outcome is all-cause 28-day in-hospital mortality, defined as death resulting from any cause occurring between enrollment and 28 days after enrollment with outcome ascertainment ending at hospital discharge.

Secondary Outcome

The sole secondary outcome is cardiovascular collapse, defined as the occurrence of any of the following between induction and 2 minutes after intubation: (1) systolic BP of $<$ 65 mm Hg, (2) new or increased vasopressor use, (3) cardiac arrest not resulting in death, and (4) cardiac arrest resulting in death.

Procedural, Clinical, and Safety Outcomes

Table 3 reports the exploratory procedural outcomes, exploratory clinical outcomes, and safety outcomes. Definitions of free-day outcomes are included in section 7 of e-Appendix 1.[4,6]

Long-Term Outcomes

The definitions, collection, and analysis of survival and functional outcomes (eg, symptoms of posttraumatic stress disorder) at 3 months and 12 months will be prespecified in a separate statistical analysis plan. Because these outcomes will not be available for more than 1 year after completion of enrollment in the trial, these long-term outcomes have been registered separately (ClinicalTrials.org Identifier: NCT06179485)[36] and will be reported separately from the 28-day outcomes described in this statistical analysis plan.

Data and Safety Monitoring Board

The composition and responsibilities of the data and safety monitoring board (DSMB) are described in section 8 of e-Appendix 1. The DSMB developed a charter, approved the trial protocol, approved the patient notification forms, and approved the trial monitoring plan before trial initiation of enrollment. The DSMB has the authority to recommend that the trial stop at any point, to request additional data, to request additional interim analyses, or to request modifications to the study protocol.

Trial Stages

The RSI was funded in 2 stages. First, the single-center feasibility stage of the trial was funded by an award from the National Heart Lung and Blood Institute (Grant: K23HL153584). Second, the multicenter stage of trial was funded by a contract from the Patient-Centered Outcomes Research Institute (PCORI; Identifier: BPS-2022C3-30021). The initial trial protocol specified both stages of the trial and the criteria that had to be met to transition from the single-center stage to the multicenter stage. On August 1, 2023, the DSMB (1)

TABLE 3] Study Outcomes

Primary outcome	All-cause 28-d in-hospital mortality
Secondary outcome	Cardiovascular collapse, a composite of any of the following between induction and 2 min after intubation: (1) systolic BP < 65 mm Hg, (2) new or increased vasopressor use, (3) cardiac arrest not resulting in death within 1 h of induction, and (4) cardiac arrest resulting in death within 1 h of induction[a]
Exploratory procedural outcomes	Cormack-Lehane grade of glottic view
	Successful intubation on the first attempt, defined as placement of an endotracheal tube in the trachea with a single insertion of a laryngoscope blade into the mouth and either a single insertion of an endotracheal tube into the mouth or a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube over the bougie into the mouth
	Time from induction to successful tracheal intubation
	Lowest oxygen saturation between induction and 2 min after intubation
	Lowest oxygen saturation < 80% between induction and 2 min after intubation
	Highest and lowest systolic BP from induction to 2 min after intubation
	Systolic BP > 180 mm Hg between induction and 2 min after intubation
	Systolic BP < 65 mm Hg between induction and 2 min after intubation
	New or increased vasopressor use between induction and 2 min after intubation
	Cardiac arrest within 2 min of intubation not resulting in death within 1 h of induction[a]
	Cardiac arrest within 2 min of intubation resulting in death within 1 h of induction[a]
Exploratory clinical outcomes	Ventilator-free days to study day 28
	Vasopressor-free days to study day 28
	ICU-free days to study day 28
Safety outcomes	Systolic BP at 24 h after induction
	Receipt of vasopressors at 24 h after induction
	Cardiac arrest receiving CPR between induction and hospital discharge

[a]Cardiac arrest occurring between induction of anesthesia and 2 min after intubation of the trachea will be considered to be a cardiac arrest that occurred during tracheal intubation. For each case of cardiac arrest occurring during tracheal intubation, we will record whether that cardiac arrest resulted in death. A cardiac arrest occurring during tracheal intubation will be considered to have resulted in death if the patient died before 1 h after induction.

reviewed information on funding for the multicenter stage; (2) reviewed data on enrollment rate, adherence to trial procedures, and completeness and quality of trial data from the single-center stage; and (3) approved transition to the multicenter stage of the trial. Neither the DSMB nor the investigators reviewed any analysis of trial outcomes as part of the transition between stages.

Interim Analysis

On January 7, 2025, the DSMB reviewed a single interim analysis, prepared by the unmasked study biostatistician at the anticipated halfway point of the trial after enrolment of 1,182 patients. The prespecified stopping boundary for efficacy was a P value of < .001 for the difference between trial groups in the primary outcome using a generalized linear mixed-effects model with a random effect for study site and a fixed effect for group assignment (ketamine group vs etomidate group). This conservative Haybittle-Peto boundary will allow the final analysis to be performed using an unchanged level of significance (2-sided P value of < .05). After reviewing the interim analysis, the DSMB recommended continuing the RSI without modification.

Sample Size Estimation

The final sample size for the RSI was calculated at the time of receipt of funding for the multicenter stage of the trial from PCORI (details of the initial sample size calculation are provided in section 9 of e-Appendix 1). Based on prior trials in the same settings,[4,6] we estimated that the incidence of all-cause, 28-day in-hospital mortality (primary outcome) in the etomidate group would be 30%. The patient and clinician partners recommended that the trial should have adequate statistical power to detect an absolute difference between groups in mortality of approximately 5 percentage points. This difference is more conservative than the median of 8 percentage points (interquartile range, 6-10 percentage

points) used as the minimum clinically important difference in the design of prior randomized trials in critical care[37] and is smaller than the observed difference in mortality between ketamine and etomidate of 6 to 7 percentage points observed in 2 previous trials.[24,28] We used the bsamsize function in R (R Foundation for Statistical Computing) to calculate that achieving 80% statistical power at a 2-sided α value of .05 to detect a difference in mortality of 5.2 percentage points (30.0% in the etomidate group vs 24.8% in the ketamine group) would require enrollment of 2,308 patients. Anticipating that, like previous Exception from Informed Consent Requirements for Emergency Research trials,[38] < 3% of participants would discontinue follow-up before ascertainment of the primary outcome, we planned to enroll a total of 2,364 patients (1,182 per group).

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R software. Categorical variables will be presented as number and percentage. Continuous variables will be presented as mean (SD) or median (interquartile range). A 2-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 analyses of secondary and exploratory outcomes, emphasis will be placed on the magnitude of differences between groups with 95% CIs (which will not be adjusted for multiple comparisons), rather than statistical significance. *P* values will not be presented. Templates for the tables that will be presented in the results manuscript and supplement for baseline, periprocedural, and in-hospital outcome variables are provided in e-Tables 1-3.

Main Analysis of the Primary Outcome

The primary analysis will be an intention-to-treat comparison of patients randomized to the ketamine group vs patients randomized to the etomidate group regarding the primary outcome of all-cause 28-day in-hospital mortality among all patients in the trial population, except those who withdrew from follow-up before ascertainment of the primary outcome. The primary outcome will be compared between the 2 trials groups using a generalized linear mixed-effects model with a random effect for study site and a fixed effect for group assignment (ketamine group vs etomidate group). The absolute difference in percentages, associated 95% CIs, and a *P* value for the comparison will be presented. A rationale for the primary outcome and its analysis can be found in section 10 of e-Appendix 1.

Additional Analyses of the Primary Outcome

Sensitivity Analyses: We will assess the robustness of the findings of the primary analysis in a series of sensitivity analyses using different approaches to defining and analyzing the primary outcome. First, we will repeat the primary analysis among all patients in the trial population, with patients who withdrew from follow-up before outcome ascertainment treated as (1) all having experienced the primary outcome or (2) all not having experienced the primary outcome. Second, we will repeat the primary analysis using all-cause, all-location mortality at 28 days (ie, including available information on deaths that occur after hospital discharge). Third, we will repeat the primary analysis using a χ^2 test, rather than a generalized linear mixed-effects model. Fourth, we will compare survival to day 28 between trial groups using the Kaplan-Meier method. Fifth, we will perform an adjusted analysis comparing the primary outcome between groups using a generalized linear mixed-effects model with a random effect for trial site and fixed effects for trial group assignment and the following prespecified baseline variables: age, sex, race, ethnicity, Area Deprivation Index (a proxy for socioeconomic status and an indicator of neighborhood disadvantage),[39] rurality,[40] number of comorbidities, and severity of illness before enrollment as assessed by the Acute Physiology and Chronic Health Evaluation II score.[41] Continuous variables will be modelled assuming a nonlinear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Analyses of Heterogeneity of Treatment Effect: Heterogeneity of treatment effect is nonrandom variation in the magnitude or direction of the effect of a treatment on an outcome across levels of a baseline covariate. We will apply the 3 complementary approaches to analysis of heterogeneity of treatment effect described in the Predictive Approaches to Treatment Effect Heterogeneity Statement: (1) traditional 1-variable-at-a-time subgroup analyses, (2) a risk-modeling approach, and (3) an effect-modeling approach.[42] Complete details of all 3 approaches are described in section 11 of e-Appendix 1.

Our subgroup analyses will examine whether prespecified baseline variables modify the effect of trial group assignment 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, a random effect for trial site, and independent variables of trial group, the proposed effect

modifier, and the interaction between the effect modifier and trial group for each of the following prespecified baseline variables: (1) sepsis or septic shock (yes or no), (2) vasopressor receipt (yes or no), (3) patient location (ED or ICU), (4) adrenal insufficiency or long-term receipt of corticosteroids (yes or no), (5) acute neurologic condition (yes or no), (6) active cardiac condition (yes or no), and (7) baseline risk of the primary outcome (continuous).

Analysis of the Secondary Outcome

We will perform an unadjusted, intention-to-treat comparison of patients randomized to the ketamine group vs patients randomized to the etomidate group regarding the secondary outcome of cardiovascular collapse. A χ^2 test will be used to generate between-group differences and the associated 95% CIs.

Analyses of Additional Outcomes

We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the ketamine group vs patients randomized to the etomidate group regarding each prespecified exploratory procedural outcome, exploratory clinical outcome, and safety outcome. Between-group differences and the associated 95% CIs will be generated using a χ^2 test for categorical outcomes and a Wilcoxon rank-sum test for continuous outcomes.

Handling of Missing Data

We anticipate that no data on the primary outcome will be missing except for patients who withdrew from participation before the collection of the primary outcome. When data are missing for an outcome, we will perform complete-case analysis, excluding patients whose data for the analyzed outcome are missing. In adjusted analyses, missing data for covariates will be imputed using multiple imputations. All variables that included in prespecified statistical models also will be included in the imputation model. This allows for the relationships held between the variables of interest to be as similar as possible with and without imputation. The specific method of multiple imputation used in adjusted analysis uses bootstrapping and predictive mean matching. Samples of nonmissing data are bootstrapped, then fit to an additive regression model to predict missing data. Imputation will be performed using the R statistical software's aregImpute function from the Hmisc package.

Discussion

This article reports the rationale, design, and analysis plan for the RSI, a 2,364-patient randomized trial of ketamine vs etomidate for induction of anesthesia among critically ill adults undergoing emergency tracheal intubation. Several elements of the trial design warrant discussion.

The RSI was designed to compare ketamine vs etomidate and does not examine other medications capable of inducing anesthesia for emergency tracheal intubation, such as propofol or benzodiazepines. These comparators were selected for several reasons. First, ketamine and etomidate are the medications most often used for emergency tracheal intubation in many EDs[14] and ICUs,[5] particularly in the United States.[3,43-45] Second, ketamine and etomidate are the only medications consistently used for emergency tracheal intubation in clinical care at the 14 sites participating in the trial.[4,6,15] Third, although propofol and benzodiazepines are used more commonly by some clinical specialties (eg, anesthesiologists)[46,47] and in some clinical settings (eg, some ICUs outside of the United States),[2] observational studies consistently have reported these medications to be associated with higher rates of hypotension during intubation, particularly for patients with preexisting hemodynamic instability.[2,48] We anticipate that approximately 1 in 4 patients in the RSI will be receiving vasopressors before enrollment. Thus, we designed the trial to compare 2 medications with a hemodynamic profile that permits their use for nearly all critically ill adults, including those with hypotension or shock before intubation.

In the RSI, clinicians determine what dose of the assigned medication each patient receives based on the clinical condition of the patient using a dosing nomogram provided by the trial. The nomogram specifies 2 mg/kg of ketamine and 0.3 mg/kg of etomidate as a full dose. These are the doses specified in the US Food and Drug Administration labeling information for the induction of anesthesia.[33,49] These also are the doses used in 2 of the largest previous randomized trials comparing ketamine vs etomidate among critically ill adults.[24,28] For patients who clinicians determine require a lower dose, the nomogram also provides information on an intermediate dose (1.5 mg/kg of ketamine or 0.25 mg/kg of etomidate) and a reduced dose (1.0 mg/kg of ketamine or 0.2 mg/kg of etomidate) across a range of patient weights.

The design of the RSI differs from that of previous trials comparing ketamine vs etomidate in several respects. First, the planned sample size of 2,364 patients is almost 3 times as large as any prior trial and will permit more precise estimates of treatment effect.[24,28,29,50] Second, unlike prior trials that excluded patients intubated in the ED,[24] that excluded patients intubated in the ICU,[29] or that enrolled only patients with sepsis,[50] the RSI includes a broad range of patients undergoing emergency tracheal intubation in an ED or ICU, which increases generalizability. The only diagnosis excluded from the RSI is a primary diagnosis of trauma before seeking treatment in the ED. Because some prior data suggest that ketamine might increase intracranial pressure[51] and the results of 1 prior trial suggested a potential difference in treatment effect between patients with and without trauma,[28] we determined that the effect of ketamine vs etomidate on outcomes for patients with trauma was best evaluated in a separate trial. Third, unlike prior trials that did not collect procedural outcomes[28] or long-term patient-centered outcomes,[24,28,29,50] the RSI collects physiologic outcomes during the procedure (eg, cardiovascular collapse during intubation), short-term patient-centered outcomes (eg, death by day 28), and long-term patient-centered outcomes (eg, survival and symptoms of posttraumatic stress disorder at 12 months).

Interpretation

The RSI will provide important evidence regarding the effect of ketamine vs etomidate on death and other clinical outcomes among critically ill adults undergoing emergency tracheal intubation in an ED or ICU. To aid in the transparency and interpretation of trial results, this article detailing the protocol and statistical analysis plan for the RSI has been finalized before the conclusion of patient enrollment.

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Disclaimer: The views and statements presented in this article are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute or the National Heart, Blood, and Lung Institute.

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

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Supplementary file to:

Protocol and Statistical Analysis Plan for the Randomized Trial of Sedative Choice for Intubation (RSI)

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2. SPIRIT 2013 Checklist

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 7
	2b	All items from the World Health Organization Trial Registration Data Set	1-6
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	2, 12-13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	1-3, 12
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1-3 Section 1 of Supplement

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-6
	6b	Explanation for choice of comparators	5-7, 19
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7, Supplement Section 1
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8-9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-12, Table 3

Participant timeline	13	Time schedule of enrollment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13-14, Supplement Section 9
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	NA
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	14, 18

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplement Section 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14-17, Supplement Section 10, 11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14-17, Supplement Section 11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplement Section 8
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Supplement Section 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplement Section 12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	7-8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplement Section 13
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Supplement Section 4

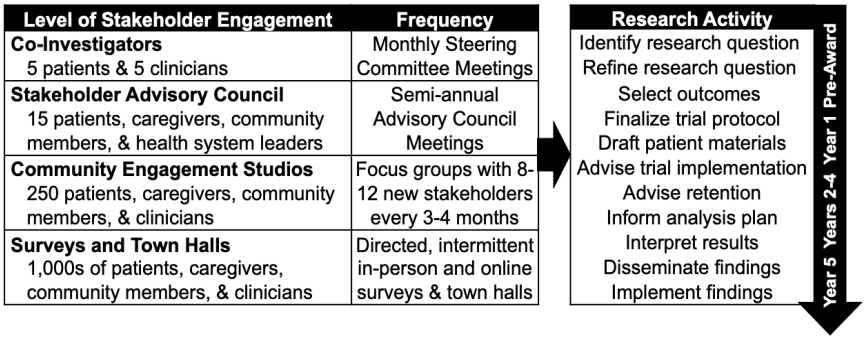
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplement Section 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	1-3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	NA
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Supplement Section 17
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Supplement Section 3
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	Supplement Section 17
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

3. Engagement of Patients, Families, and Community Members

The RSI trial has engaged patients, families, and community members in every phase of the research. Prior to beginning the research, community engagement studios with more than 75 unique patient, family, community member, and clinician partners first identified the choice between ketamine and etomidate as a critical evidence gap and identified mortality as the most relevant and important short-term outcomes and symptoms of post-traumatic stress disorder (PTSD) as the most important non-mortality long-term outcome.

Throughout the conduct of the RSI trial, engagement with patients, families, and community partners occurs at the four levels of engagement shown in the adjacent figure.



Six **Patient Co-investigators**, 5 of whom are survivors of emergency tracheal intubation, serve on the Steering Committee for the RSI trial, contributing to each monthly meeting as equal partners with equal votes. In this role, they have applied their experience building community-research partnerships to the design of pre-trial Community Consultation, their expertise in lay presentation of medical information to optimize the RSI trial's patient-facing materials and website, and the acceptability to ICU survivors of the approach to informed consent and outcome assessment. At trial completion, the patient co-investigators will help write publications, design dissemination materials, and present the results of the trial to lay and medical audiences.

A **Stakeholder Advisory Council**, composed of 15 patient and community stakeholders knowledgeable about critical illness and representative of the full diversity of their communities, helped design the trial protocol, and meets twice a year with investigators to monitor the impact of the trial on participants, review patient-facing materials, inform participant compensation, and identify opportunities to disseminate results through community organizations and health systems.

In a **Community Engagement Studio**, a unique panel of 8-12 patients, community members, or clinicians (selected for their firsthand knowledge of a particular condition) serve as paid experts during a 2-hour face-to-face session with researchers. During the RSI trial, three-yearly Community Engagement Studios focus on: Community Consultation; integration of the trial into clinical care, retention, and long-term outcome assessments; analysis plan development; and interpretation of results, dissemination, and implementation.

Through **Surveys and Town Halls**, we have received input on the RSI trial from hundreds of patients, caregivers, clinicians, and community members. During pre-trial Community Consultation, we conducted in-person surveys with almost 800 patients and family members in ED and ICU waiting rooms to solicit input on the conduct of the RSI trial. ICU survivors, caregivers, and community members in our town halls shared what outcomes they valued, how to make enrollment represent them, and how to communicate with patients about the trial. Through Facebook ads, we solicited input from >1.1 million community members on the trial design. The full details of the Community Consultation and Public Disclosure processes for the RSI trial are publicly available through FDA Docket Number 95S-0158 in the Division of Dockets Management (HFA-305) (https://www.regulations.gov/document/FDA-1995-S-0036-0230). The details of the Community Consultation and Public Disclosure processes and the feedback received from patients and community members for the RSI trial will be published separately.

4. Ethics and Informed Consent Processes

4.1 Exception from Informed Consent Requirements for Emergency Research (EFIC)

The RSI trial has been approved by the institutional review board at Vanderbilt University Medical Center (IRB number: 210500) and the US Food and Drug Administration (IND 141424). The RSI trial meets all the requirements to enroll patients under 21 CFR 50.24 for emergency research in which prospective informed consent is infeasible.[1] These requirements include:

1. Human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory
2. Obtaining informed consent is not feasible
3. Participation in the research holds out the prospect of direct benefit to the subjects
4. The clinical investigation could not practicably be carried out without the waiver
5. The investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and, if feasible, to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent
6. The IRB has reviewed and approved informed consent procedures and an informed consent document consistent with 50.25; and
7. Additional protections of the rights and welfare of the subjects are provided.

Additional protections of the rights and welfare of the subjects in the RSI trial include:

- Completion of consultation with representatives of the communities in which the clinical investigation will be conducted and from which the subjects will be drawn (community consultation)
- Completion of public disclosure to the communities in which the clinical investigation will be conducted and from which the subjects will be drawn, prior to initiation of the clinical investigation, of plans for the investigation and its risks and expected benefits

- A plan for public disclosure of sufficient information following completion of the clinical investigation to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results
- Establishment of an independent data monitoring committee to exercise oversight of the clinical investigation; and
- A plan, when feasible, to provide an opportunity for patients, LARs, or family members to object to the subject's participation in the clinical investigation when informed consent is not feasible;

A summary of the pre-trial community consultation and public disclosure activities is publicly available through FDA Docket Number 95S-0158 in the Division of Dockets Management (HFA-305) (https://www.regulations.gov/document/FDA-1995-S-0036-0230).

4.2 Informed Consent Processes in the RSI trial

As required under 21 CFR 50.24,[1] the RSI trial uses three approaches to informed consent, tailored to the capacity of the patient and the urgency of the intubation procedure.

4.2.1 Written Informed Consent

When a patient has decisional capacity or a legally authorized representative (LAR) is available and the clinical urgency of the procedure permits sufficient time for trial personnel to complete an informed consent process, written informed consent is obtained from the patient or LAR by trial personnel. The decisional capacity of the patient and the safety and feasibility of providing an opportunity for patients or LARs to complete an informed consent process is determined by treating clinicians.

4.2.2 Opportunity to Decline Participation

The RSI trial provides two mechanisms for patients to decline participation. First, medical alert bracelets have been made available prior to and throughout the trial for any community members who wishes to opt out of participation in the trial, should they become critically ill and require tracheal intubation.

Second, when the clinical urgency of the intubation procedure precludes completion of a full informed consent process but permits a brief discussion of the research prior to the procedure, research personnel provide patients, LARs, or family members with an opportunity to express their objection to enrollment in the trial. The decisional capacity of the patient and the safety and feasibility of providing an opportunity for patients, LARs, or family members to express their objection to research enrollment is determined by treating clinicians.

4.2.3 Exception from Informed Consent

Because most critically ill patients undergoing emergency tracheal intubation lack decisional capacity due to their critical illness, LARs and family members are frequently unavailable, and tracheal intubation is a time-sensitive procedure with only minutes between the decision to intubate and the completion of the procedure, most patients in the RSI trial are enrolled under EFIC. When a patient is enrolled under EFIC, research personnel notify the patient, LAR, or a family member of the patient's enrolment in the trial at the earliest feasible opportunity and provide an opportunity to discontinue participation in the trial.

5. Group Assignment Sheets with Nomogram (Ketamine)

RSI Study ID # _____

Ketamine

Use ketamine as the sedative for tracheal intubation.
Select the dose you feel is optimal for this patient.

Weight	Dose of Ketamine		
	Reduced Dose 1.0 mg/kg	**Intermediate Dose 1.5 mg/kg**	**Full Dose 2.0 mg/kg**
40 kg (88 lbs)	40 mg	60 mg	80 mg
45 kg (99 lbs)	45 mg	68 mg	90 mg
50 kg (110 lbs)	50 mg	75 mg	100 mg
55 kg (121 lbs)	55 mg	83 mg	110 mg
60 kg (132 lbs)	60 mg	90 mg	120 mg
65 kg (143 lbs)	65 mg	98 mg	130 mg
70 kg (154 lbs)	70 mg	105 mg	140 mg
75 kg (165 lbs)	75 mg	113 mg	150 mg
80 kg (176 lbs)	80 mg	120 mg	160 mg
85 kg (187 lbs)	85 mg	128 mg	170 mg
90 kg (198 lbs)	90 mg	135 mg	180 mg
95 kg (209 lbs)	95 mg	143 mg	190 mg
100 kg (220 lbs)	100 mg	150 mg	200 mg
105 kg (231 lbs)	105 mg	158 mg	210 mg
110 kg (243 lbs)	110 mg	165 mg	220 mg
115 kg (254 lbs)	115 mg	173 mg	230 mg
120 kg (265 lbs)	120 mg	180 mg	240 mg

6. Group Assignment Sheets with Nomogram (Etomidate)

RSI Study ID # _____

Etomidate

Use etomidate as the sedative for tracheal intubation.
Select the dose you feel is optimal for this patient.

Weight	Dose of Etomidate		
	Reduced Dose 0.2 mg/kg	**Intermediate 0.25 mg/kg**	**Full Dose 0.3 mg/kg**
40 kg (88 lbs)	8 mg	10 mg	12 mg
45 kg (99 lbs)	9 mg	11 mg	14 mg
50 kg (110 lbs)	10 mg	13 mg	15 mg
55 kg (121 lbs)	11 mg	14 mg	17 mg
60 kg (132 lbs)	12 mg	15 mg	18 mg
65 kg (143 lbs)	13 mg	16 mg	20 mg
70 kg (154 lbs)	14 mg	18 mg	21 mg
75 kg (165 lbs)	15 mg	19 mg	23 mg
80 kg (176 lbs)	16 mg	20 mg	24 mg
85 kg (187 lbs)	17 mg	21 mg	26 mg
90 kg (198 lbs)	18 mg	23 mg	27 mg
95 kg (209 lbs)	19 mg	24 mg	29 mg
100 kg (220 lbs)	20 mg	25 mg	30 mg
105 kg (231 lbs)	21 mg	26 mg	32 mg
110 kg (243 lbs)	22 mg	28 mg	33 mg
115 kg (254 lbs)	23 mg	29 mg	35 mg
120 kg (265 lbs)	24 mg	30 mg	36 mg

7. Definitions of Free-Day Outcomes

Ventilator-free days to day 28 (VFDs): VFDs are defined as the number of calendar days, between enrollment and 28 days after enrollment, on which the patient is alive and free of invasive mechanical ventilation. If a patient is liberated from invasive mechanical ventilation, returns to invasive mechanical ventilation and subsequently is liberated from invasive mechanical ventilation again prior to day 28, the number of VFDs will be counted from the end of the last period of invasive mechanical ventilation to day 28. If the patient is receiving invasive mechanical ventilation at day 28 or dies prior to day 28, VFDs are 0. If a patient is discharged while receiving invasive mechanical ventilation, VFDs are 0. Outcome ascertainment ends at 28 days or hospital discharge, whichever occurs first.

ICU-free days to day 28 (ICU-FDs): ICU-FDs are defined as the number of calendar days, between enrollment and 28 days after enrollment, on which the patient is alive and not admitted to an intensive care unit after the patient's final transfer out of the intensive care unit. Patients who are never transferred out of the intensive care unit receive a value of 0. Patients who die before day 28 receive a value of 0. For patients who are transferred out of the ICU, return to an ICU, and are subsequently transferred out of the ICU again prior to day 28, ICU-free days are counted from the date of final transfer out of the ICU. Outcome ascertainment ends at 28 days or hospital discharge, whichever occurs first.

Vasopressor-free days to study day 28: Vasopressor-free days are defined as the number of calendar days, between enrollment and 28 days after enrollment, on which the patient is alive and not receiving vasopressors including days before the first receipt of vasopressors and after the last receipt of vasopressors. If a patient is weaned off vasopressors, returns to receiving vasopressors, and is subsequently weaned off vasopressors again, vasopressors free days will not include any days between the first and last receipt of vasopressors. If the patient is receiving vasopressors at day 28 or dies prior to day 28, vasopressor-free days are 0. If a patient is discharged while receiving

vasopressors (e.g., transfer to long-term acute care hospital), vasopressors-free days are 0. Outcome ascertainment ends at 28 days or hospital discharge, whichever occurs first.

8. Composition and Responsibilities of the Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) consists of members with expertise in bioethics, emergency medicine, pulmonary and critical care medicine, anesthesia, biostatistics, and clinical trials. One patient partner who is a survivor of critical illness requiring emergency tracheal intubation serves as a member of the DSMB. All members of the DSMB are voting members. The DSMB developed a charter, approved the trial protocol, approved the patient notification forms, and approved the trial monitoring plan prior to trial initiation of enrollment. The DSMB has the ability at any point to recommend that the trial end, be modified, or continue unchanged.

The principal role of the DSMB is to assure the safety of patients in the trial. The DSMB monitors data from the trial at semi-annual meetings, reviews and assesses the performance of its operations, and makes recommendations to the Steering Committee and Sponsor with respect to:

- Review of adverse events
- Interim results of the study for evidence of efficacy or adverse events
- Possible early termination of the trial because of new external information, early attainment of study objectives, safety concerns, or inadequate performance
- Possible modifications in the clinical trial protocol
- Performance of individual centers

9. Details of Sample Size Calculation

Initial Sample Size Estimate

The initial version of the sample size estimate, included in version 1.0 of the trial protocol submitted on March 9, 2022, is described here.

To estimate the expected incidence of in-hospital mortality in the etomidate group of the RSI trial, we used data from 656 adults undergoing tracheal intubation for non-traumatic critical illness who were recently enrolled from EDs and ICUs in two recent randomized trials.[2,3] Among these patients, the incidence of 28-day in-hospital mortality was 31%. The minimum clinically important difference (MCID) in mortality used in the design of prior critical care RCTs was an absolute risk reduction of a median of 8 percent (IQR, 6-10).[4] We powered the RSI trial to detect a more conservative absolute risk reduction of 6 percent. This equated to an incidence of the primary outcome of 25% in the ketamine group and a relative risk of mortality with ketamine compared to etomidate of 0.81 – comparable to the relative risk of 0.827 among adults with non-traumatic critical illness observed in the only prior RCT comparing ketamine vs etomidate.[5] Achieving 80% statistical power at a two-sided alpha of 0.05 to detect a 6 percent absolute difference between groups in the primary outcome would require enrolling 911 patients per group (1,822 overall). Anticipating that, like prior Exception from Informed Consent Requirements for Emergency Research (EFIC) trials, less than 5% of patients would discontinue participation after enrollment, we planned to enroll a total of 1,900 patients.

Final Sample Size Estimate

The final version of the sample size estimate, included in the trial protocol on October 18, 2023, at the time of funding of the multicenter stage of the RSI trial, is described here.

At the time of funding of the multicenter stage of the RSI trial through a Patient-Centered Outcomes Research Institute® Award (BPS-2022C3-30021), the sample size was re-estimated using updated estimates of mortality and discontinuation of participation by patients. Based on two newly completed trials in the same settings,[2,3] we updated our estimate for the incidence of all-

cause, 28-day in-hospital mortality (primary outcome) in the etomidate group to 30%. The patient and clinician partners who participated in the development of the PCORI® application also recommended that, for two common and inexpensive interventions, the trial should have adequate statistical power to detect an absolute difference between groups in mortality of approximately 5 percentage points. We used the *bsamsize* R function to calculate that achieving 80% statistical power at a two-sided alpha of 0.05 to detect a difference in mortality of 5.2 percentage points (30.0% in the etomidate group vs 24.8% in the ketamine group) would require enrollment of 2,308 patients. Anticipating that, like prior EFIC trials, less than 3% of participants would discontinue follow up before ascertainment of the primary outcome, we planned to enroll a total of 2,364 patients (1,182 per group).

10. Rationale for the Choice and Analysis of the Primary Outcome

Patients, caregivers, and clinicians on our Steering Committee and in our town halls, Community Engagement Studios, and surveys consistently identified death as a relevant and important outcome of critical illness. Similarly, survival was a universally-recommended outcome in recent international surveys of patients,[6–9] clinicians,[10] and professional societies.[11,12] The 1-month (28 day) timeframe was chosen because any effects of ketamine vs etomidate on the risk of death likely occur over days to weeks, and the risk of death from comorbidities or new health conditions unrelated to the initial critical illness increases over time.

The choice to analyze mortality as a binary variable rather than a time-to-event analysis was based on input from patient stakeholders who reported that, for patients on a breathing machine, death after a prolonged period on a breathing machine did not represent a better outcome than dying sooner.[13] This position is consistent with those expressed by patients and caregivers in prior studies.[14–16]

11. Effect Modification

We will apply the three complementary approaches to analysis of heterogeneity of treatment effect described in the Predictive Approaches to Treatment effect Heterogeneity (PATH) Statement: (1) traditional one-variable-at-a-time subgroup analyses; (2) a risk-modeling approach; and (3) an effect-modeling approach.

Subgroup Analyses. We will examine whether prespecified baseline variables modify the effect of trial group assignment 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, a random effect for trial site, and independent variables of trial group, the proposed effect modifier, and the interaction between the effect modifier and trial group. For categorical variables, we will present the absolute difference 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,[17] we have prespecified the following baseline variables as potential effect modifiers and hypothesized the direction of effect modification for each:

1. Sepsis or septic shock (Yes vs No): We hypothesize that the presence of sepsis or septic shock at enrollment, assessed using the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definition,[18] will modify the effect of trial group assignment on the primary outcome, with a greater decrease in 28-day in-hospital mortality in the ketamine group compared to the etomidate group among patients with sepsis or septic shock, compared to patients without sepsis or septic shock. This hypothesis is supported by inconsistent evidence from prior clinical trials and observational studies suggesting that etomidate-induced decreases in cortisol production may have a larger detrimental effect on outcomes for patients with sepsis or septic shock.[19–26]
2. Vasopressor receipt (Yes vs No): We hypothesize that receipt of vasopressors in the hour prior to enrollment will modify the effect of trial group assignment on the primary outcome,

with a greater decrease in 28-day in-hospital mortality in the ketamine group compared to the etomidate group among patients receiving vasopressors, compared to patients not receiving vasopressors. This hypothesis is supported by secondary outcomes of prior randomized trials and observational studies that suggest etomidate may worsen shock through causing adrenal insufficiency.[26]

3. Patient location (ED vs ICU): We hypothesize that patient location at enrollment will not modify the effect of trial group assignment on the primary outcome.
4. Adrenal insufficiency or chronic receipt of corticosteroids (Yes vs No): We hypothesize that a pre-existing diagnosis of adrenal insufficiency or chronic receipt of corticosteroids prior to enrollment will modify the effect of trial group assignment on the primary outcome, with a greater decrease in 28-day in-hospital mortality in the ketamine group compared the etomidate group among patients with adrenal insufficiency or chronic receipt of corticosteroids, compared to patients without adrenal insufficiency or chronic receipt of corticosteroids. This hypothesis is supported by mechanistic information on the effect of etomidate on synthesis of cortisol by the adrenal glands.[27] In prior observational and interventional studies, the administration of corticosteroids during the acute illness has not appeared to affect the association between receipt of etomidate and death.[19,28]
5. Acute neurologic condition (Yes vs. No). We hypothesize that the presence at the time of enrollment of an acute neurologic condition associated with an increased risk for elevated intracranial pressure, defined as intracranial bleeding, meningitis or encephalitis, or stroke, will modify the effect of trial group assignment on the primary outcome, with a lesser decrease in 28-day in-hospital mortality in the ketamine group compared to the etomidate group among patients with an acute neurologic condition, compared to patients without an acute neurologic condition. This hypothesis is supported by inconsistent evidence that ketamine may increase intracranial pressure in some patients.[29]
6. Active cardiac condition (Yes vs. No). We hypothesize that the presence at the time of enrollment of an active cardiac condition, defined as cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or

myocardial infarction, will modify the effect of trial group assignment on the primary outcome, with a lesser decrease in 28-day in-hospital mortality in the ketamine group compared to the etomidate group among patients with an active cardiac condition, compared to patients without an active cardiac condition. This hypothesis is supported by inconsistent pre-clinical evidence that ketamine may exert a negative ionotropic effect.[30,31]

7. Baseline risk of the primary outcome (continuous): We hypothesize that increased risk of death (increased severity of illness), will modify the effect of trial group assignment on the primary outcome, with a greater decrease in 28-day in-hospital mortality in the ketamine group compared the etomidate group among patients at higher risk of death. This hypothesis is supported by prior research suggesting that patients in critical care trials at higher risk of an outcome frequently experience a larger absolute treatment effect.[32]

Risk-modeling approach. We will examine whether patients' baseline risk of the primary outcome modifies the effect of trial group assignment 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, a random effect for trial site, and independent variables of trial group, patients' baseline risk of the primary outcome, and the interaction between baseline risk of the primary outcome and trial group. Patients' baseline risk of the primary outcome will be defined using two approaches. First, a previously derived and validated multivariable model that uses patient characteristics at the time of intubation to predict the probability of 28-day in-hospital mortality for critically ill adults will be used to generate a predicted probability of the primary outcome (ranging from 0.0 to 1.0) for each patient in the trial. Second, each patient's value at enrolment for the APACHE II score will be used as a measure of the baseline risk.[33]

Effect-modeling approach. The goal of our effect-modeling analyses is to estimate the effect of ketamine vs etomidate on 28-day in-hospital mortality for an individual patient based on his or her baseline characteristics considered simultaneously ("individualized treatment effect").[34–36] First, in a *derivation cohort* of the initial 1,700 patients enrolled in the trial, we will compare the performance of

candidate effect models using 5-fold cross-validation. Specifically, we will consider X-learners with elastic net and random forest base-learners, S-learners with random forest and conditional random forest (cforest) base-learners, T-learner with Bayesian Adaptive Regression Trees (BART) as the base-learner, R-learner with Extreme Gradient Boosting (Xgboost) as the base-learner, and causal forest. The algorithm and base-learner combination resulting in the highest qini coefficient in the out-of-sample predictions from the 5-fold cross-validation will then be fit using all the derivation data to create a final effect model.

Second, in a *validation cohort* of the final 664 patients enrolled in the trial, we will validate the performance of the individualized treatment effect model. To do this, we will use the model to predict the effect of ketamine vs etomidate on 28-day in-hospital mortality for each of the 664 patients in the validation cohort (the patient's predicted individualized treatment effect at the time of enrolment). We will compare the treatment effect predicted by the model to the treatment effect observed in the validation cohort using the qini coefficient,[37] the C statistic for benefit,[38] and measures of clinical utility, in alignment with the PATH guidelines (examining characteristics by quantile of predicted benefit). The effect-modeling analyses may be presented separately from the other trial results if the time required to conduct them or the space required to present them requires doing so.

12. Safety Monitoring and Adverse Events

Ensuring patient safety is an essential component of the RSI trial. Both ketamine and etomidate have been approved by the Food and Drug Administration and used in clinical practice for decades with an established safety profile.[39,40] However, any trial conducted during a high-risk, time-sensitive procedure like tracheal intubation of critically ill patients raises unique safety considerations. This RSI trial addresses these considerations through:

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from ketamine or etomidate;
2. Systematic collection of safety outcomes relevant to use of ketamine and etomidate in this setting;
3. Structured reporting of adverse events.

13. Plan for Communication of Protocol Changes

Any changes to the trial protocol, including changes to eligibility, outcomes, and analyses, will be implemented via a new version of the full trial protocol, tracked with the date of the update, and the version number of the trial protocol. A list summarizing the changes made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the sIRB for approval and tracking prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol version, will be included in the supplementary material for publication.

14. Patient Privacy, Data Storage, and Sharing

Federal regulations 45 CFR 46 111 (a) (7) requires that, when appropriate, there are adequate provisions to protect the privacy of patients and to maintain the confidentiality of data. 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. All patients will be assigned a unique study ID number for tracking. All data collected for this study will be entered into a secure online database. Tools within the secure online database will be used so that only the coordinating center and investigators from the enrolling site will have access to data from patients enrolled at that site. All data will be maintained in the secure online database until the time of study publication. At the time of publication, a de-identified version of the database will be generated. Deidentified data will be available for sharing following trial publication with the requirements and terms of data sharing specified in the trial results manuscript.

15. Trial Status

The RSI trial is a pragmatic, multi-center, non-blinded randomized clinical trial comparing the use of ketamine vs the use of etomidate for induction of anesthesia during emergency tracheal intubation of critically ill adults. Enrollment began on April 6, 2022, and is expected to conclude in 2025.

16. Supplementary Tables

Supplementary Table 1. Example of the table of baseline characteristics for the results manuscript.

Table 1. Characteristics of the Patients at Baseline		
Characteristic	**Ketamine (N=xxx)**	**Etomidate (N=xxx)**
Age, years – median (IQR)*		
Female sex – no. (%)		
Race or ethnic group – no. (%) **		
Non-Hispanic White		
Non-Hispanic Black		
Hispanic		
Other		
Not reported		
Weight, kg – median (IQR)		
Body mass index – median (IQR) ***		
Location of intubation – no. (%)		
Emergency department		
Intensive care unit		
Chronic conditions – no. (%)		
Adrenal insufficiency or chronic receipt of corticosteroids		
Cirrhosis		
Congestive heart failure		
Coronary artery disease		
Hypertension		
Malignancy ****		
Acute conditions – no. (%) *****		
Acute cardiac condition ******		
Acute respiratory failure		
Acute neurologic condition *******		
Sepsis or septic shock		
Glasgow Coma Scale score – median (IQR)		
APACHE II score – median (IQR) ********		
Measurement or treatment within the hour before enrollment		
Highest heart rate, bpm – median (IQR)		
Lowest systolic blood pressure, mm Hg – median (IQR)		
Vasopressor receipt – no. (%)		

* IQR denotes interquartile range.
* Race and ethnicity were reported by patients or their surrogates as part of clinical care and collected from the electronic medical record by research personnel using fixed categories.
*** Body-mass index is computed by the weight in kilograms divided by the square of the height in meters.
**** Malignancy is defined as pulmonary/pleural malignancy, active liquid (leukemia or lymphoma), or malignancy solid non-pulmonary.
***** Data on acute conditions were abstracted from the electronic health record and grouped into prespecified categories. Patients could have had more than one active condition.

****** Acute cardiac condition is defined as cardiac arrest, cardiogenic shock, congestive heart failure, cardiogenic pulmonary edema, pulmonary hypertension, or myocardial infarction present at the time of enrolment.
******* Acute neurologic condition is defined as intracranial bleeding, meningitis or encephalitis, or stroke present at the time of enrolment.
******** Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.

Supplementary Table 2. Example of the table of characteristics of the intubation procedure for the results manuscript.

Table 2. Characteristics of the Intubation Procedure			
Characteristic	**Ketamine (N=xxx)**	**Etomidate (N=xxx)**	**Difference (95% CI)**
Sedative – no. (%)			
Ketamine			
Etomidate			
Other			
None			
Neuromuscular blocking agent – no. (%)			
Rocuronium			
Succinylcholine			
None			
Measurements or treatments at induction of anesthesia			
Oxygen saturation – median (IQR)			
Preoxygenation – no. (%)			
Systolic blood pressure, mm Hg – median (IQR)			
Vasopressor bolus or increase – no. (%)			
Laryngoscope – no. (%)			
Video			
Direct			
Instrument used on the first attempt — no. (%)			
Endotracheal tube with stylet			
Bougie			

Supplementary Table 3. Example of the table of outcomes for the results manuscript.

Outcome	Ketamine (N=xxx)	Etomidate (N=xxx)	Difference (95% CI)
Primary outcome			
All-cause, 28-day in-hospital mortality – no./total no. (%)			
Secondary outcome			
Cardiovascular collapse between induction and 2 minutes after intubation – no./total no. (%)			
Systolic blood pressure < 65 mmHg			
New or increased vasopressor receipt			
Cardiac arrest not resulting in death within 1 hour of induction			
Cardiac arrest resulting in death within 1 hour of induction			
Procedural outcomes			
Successful intubation on the first attempt – no./total no. (%)			
Median time from induction to intubation (IQR) – seconds			
Lowest oxygen saturation, % – median (IQR)			
Lowest oxygen saturation <80% – no./total no. (%)			
Systolic blood pressure > 180 mm Hg – no./total no. (%)			
Safety outcomes			
Systolic blood pressure at 24 hours, mm Hg – median (IQR)			
Receipt of vasopressors at 24 hours – no./total no. (%)			
Cardiac arrest between induction of anesthesia and hospital discharge – no./total no. (%)			
Clinical outcomes*			
Ventilator-free days – median (IQR)			
Vasopressor-free days – median (IQR)			
ICU-free days – median – median (IQR)			

17. Appendices

B. Example Informed Consent Document.

An example of the informed consent document used by trial personnel to obtain prospective, written informed consent for participation in the RSI trial in instances when a patient or Legally Authorized Representative is able to provide informed consent is shown below.

[image redacted for anonymized peer review]

B. Example Notification Document.

For patients for whom neither the patient nor a Legally Authorized Representative were able to provide prospective, written informed consent for participation in the RSI trial prior to enrolment, an example of the notification document used to inform the participant or a Legally Authorized Representative of family member of the patient's enrolment in the trial is shown below.

[image redacted for anonymized peer review]

18. References

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Randomized Trial of Sedative Choice for Intubation

Statistical Analysis Plan Revision Sequence

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