Clinical Trial Protocol

Title	DirEct Versus VIdeo LaryngosCopE Trial (DEVICE)
Acronym	DEVICE
Version	Version 1.0
Date	September 30, 2021
Protocol Chairs	Matthew E. Prekker, MD, MPH Hennepin County Medical Center and University of Minnesota Medical School Brian E. Driver, MD Hennepin County Medical Center and University of Minnesota Medical School Stacy A. Trent, MD, MPH Denver Health Medical Center and University of Colorado School of Medicine Matthew W. Semler MD, MSc Vanderbilt University Medical Center
Coordinating Center	Vanderbilt University Medical Center Director: Jonathan D. Casey, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler MD, MSc
Military Principal Investigators	Maj Brit J Long, MD US Air Force 59MDW MAJ. Steven G. Schauer, MD, MS US Army Institute of Surgical Research and US Air Force 59MDW
Civilian Principal Investigators	Adit A. Ginde, MD, MPH University of Colorado School of Medicine Matthew W. Semler MD, MSc Vanderbilt University Medical Center
Sponsor	Department of Defense

Table of Contents

Trial Summary

Title	DirEct Versus VIdeo LaryngosCopE Trial (DEVICE)
Background	Clinicians perform rapid sequence induction, laryngoscopy, and tracheal intubation for more than 5 million critically ill adults as a part of clinical care each year in the United States. Failure to intubate the trachea on the first attempt occurs in more than 10% of all tracheal intubation procedures performed in the emergency department (ED) and intensive care unit (ICU). Improving clinicians rate of intubation on the first attempt could reduce the risk of serious procedural complications. In current clinical practice, two classes of laryngoscopes are commonly used to help clinicians view the larynx while intubating the trachea: a video laryngoscope (equipped with a camera and a video screen) and a direct laryngoscope (not equipped with a camera or video screen). For every laryngoscopy and intubation procedure performed in current clinical practice, clinicians use either a video or a direct laryngoscope. Prior research has shown that use of a video laryngoscope improves the operator's view of the larynx compared to a direct laryngoscope. Whether use of a video laryngoscope increases the likelihood of successful intubation on the first attempt remains uncertain. A better understanding of the comparative effectiveness of these two common, standard-of-care approaches to laryngoscopy and intubation could improve the care clinicians deliver and patient outcomes.
Study Design	Multi-center, parallel-group, non-blinded, randomized clinical trial
Trial Groups	1. Video laryngoscope group 2. Direct laryngoscope group
Inclusion Criteria	1. Patient is located in a participating 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. Immediate need for tracheal intubation precludes safe performance of study procedures 5. Operator has determined that use of a video laryngoscope or use of a direct laryngoscope is required or contraindicated for the optimal care of the patient
Risks	Participation in this study involves minimal incremental risk because:

	• All patients eligible for the study are already undergoing tracheal intubation with a video laryngoscope or a direct laryngoscope as part of their clinical care • Use of a video laryngoscope and use of a direct laryngoscope are the most common approaches to tracheal intubation of critically ill adults in clinical care • No benefits or risks are currently known to differ between the two approaches • If clinicians determine either approach to be required or contraindicated for the optimal care of an individual patient, the patient is excluded from the study
Benefits	The benefits of the DEVICE trial are largely the indirect benefits to future patients that will result by a better understanding of whether use of video laryngoscope or use of a direct laryngoscope is found to prevent complications.
Consent	The trial will be conducted with waiver of informed consent because: • Participation in the study involves minimal incremental risk • Obtaining informed consent prior to emergency tracheal intubation of critically ill adults is impracticable
Randomization	Using opaque envelopes available in participating units, participants will be randomized 1:1 to either use of a video laryngoscope or use of a direct laryngoscope on the first laryngoscopy attempt. Randomization will be completed in permuted blocks of variable size and stratified by site.
Primary Outcome	Successful intubation on the first attempt, defined as the 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.
Secondary Outcome	Incidence of severe complications, defined as the occurrence of one or more of the following between induction and 2 minutes after intubation: [1] severe hypoxemia (SpO2 <80%), [2] severe hypotension (systolic blood pressure <65 mm Hg or new or increased vasopressor administration), [3] cardiac arrest not resulting in death within 1 hour of induction, or [4] cardiac arrest resulting in death within 1 hour of induction.
Exploratory Outcomes	Procedural: ● Duration from laryngoscopy to tracheal intubation – defined as the interval (in seconds) between insertion of the laryngoscope into the mouth on the first laryngoscopy attempt and final placement of an endotracheal tube or tracheostomy tube in the trachea. ● Number of laryngoscopy attempts

	● Number of attempts to cannulate the trachea with a bougie ● Number of attempts to cannulate the trachea with an endotracheal tube ● Reason for failure to intubate on the first attempt ● Operator-reported aspiration into the airway <u>Safety</u>: ● Esophageal intubation ● Injury to the teeth <u>Clinical</u>: ● ICU-free days in the first 28 days ● Ventilator free days in the first 28 days ● 28-day, all-cause in-hospital mortality
Analysis	The primary analysis will be an intention-to-treat comparison of patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group with regard to the primary outcome of successful intubation on the first attempt. The difference in proportion and the associated 95% confidence interval will be presented. Between group differences will be examined using a Chi-square test.
Sample Size	2,000 patients
Expected Duration	18 months

1 Background

Clinicians frequently perform tracheal intubation of critically ill patients in the emergency department (ED) or intensive care unit (ICU). In 10-20% of emergency tracheal intubations, clinicians are unable intubate the trachea on the first attempt, which increases the risk of peri-intubation complications.[1–4] Successful laryngoscopy and tracheal intubation requires using a laryngoscope to [1] visualize the larynx and vocal cords and [2] create a pathway through which an endotracheal tube can be advanced through the oropharynx and larynx and into the trachea.

In current clinical practice, two classes of laryngoscopes are commonly used by clinicians to view the larynx while intubating the trachea: a video laryngoscope (equipped with a camera and a video screen) and a direct laryngoscope (not equipped with a camera or video screen). Clinicians use either a video laryngoscope or a direct laryngoscope as standard of care for every laryngoscopy and intubation procedure performed in current clinical practice.

Figure 1. Macinosh direct laryngoscope creating a direct line-of-sight to the airway opening (from: Walls Manual of Emergency Airway Management, 5th ed. 2018).

Direct Laryngoscope. The Macintosh direct laryngoscope (Fig. 1) consists of a battery-containing handle and a blade with a light source. The operator achieves a direct line of sight –from the operator's eye through the mouth to the larynx and trachea – by using the laryngoscope blade to displace the tongue and elevate the epiglottis.[5,6]

Video Laryngoscope. Video laryngoscopes consist of a fiberoptic camera and light source near the tip of the laryngoscope blade, which transmits images to a video screen (Fig. 2). The position of the camera near the tip of the laryngoscope blade facilitates visualization of the larynx and trachea.

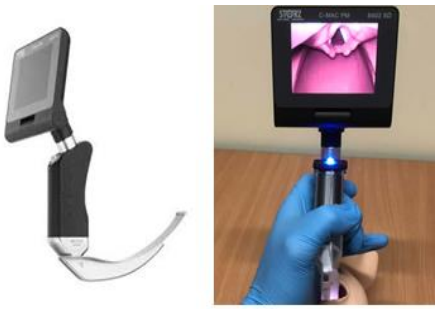

Figure 2. Example of a video laryngoscope with standard geometry blade (C-MAC with pocket monitor, Karl Storz Inc).

Use of a video laryngoscope and use of a direct laryngoscope are both common, standard-of-care approaches the clinicians use to perform tracheal intubation in the ED and ICU in current clinical care.

Currently, it is unknown whether use of a video laryngoscope or use of a direct laryngoscope has any effect on successful intubation on the first attempt or any other outcome. Some prior research has raised the hypothesis that using a video laryngoscope would increase clinicians' rate of successful intubation on the first attempt by facilitating the view of the larynx.[7] Some prior research has raised the hypothesis that using a direct laryngoscope would increase clinicians' rate of successful intubation on the first attempt by facilitating a clear pathway for placement of the tube through the mouth into the trachea.

To date, 8 small single-center randomized trials[8–15] and one 371-patient multicenter randomized clinical trial[16] have been conducted under waiver of or alteration of informed consent to compare use of a video vs a direct laryngoscope in the setting of emergency tracheal intubation in the ED or ICU. Two of these trials provide the most direct preliminary data for this proposal. The "Facilitating EndotracheaL intubation by Laryngoscopy technique and apneic Oxygenation Within the ICU (FELLOW)" randomized clinical trial, conducted under waiver of informed consent, compared these two standard-of-

care approaches during 150 emergency tracheal intubations at Vanderbilt University Medical Center, finding no difference in the rate of successful intubation on the first attempt between use of a video and use of a direct laryngoscope.[11] The "McGrath Mac Videolaryngoscope Versus Macintosh Laryngoscope for Orotracheal Intubation in the Critical Care Unit (MACMAN)" randomized clinical trial among 371 critically ill adults found no difference between use of a video vs direct laryngoscope in the rate of successful intubation on the first attempt. However, a hypothesis-forming post-hoc exploratory analysis of peri-intubation complications suggested that use of a video laryngoscope may be associated with a higher rate of complications than direct laryngoscope (9.5% vs 2.8%, respectively, p=0.01).[16] These trials were underpowered to rule out small but clinically significant differences in first pass success, and were limited to intubations performed by inexperienced trainees in one practice setting (intensive care units), but they demonstrated hypothesis-generating findings requiring validation in larger trials that reflect the full spectrum of settings, operator specialties, and operator experience levels in which emergency tracheal intubation is routinely performed.

Because of the imperative to optimize emergency tracheal intubation in clinical care, the common use of both video and direct laryngoscopes in current clinical practice, and the lack of definitive data from randomized trials to definitively inform whether use of a video laryngoscope or a direct laryngoscope effects the rate of successful intubation on the first attempt, examining whether one approach increases the odds of successful intubation on the first attempt represents an urgent research priority. To address this knowledge gap, we propose to conduct a large, multicenter, randomized clinical trial comparing use of a video laryngoscope versus use of a direct laryngoscope with regard to successful intubation on the first attempt among critically ill adults undergoing tracheal intubation in the ED or ICU.

2 Aims, Hypotheses, and Study Description

2.1 Study Aims

- Primary:
  - To compare the effect of use of a video laryngoscope versus a direct laryngoscope on successful intubation on the first attempt among critically ill adults undergoing tracheal intubation in the acute care setting.

- Secondary:
  - To compare the effect of use of a video laryngoscope versus a direct laryngoscope on severe complications among critically ill adults undergoing tracheal intubation in the acute care setting.

2.2 Study Hypotheses

- Primary:
  - Among critically ill adults undergoing tracheal intubation, use of a video laryngoscope will increase the proportion of patients who experience successful intubation on the first attempt, compared with use of a direct laryngoscope.

- Secondary
    - Among critically ill adults undergoing tracheal intubation, use of a video laryngoscope will decrease the proportion of patient who experience a severe complication, compared with use of a direct laryngoscope.

2.3 Study Description

To address these aims, we propose a multi-center, non-blinded, parallel-group, randomized clinical trial evaluating the effect of use of a video laryngoscope versus a direct laryngoscope on successful intubation on the first attempt among critically ill adults undergoing tracheal intubation. Patients located in participating EDs and ICUs who are determined by treating clinicians to require tracheal intubation and who meet eligibility criteria will be enrolled and randomly assigned to either use of a video laryngoscope or use of a direct laryngoscope. All other decisions regarding the intubation procedure will be at the discretion of the treating clinicians.

3 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Patient is located in a participating 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. Immediate need for tracheal intubation precludes safe performance of study procedures.
5. Operator has determined that use of a video laryngoscope or use of a direct laryngoscope is required or contraindicated for the optimal care of the patient.

4 Consent

Use of a video laryngoscope and use of a direct laryngoscope are both common approaches to emergency tracheal intubation during emergency tracheal intubation in the ED and ICU. Both represent standard-of-care treatment in current clinical practice. Results from prior clinical trials are conflicting and do not demonstrate superiority of one approach over the other. Consequently, some guidelines do not strongly recommend for or against the use of a video laryngoscope or a direct laryngoscope on the first attempt at tracheal intubation of critically ill adults.[17] As a result, significant variation exists in the use of a video laryngoscope vs use of a direct laryngoscope in current clinical practice.[2] This trial will only enroll patients who are undergoing emergency tracheal intubation as part of their clinical care for whom the treating clinicians feel that either a video laryngoscope or a direct laryngoscope would be consistent with the optimal care of the patient. We will request a waiver of informed consent because the study involves minimal incremental risk and obtaining informed consent would be impracticable.

Participation in this study involves minimal incremental risk because:

- Both approaches to tracheal intubation being compared are commonly used in routine clinical care;
- Both are interventions to which patients would be exposed even if not participating in the study (all patients undergoing laryngoscopy and tracheal intubation receive either a video laryngoscope or a direct laryngoscope);
- No established differences in risk and benefit are known to exist between the two approaches based on the currently available data; and
- Patients are only eligible to participate if their treating clinicians have determined that both approaches are acceptable for the optimal care of the patient.

Obtaining informed consent would be impracticable because:

- **The expected medical condition of patients requiring emergency tracheal intubation in the ED or ICU is critical.** Based on prior trials in the same patient population and setting, approximately 70% of patients eligible for the DEVICE trial will be experiencing encephalopathy (altered mental status) due to their illness. The anticipated 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 DEVICE will not have the capacity to provide informed consent. Further, family members or legally authorized representatives (LAR) are frequently unavailable when critically ill patients undergo intubation in the ED or ICU.
- **The time available for patients or LARs to consider participation will be insufficient.** Even in instances in which a patient retains capacity, or an LAR is immediately available, a meaningful informed consent is precluded by the rapid clinical events leading up to emergency tracheal intubation. No published literature has quantified the time from the decision to perform emergency tracheal intubation (the inclusion criteria for DEVICE) until the initiation of the intubation procedure (the trial intervention). In a convenience sample of 25 consecutive intubations in the VUMC ED or ICU, approximately 50% of intubations occurred within 5 minutes after treating clinicians verbalized the decision to intubate (or placed a written order for an induction medication). Obtaining informed consent for research requires study 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 question. Meaningful informed consent cannot be executed in the 5 minutes between the decision to perform emergency tracheal intubation and the initiation of the procedure. Emergency tracheal intubation of critically ill adults is a time-sensitive procedure for which every minute of delay increases the likelihood of hypoxemia, hypotension, and peri-procedural cardiac arrest. Delaying emergency tracheal intubation for a critically ill adult to attempt a meaningful informed consent process would be unsafe, impracticable, and unethical.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, we will request a waiver of informed consent. Numerous previous randomized trials comparing two standards of

care for emergency intubation have also been completed under a waiver of informed consent, including multiple small trials comparing the identical interventions studied in DEVICE.[8–16,18–25]

4.1 Information for Patients and Families

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

5 Study Sites, Enrollment, and Randomization

5.1 Study Enrollment Locations

1. Participating emergency departments
2. Participating intensive care units

5.2 Study Enrollment Location

- Participating emergency departments
- Participating intensive care units

5.3 Enrollment and Randomization

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

At enrollment, patients will be randomized in a 1:1 ratio to undergo intubation using a video laryngoscope or a direct laryngoscope using randomly permuted blocks of variable size. The randomization will be stratified by study site (each participating ED and ICU will comprise a different stratum). The study group assignments will be placed in opaque randomization envelopes, which will be located within participating units. Study group assignment will remain concealed to study personnel and treating clinicians until after the decision has been made to enroll the patient in the study.

To facilitate rapid enrollment during this time-sensitive procedure, sequentially numbered randomization envelopes will be located adjacent to the equipment required for emergency tracheal intubation (i.e., airway equipment cart, ICU work room). When the need for emergency tracheal intubation is recognized, envelopes will be obtained by the treating clinician performing the intubation (referred to as the "operator") or by a delegate while the operator sets up the equipment required for intubation. Inclusion and exclusion criteria will be posted with randomization envelopes and printed on the outside of enrollment envelopes. As the operator sets up the equipment for emergency tracheal intubation, a verbal "pre-procedural time-out" (described below) will be performed. Based on the experience from our 8 prior randomized clinical trials using the same process to perform randomization and group assignment during emergency tracheal intubation, all enrollment procedures can be completed

in less than one minute. For a small number of particularly urgent intubations (e.g., an intubation for cardiac arrest), the urgency of the procedure or the limited availability of clinical personnel will preclude obtaining and opening the randomization envelope. These cases will be excluded using the exclusion criterion that states "Immediate need for tracheal intubation precludes safe performance of study procedures" (see Section 3).

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

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

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

5.3.2 Monitoring and Reporting of Eligibility of Enrolled Patients

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

5.3.3 Handling of Patients Found to Be Prisoners after Enrollment

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

If a patient who presents to the ED or ICU is not known to be a prisoner at the time of enrollment and following enrollment is discovered to be a prisoner or becomes a prisoner between enrollment and the end of study follow up, all study procedures will stop immediately, the patient will be withdrawn from the study, and the patient's study record will be expunged of all study data except the anonymous study ID and randomized group assignment. 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 Study Procedures

For enrolled patients, study group assignment determines only the choice of laryngoscope. Operators may opt to use the non-assigned laryngoscope type on the first laryngoscopy attempt if it is felt to be required for the safe care of the patient. The occurrence of such "crossover" event will be recorded along with the indication. All other aspects of the intubation procedure in both study groups will be at the discretion of the operator. For all patients in the trial, best practices in tracheal intubation will be encouraged according to clinical protocols in the study settings.

6.1 Video Laryngoscope Group

For patients assigned to the video laryngoscope group, the operator will use a video laryngoscope on the first laryngoscopy attempt. A video laryngoscope will be defined as a laryngoscope with a camera and a video screen. Trial protocol will not dictate the brand of video laryngoscope.

6.2 Direct Laryngoscope Group

For patients assigned to the direct laryngoscope group, the operator will use a direct laryngoscope on the first laryngoscopy attempt. A direct laryngoscope will be defined as a laryngoscope without a camera and a video screen. Trial protocol will not dictate the brand of direct laryngoscope or the blade shape. E

7 Data Collection and Outcome Measures

7.1 Data Collection

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

The following variables will be recorded:

Baseline:

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

Peri-procedural:

Enrollment to induction

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

Induction to first laryngoscopy attempt

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

First laryngoscopy attempt to successful intubation

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

In-hospital:

24 hours after enrollment

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

28 days after enrollment

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

7.2 Recorded Study Outcomes

7.2.1 Primary Outcome

The primary outcome is successful intubation on the first attempt. Successful intubation on the first attempt is 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.

The primary outcome will be collected by an observer trained in recording the number of insertions of the laryngoscope blade into the mouth and the number of insertions of a bougie and endotracheal tube into the mouth. If data on the primary outcome from the independent observer are missing, the operator's self-report of successful intubation on the first attempt will be used.

7.2.2 Secondary Outcome

The secondary outcome is severe complications occurring between induction and 2 minutes after successful intubation, defined as one or more of the following:

1. severe hypoxemia (lowest oxygen saturation measured by pulse oximetry < 80%);
2. severe hypotension (systolic blood pressure < 65 mm Hg or new or increased vasopressor administration);
3. cardiac arrest not resulting in death; or
4. cardiac arrest resulting in death.

Cardiac arrest will be considered to have resulted in death if a patient who experienced cardiac arrest between induction and 2 minutes after intubation died within the 1 hour following intubation.

7.2.3 Exploratory Outcomes

Exploratory procedural outcomes:

- Duration of laryngoscopy and tracheal intubation – defined as the interval (in seconds) between the first insertion of a laryngoscope blade into the mouth and the final placement of an endotracheal tube or tracheostomy tube in the trachea.
- Number of laryngoscopy attempts
- Number of attempts to cannulate the trachea with a bougie or an endotracheal tube
- Successful intubation on the first attempt without a severe complication
- Reason for failure to intubate on the first attempt
    - Inadequate view of the larynx
    - Inability to intubate the trachea with an endotracheal tube
    - Inability to cannulate the trachea with a bougie
    - Attempt aborted due to change in patient condition (e.g., worsening hypoxemia, hypotension, bradycardia, vomiting, bleeding)
    - Technical failure of the laryngoscope (e.g., battery, light source, camera, screen)
    - Other
- Operator-reported aspiration

Exploratory safety outcomes:

- Esophageal intubation
- Injury to the teeth

Exploratory clinical outcomes:

- ICU-free days in the first 28 days
- Ventilator free days in the first 28 days
- 28-day all-cause in-hospital mortality

8 Risks and Benefits

8.1 Risks of Tracheal Intubation in the ED or ICU

Patients who are severely ill enough to require emergency tracheal intubation in the ED or ICU as part of their clinical care are at high risk of complications. Many patients are undergoing intubation for hypoxemia or hemodynamic instability. Severe hypoxemia or cardiovascular instability occurs during nearly half of intubations in the ED and ICU, and cardiac arrest occurs in approximately 1-in-25 cases. In 10-20% of emergency tracheal intubations, clinicians are unable intubate the trachea on the first attempt, which increases the risk of these severe peri-intubation complications.[1–4]

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

8.2 Potential Risks of Participation in the DEVICE Trial

Participation in this study involves minimal incremental risk because:

- Both approaches to tracheal intubation being compared are commonly used in routine clinical care;
- Both are interventions to which patients would be exposed even if not participating in the study (all patients undergoing emergency tracheal intubation receive either a video or a direct laryngoscopy);
- No established differences in risk and benefit are known to exist between the two approaches based on the currently available data; and
- Patients are only eligible to participate if their treating clinicians have determined that both approaches are acceptable for the optimal care of the patient.

Although no risks are currently known to differ between intubation with a video laryngoscope and intubation with a direct laryngoscope (both standard-of-care approaches in currently clinical care), it is possible that the results of the DEVICE trial will ultimately demonstrate a difference between the two approaches in the risk of hypoxemia, hypotension, cardiac arrest, aspiration, or another outcome.

8.3 Potential Benefits of Participation in the DEVICE Trial

The primary benefits of the DEVICE trial will be the indirect benefits to society that would result if one type of laryngoscope is found to prevent complications. Because millions of critically ill adults undergo

emergency tracheal intubation each year, if one of the two approaches were found to prevent serious complications, the findings would immediately improve the care provided to millions of severely ill patients. Compared to the minimal risks of participation in the study, the pursuit of these benefits is reasonable.

8.4 Minimization of Risk

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

Both video laryngoscopy and direct laryngoscopy have been used in clinical practice for years with an established safety profile in the same populations included in the DEVICE trial. To further mitigate risk, we will exclude patients for whom treating clinicians determine that a specific laryngoscope is required or contraindicated for the optimal care of the patient.

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

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

9 Statistical Considerations

9.1 General Considerations

We will present summary tabulations by treatment group. For categorical variables, the number and proportion of patients within each category (with a category for missing data as needed) of the parameter will be presented. For continuous variables, the number of patients, mean or median as appropriate, and standard deviation or interquartile range as appropriate, will be presented.

We will analyze a single pre-specified primary outcome and a single pre-specified secondary outcome using a chi-square test. Consistent with recommendations of the Food and Drug Administration[26] and the European Medicines Agency,[27] each will be tested using a two-sided P value with a significance level of 0.05. For all other analyses except safety analyses, emphasis will be placed on the estimate of effect size with 95% confidence intervals, as recommended by the *International Committee of Medical Journal Editors*,[28] and no corrections for multiple comparisons will be performed.

9.2 Sample Size Estimation

The minimum clinically important difference in successful intubation on the first attempt that would be required to justify routine use of a video laryngoscope rather than a direct laryngoscope in clinical care is uncertain. The current trial will be designed to detect a 5% absolute difference between groups in the incidence of successful intubation on the first attempt. An absolute difference of 5% in successful intubation on the first attempt is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.[8,11,24] Assuming an incidence of successful intubation on the first laryngoscopy attempt of 80% in the direct laryngoscope group based on data from a recently completed trial in the same ED and ICU settings, detecting a 5% absolute increase in the incidence of successful intubation on the first attempt with 90% power at a two-sided alpha level of 0.05 would require enrollment of 1,920 patients (960 per group), anticipating 16 enrolling sites (clusters) and an intra-cluster correlation of 0.05. Anticipating missing data for up to 4% of patients, we will plan to enroll a total of 2,000 patients (1,000 per group).

9.3 Analysis Populations

The primary analysis will occur in an intent-to-treat (ITT) fashion among all patients randomized, excluding only those patients whose data was withdrawn from the study (e.g., a patient who became a prisoner during the follow up period).

9.4 Statistical Analysis

Before enrollment is complete, a complete final statistical analysis plan will be made publicly available. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers after completion of enrollment will be identified as *post hoc*.

9.4.1 Primary Analysis

Main analysis of the primary outcome. The primary analysis will be an intention-to-treat comparison of patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group with regard to the primary outcome of successful intubation on the first attempt. The difference in proportion and the associated 95% confidence interval will be presented. Between group differences will be examined using a Chi-square test.

9.4.2 Secondary Analyses

We will perform:

1. Intention-to-treat comparisons of secondary, exploratory, and safety outcomes; and
2. Intention-to-treat comparison of the primary outcome between groups using a generalized linear mixed effects model including a random effect for site and fixed effects for group assignment and pre-specified baseline variables, including: age; sex; body mass index; and location at enrollment (ED or ICU).

9.4.3 Effect Modification (Subgroup Analyses)

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

- Operator Experience
    - Total number of previous intubations performed by operator
    - Number of previous intubations performed by operator with a direct laryngoscope
- Operator's planned video laryngoscope (hyperangulated blade vs. non-hyperangulated blade)
- Location (ED vs ICU)
- Presence of difficult airway characteristics
- Indication for tracheal intubation of trauma (Yes vs No)
- Chest compressions being delivered during the first laryngoscopy attempt (Yes vs No)

9.4.4 Handling of Missing Data

We anticipate that no data on the primary outcome will be missing. When data are missing for the secondary or exploratory outcomes, we will perform complete-case analysis, excluding cases where the data for the analyzed outcome are missing. There will be no imputation of missing data for these outcomes. In adjusted analyses, missing data for covariates will be imputed using multiple imputations.

9.4.5 Interim Analysis

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, after enrollment of 1,000 patients. The stopping boundary for efficacy will be met if the P value for the difference in the primary outcome (successful intubation on the first attempt) between groups using a Chi-square test is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

At the interim analysis, the DSMB will evaluate the rate of the primary outcome in the direct laryngoscope group. If the rate of the primary outcome in the direct laryngoscope group differs substantially from the original estimate of 80.0%, the DSMB may suggest that the investigators perform a sample size re-estimation to maintain adequate statistical power to detect the planned relative risk difference in the primary outcome between groups.

10 Privacy and Confidentiality

All patients will be assigned a unique study ID number for use in the coded study database. Study personnel will access patients' electronic health records at three planned time points: immediately following enrollment; when collecting baseline demographics and comorbidities (may occur anytime between enrollment and final data collection); and when collecting clinical outcomes (any time after the first of discharge or 28 days following intubation). The electronic health record may be accessed again, as needed, between enrollment and study publication to respond to queries from the coordinating center focused on ensuring data completeness and quality. The minimal PHI that is collected will be visible only to site investigators at the site where the patient was enrolled. The dataset for analysis will contain the unique study ID and no other patient identifiers. At the time of publication, a fully de-identified version of the database will be generated.

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

11 Follow-up and Record Retention

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

12 Safety Monitoring and Adverse Events

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

1. Exclusion criteria designed to prevent enrollment of patients likely to experience adverse events from intubation using a video laryngoscope or intubation using a direct laryngoscope;
2. Systematic collection of outcomes relevant to the safety of intubation using a video laryngoscope or intubation using a direct laryngoscope;
3. Structured monitoring, assessment, recording, and reporting of adverse events.

12.1 Adverse Event Definitions

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

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

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

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

12.2 Monitoring for Adverse Events

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

12.3 Recording and Reporting Adverse Events

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

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

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

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

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

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

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

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

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

Note: A study-specific clinical outcome may also qualify as an adverse event meeting criteria for recording and reporting. For example, an injury to the teeth that the investigator considers Definitely Related to randomization to use of a direct laryngoscope would be both recorded as a study-specific clinical outcome and recorded and reported as a Serious and Definitely Related adverse event.

12.5 Unanticipated Problems involving Risks to Subjects or Others

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

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

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

13 Data and Safety Monitoring Board (DSMB)

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

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

The DSMB will consist of members with expertise in bioethics, emergency medicine, pulmonary and critical care medicine, anesthesia, biostatistics, and clinical trials. Appointment of all members is contingent upon the absence of any conflicts of interest. All the members of the DSMB are voting members. The coordinating center, principal investigators, and unblinded study biostatistician will be responsible for the preparation of all DSMB and adverse event reports. The DSMB will develop a charter and review the protocol and patient notification forms during its first meeting. Subsequent DSMB meetings will be scheduled in accordance with the DSMB Charter. The DSMB will have the ability to recommend that the trial end, be modified, or continued unchanged.

14 References

1. Sakles JC, Chiu S, Mosier J, Walker C, Stolz U. The importance of first pass success when performing orotracheal intubation in the emergency department. *Acad Emerg Med*. 2013;20(1):71-78.

2. Russotto V, Myatra SN, Laffey JG, et al. Intubation Practices and Adverse Peri-intubation Events in Critically Ill Patients From 29 Countries. *JAMA*. 2021;325(12):1164-1172.

3. Brown CA 3rd, Bair AE, Pallin DJ, Walls RM, NEAR III Investigators. Techniques, success, and adverse events of emergency department adult intubations. *Ann Emerg Med*. 2015;65(4):363-370.e1.

4. Park L, Zeng I, Brainard A. Systematic review and meta-analysis of first-pass success rates in emergency department intubation: Creating a benchmark for emergency airway care. *Emerg Med Australas*. 2017;29(1):40-47.

5. Hirsch NP, Smith GB, Hirsch PO. Alfred Kirstein. Pioneer of direct laryngoscopy. *Anaesthesia*. 1986;41(1):42-45.

6. Burkle CM, Zepeda FA, Bacon DR, Rose SH. A historical perspective on use of the laryngoscope as a tool in anesthesiology. *The Journal of the American Society of Anesthesiologists*. 2004;100(4):1003-1006.

7. Mosier JM, Sakles JC, Law JA, Brown CA 3rd, Brindley PG. Tracheal Intubation in the Critically Ill. Where We Came from and Where We Should Go. *Am J Respir Crit Care Med*. 2020;201(7):775-788.

8. Driver BE, Prekker ME, Moore JC, Schick AL, Reardon RF, Miner JR. Direct Versus Video Laryngoscopy Using the C-MAC for Tracheal Intubation in the Emergency Department, a Randomized Controlled Trial. *Acad Emerg Med*. 2016;23(4):433-439.

9. Goksu E, Kilic T, Yildiz G, Unal A, Kartal M. Comparison of the C-MAC video laryngoscope to the Macintosh laryngoscope for intubation of blunt trauma patients in the ED. *Turk J Emerg Med*. 2016;16(2):53-56.

10. Griesdale DEG, Chau A, Isac G, et al. Video-laryngoscopy versus direct laryngoscopy in critically ill patients: a pilot randomized trial. *Can J Anaesth*. 2012;59(11):1032-1039.

11. Janz DR, Semler MW, Lentz RJ, et al. Randomized Trial of Video Laryngoscopy for Endotracheal Intubation of Critically Ill Adults. *Crit Care Med*. 2016;44(11):1980-1987.

12. Kim JW, Park SO, Lee KR, et al. Video laryngoscopy vs. direct laryngoscopy: Which should be chosen for endotracheal intubation during cardiopulmonary resuscitation? A prospective randomized controlled study of experienced intubators. *Resuscitation*. 2016;105:196-202.

13. Silverberg MJ, Li N, Acquah SO, Kory PD. Comparison of video laryngoscopy versus direct laryngoscopy during urgent endotracheal intubation: a randomized controlled trial. *Crit Care Med*. 2015;43(3):636-641.

14. Sulser S, Ubmann D, Schlaepfer M, et al. C-MAC videolaryngoscope compared with direct laryngoscopy for rapid sequence intubation in an emergency department: A randomised clinical trial. *Eur J Anaesthesiol*. 2016;33(12):943-948.

15. Yeatts DJ, Dutton RP, Hu PF, et al. Effect of video laryngoscopy on trauma patient survival: a randomized controlled trial. *J Trauma Acute Care Surg*. 2013;75(2):212-219.

16. Lascarrou JB, Boisrame-Helms J, Bailly A, et al. Video Laryngoscopy vs Direct Laryngoscopy on

Successful First-Pass Orotracheal Intubation Among ICU Patients: A Randomized Clinical Trial. *JAMA*. 2017;317(5):483-493.

17. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth*. Published online 2017. https://www.sciencedirect.com/science/article/pii/S000709121754060X

18. Tekwani KL, Watts HF, Sweis RT, Rzechula KH, Kulstad EB. A comparison of the effects of etomidate and midazolam on hospital length of stay in patients with suspected sepsis: a prospective, randomized study. *Ann Emerg Med*. 2010;56(5):481-489.

19. Jabre P, Combes X, Lapostolle F, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet*. 2009;374(9686):293-300.

20. Semler MW, Janz DR, Lentz RJ, et al. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med*. 2016;193(3):273-280.

21. Janz DR, Semler MW, Joffe AM, et al. A Multicenter Randomized Trial of a Checklist for Endotracheal Intubation of Critically Ill Adults. *Chest*. 2018;153(4):816-824.

22. Semler MW, Janz DR, Russell DW, et al. A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults. *Chest*. 2017;152(4):712-722.

23. Caputo N, Azan B, Domingues R, et al. Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial). *Acad Emerg Med*. 2017;24(11):1387-1394.

24. Driver BE, Prekker ME, Klein LR, et al. Effect of Use of a Bougie vs Endotracheal Tube and Stylet on First-Attempt Intubation Success Among Patients With Difficult Airways Undergoing Emergency Intubation: A Randomized Clinical Trial. *JAMA*. 2018;319(21):2179-2189.

25. Casey JD, Janz DR, Russell DW, et al. Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. *N Engl J Med*. 2019;380(9):811-821.

26. E9 Statistical Principles for Clinical Trials. Food and Drug Administration. Accessed June 9, 2021. https://www.fda.gov/media/71336/download

27. Statistical Principles for Clinical Trials. European Medicines Agency. Accessed June 9, 2021. https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

28. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. International Committee of Medical Journal Editors. Accessed June 9, 2021. http://www.icmje.org/icmje-recommendations.pdf

Tracking of Protocol Versions:

Version 1.0 – Initial Submission (September 30, 2021)