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DirEct Versus VIdeo LaryngosCopE (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial in critically ill adults undergoing emergency tracheal intubation

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Abstract:

Introduction:

Among critically ill patients undergoing orotracheal intubation in the emergency department (ED) or intensive care unit (ICU), failure to visualize the vocal cords and intubate the trachea on the first attempt is associated with an increased risk of complications. Two types of laryngoscopes are commonly available: direct laryngoscopes and video laryngoscopes. For critically ill adults undergoing emergency tracheal intubation, it remains uncertain whether use of a video laryngoscope increases the incidence of successful intubation on the first attempt compared with use of a direct laryngoscope.

Methods and Analysis:

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a prospective, multi-center, non-blinded, randomized trial being conducted in 6 EDs and 10 ICUs in the United States. The trial plans to enroll up to 2,000 critically ill adults undergoing orotracheal intubation with a laryngoscope. Eligible patients are randomized 1:1 to the use of a video laryngoscope or a direct laryngoscope for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is the incidence of severe complications between induction and 2 minutes after intubation, defined as the occurrence of one or more of the following: severe hypoxemia (lowest oxygen saturation < 80%); severe hypotension (systolic blood pressure < 65 mm Hg or new or increased vasopressor administration); cardiac arrest; or death. Enrollment began on March 16, 2022 and is expected to be completed in 2023.

Ethics and Dissemination:

The trial protocol was approved with waiver of informed consent by the single institutional review board at Vanderbilt University Medical Center and the Human Research Protection

Office of the Department of Defense. The results will be presented at scientific conferences and submitted for publication in a peer-reviewed journal.

Trial Registration

ClinicalTrials.gov registration (NCT05239195) on February 14, 2022, prior to the enrollment of the first patient.

Strengths and Limitations of this Study

- This protocol describes in detail the design and methods for a large, pragmatic trial of laryngoscope type for the emergency tracheal intubation of critically ill adults.
- Conduct in the emergency departments and intensive care units of multiple centers among operators with diverse prior experience with tracheal intubation, as well as broad patient eligibility criteria, will increase the external validity of trial results.
- Patients, clinicians, and investigators are not blinded to the study group assignment after randomization.

Introduction

Tracheal intubation is a common procedure in the emergency department (ED) and intensive care unit (ICU). Among critically ill patients undergoing tracheal intubation, failure to intubate the trachea on the first attempt is associated with increased risk of complications, including hypoxemia, hypotension, aspiration, and cardiac arrest.[1,2]

Emergency tracheal intubation is typically performed in three discrete steps. First, the patient is administered medications to facilitate optimal intubating conditions (rapid sequence induction). Second, a clinician inserts a laryngoscope into the patient's mouth to visualize the vocal cords (laryngoscopy). Third, an endotracheal tube is inserted into the mouth, alongside the laryngoscope, and the tube is advanced past the vocal cords into the trachea (intubation).

The direct laryngoscope, the traditional instrument consisting of a battery-containing handle attached to a blade with a light source, has been used to visualize the vocal cords for tracheal intubation for over 100 years and remains the most commonly used device for the intubation of critically ill adults in the ED or ICU.[2–5] The operator uses the direct laryngoscope to displace the tongue and elevate the epiglottis to facilitate intubation of the trachea under direct visualization. Obtaining an adequate view of the larynx with a direct laryngoscope can be challenging, especially for inexperienced operators. Once a view of the larynx is obtained, passage of the endotracheal tube follows the operator's direct line-of-sight through the mouth to the vocal cords.

Over the last two decades, video laryngoscopes have provided an alternative to direct laryngoscopes for visualizing the vocal cords to facilitate tracheal intubation.[6,7] A camera embedded near the tip of the video laryngoscope blade transmits an image of the vocal cords to a screen that the operator can view during the procedure.[8] Because the camera is located near the tip of the laryngoscope blade, obtaining a view of the larynx may be easier with a video laryngoscope compared with a direct laryngoscope. However, because this view can be obtained without generating a direct line-of-sight through the mouth to the vocal cords, the

process of passing an endotracheal tube may be more difficult when using a video laryngoscope. When considering both aspects of tracheal intubation, visualizing the vocal cords and passing the endotracheal tube, it remains uncertain whether use of a video laryngoscope increases the incidence of successful intubation on the first attempt.

Among elective tracheal intubations in the operating room, use of video laryngoscope probably increases the incidence of successful intubation on the first attempt and decreases complications compared to use of a direct laryngoscope, supported with moderate certainty in the existing anesthesiology literature.[9] Extrapolating the results of randomized clinical trials conducted in the operating room to non-operating room settings is problematic because of factors related to the patient, the operator, and the environment.[10,11] Because tracheal intubation of critically ill adults outside of the operating room is common, complications of intubation in the ED and ICU are common, and use of a video laryngoscope during intubation in the ED and ICU has increased significantly over time,[9,12] understanding the effects of use of a video laryngoscope vs direct laryngoscope on successful intubation on the first attempt in these settings is a priority.

Previous trials randomizing patients to use of a video laryngoscope or a direct laryngoscope during emergency tracheal intubation in prehospital[13–18], ED[19–25], and ICU settings[26–32] have been small and heterogeneous and have generally suggested that while a video laryngoscope improves the view of the larynx and reduces the incidence of esophageal intubation, it may not affect the incidence of successful intubation on the first attempt. Findings were similar in the largest such trial to date, a 371-patient, multicenter, randomized clinical trial in French medical ICUs in which use of video laryngoscope failed to improve successful intubation on the first attempt (68% vs. 70%; p = 0.60) and was associated with a greater incidence of severe peri-procedural complications in post-hoc analyses.[33]

The sample size of these prior trials did not provide sufficient statistical power to definitively rule out a clinically important effect of use of a video laryngoscope vs direct

laryngoscope on successful intubation on the first laryngoscopy attempt or the incidence of complications. To compare the effectiveness of these two commonly used devices during this important emergency procedure, a large trial conducted across a wide variety of clinical settings, operator specialties, and levels of operator experience is required. Therefore, we designed the DirEct Versus VIdeo LaryngosCopE (DEVICE) trial to test the hypothesis that, among critically ill adults undergoing emergency tracheal intubation in the ED or ICU, use of a video laryngoscope will increase the incidence of successful intubation on the first attempt compared with use of a direct laryngoscope.

Methods and Analysis

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Figure 1; supplementary file, section 1).[34]

Patient and Public Involvement

Materials used to communicate details of the study with patients and family members were developed with input from the Vanderbilt Community Advisory Council. Study authors will disseminate the results of this study online and via social media in forms suitable for public understanding.

Study Design

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing use of a video laryngoscope to use of a direct laryngoscope for the first attempt at emergency tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. An

independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study institutions and investigators are listed in the supplementary file, section 2.

Study Population

The inclusion criteria for this study are:

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.

The exclusion criteria for the study are:

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.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo intubation using a video laryngoscope or using a direct laryngoscope for the first attempt in permuted blocks of variable size, stratified by study site. Study-group assignments are generated using a computerized randomization sequence, placed in sequentially numbered opaque envelopes, and distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets eligibility criteria, records the predicted difficulty of intubation (“easy”, “moderate”, or “difficult”) and selects the blade shape the operator plans to use if the patient is randomized to the video laryngoscope group (“hyperangulated” or “non-hyperangulated / standard geometry”). The

operator or delegate then opens the envelope. Patients are enrolled once the envelope is opened to reveal the study group assignment. After enrollment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Video Laryngoscope Group

For patients assigned to the video laryngoscope group, operators are instructed to use a video laryngoscope on the first laryngoscopy attempt. A video laryngoscope is defined as a laryngoscope with a camera and a video screen. Trial protocol does not dictate the brand of video laryngoscope or the geometry of the laryngoscope blade (e.g. hyperangulated vs. non-hyperangulated), but these details will be recorded. Operators are encouraged, but not required, to view the video screen during laryngoscopy ("indirect laryngoscopy") and tracheal intubation.

Direct Laryngoscope Group

For patients assigned to the direct laryngoscope group, operators are instructed to use a direct laryngoscope on the first laryngoscopy attempt. A direct laryngoscope is defined as a laryngoscope without a camera and a video screen. Trial protocol does not dictate the brand of direct laryngoscope or the geometry of the laryngoscope blade (e.g. curved [Macintosh] vs. straight [Miller]), but these details will be recorded.

Co-Interventions and Subsequent Attempts at Laryngoscopy and Intubation

Study group assignment determines only the type of laryngoscope (video vs direct) used on the first laryngoscopy attempt. If determined to be required to ensure optimal care of the patient, treating clinicians may use any device at any time, regardless of study group assignment. Cases in which clinicians use a laryngoscope discordant with randomized assignment on the first intubation attempt will be documented and tracked. All aspects of the

intubation procedure, except the type of laryngoscope used on the first attempt, are at the discretion of treating clinicians, including selection of sedative and neuromuscular blocking medications, patient positioning, approach to pre-oxygenation, use of a bougie or a stylet, and endotracheal tube size. Best practices in tracheal intubation will be encouraged according to clinical protocols at the study sites. The trial intervention ends after the first attempt at laryngoscopy. If the first attempt is unsuccessful, the operator may use any method of intubation on subsequent intubation attempts, including use of a direct laryngoscope in the video laryngoscope group or use of a video laryngoscope in the direct laryngoscope group. The type of laryngoscope used during the initial and final laryngoscopy attempt will be collected and reported.

Data Collection

A trained observer, not directly involved with the intubation procedure, collects data for key peri-procedural outcomes. These outcomes include successful intubation on the first attempt, time interval between laryngoscopy and successful intubation, the oxygen saturation and systolic blood pressure at induction, the lowest oxygen saturation and systolic blood pressure between induction and 2 minutes after successful intubation, and new or increased vasopressor administration between induction and 2 minutes after successful intubation. Observers may be clinical personnel on the enrolling unit (e.g., physician, nurse, or pharmacist) or research study personnel.

Immediately following the intubation procedure, the operator completes a paper data collection form to record the approach to preoxygenation, oxygenation and ventilation between induction and laryngoscopy, the brand of laryngoscope used, the blade shape, the Cormack-Lehane grade of laryngeal view[35], use of the video screen to visualize the larynx (if applicable), use of a bougie or a stylet, reasons for failure to intubate on the first attempt (if applicable), intubation approaches on subsequent attempts, difficult airway characteristics observed before

or during the procedure (facial trauma, small mouth opening, limited neck mobility, cervical collar, large neck, obesity, fluids obscuring view of vocal cords, upper airway obstruction or edema), and complications of intubation (witnessed pulmonary aspiration, esophageal intubation, injury to airways, injury to teeth, cardiac arrest between induction and 2 minutes following intubation). Operators record their specialty, training level, and estimates of the number of previous intubations they have performed and the number of previous intubations they have performed using a direct laryngoscope.

Study personnel at each site review the medical record to collect data on baseline patient characteristics, pre- and post-laryngoscopy management, and clinical outcomes at 28 days after enrollment.

The following variables are collected:

1. Baseline: Age, sex, height, weight, race, ethnicity, Acute Physiology and Chronic Health Evaluation II (APACHE II) score[36], active medical problems at the time of enrollment, comorbidities, indication for intubation, vasopressor receipt in the hour prior to enrollment, highest FIO_2 in the hour prior to enrollment, lowest SpO_2/FIO_2 (or PaO_2/FIO_2) ratio in the hour prior to enrollment, pre-procedural Glasgow Coma Scale (GCS) score[37], oxygen delivery device at enrollment, assessment of the likelihood of a difficult intubation, presence of difficult airway characteristics (limited mouth opening, small mandible, large tongue, short neck, large neck circumference, limited anatomic neck mobility, cervical immobilization due to trauma, obesity), operator's level of training and specialty, operator's prior intubation experience.
2. Peri-procedural: Lowest SpO_2 from enrollment to induction, approach to and duration of pre-oxygenation, time of sedative administration, sedative agent and dose administered, neuromuscular blocking agent and dose administered, SpO_2 and systolic blood pressure at the time of induction, approach to oxygen administration and ventilation between

induction and the first attempt at laryngoscopy, time of start of first laryngoscopy attempt, laryngoscope used on first attempt (model, blade size, blade shape), use of video screen (if applicable) on the first laryngoscopy attempt, best Cormack-Lehane grade of view[35] on the first laryngoscopy attempt, presence of body fluid obstructing view of the larynx, presence of upper airway obstruction or edema, number of intubation attempts (number of times the laryngoscope entered the mouth, number of times the bougie entered mouth [if applicable], number of times the endotracheal tube entered the mouth), reason for failure of the first intubation attempt (if applicable), procedural adjustments made for the final intubation attempt, esophageal intubation, injury to teeth, operator-reported pulmonary aspiration between induction and intubation, time of successful tracheal intubation, endotracheal tube size, lowest SpO_2 from induction until 2 minutes after intubation, lowest systolic blood pressure from induction until 2 minutes after intubation, new or increased vasopressor administration 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.

3. 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, positive end-expiratory pressure (PEEP) at 24 hours after induction, systolic blood pressure at 24 hours after induction.
4. In-Hospital Outcomes: Ventilator-free days in the first 28 days, ICU-free days in the first 28 days, and in-hospital mortality at 28 days. Definitions for ICU-free days and ventilator-free days are provided in the supplementary file, sections 3 and 4.

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 following 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 into the mouth.

Data for the assessment of the primary outcome are collected by a trained independent observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie (if used), and endotracheal tube into the patient's mouth. In the event that data from the independent observer are missing, data from the operator's self-report of successful intubation on the first attempt will be used.

Secondary Outcome

The secondary outcome is the incidence of severe complications occurring between induction and 2 minutes following successful intubation. Severe complications are defined as one or more of the following:

- Severe hypoxemia (lowest oxygen saturation measured by pulse oximetry < 80%);
- Severe hypotension (systolic blood pressure < 65 mm Hg or new or increased vasopressor administration);
- Cardiac arrest not resulting in death
- 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.

Exploratory Outcomes

Exploratory procedural outcomes are as follows:

- Duration of laryngoscopy and tracheal intubation. This is 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 endotracheal tube
- Successful intubation on the first attempt without a severe complication
- Reason for failure to intubate the trachea on the first attempt, which include:
    - 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 a change in patient condition (e.g. worsened hypoxemia, hypotension, bradycardia, vomiting, bleeding)
    - Technical failure of the laryngoscope (e.g. battery, light source, camera, screen)
    - Other
- Operator-reported aspiration

Exploratory safety outcomes are as follows:

- Esophageal intubation
- Injury to the teeth

Exploratory clinical outcomes are as follows:

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

Sample Size Estimation

The minimum clinically important difference in successful intubation on the first attempt that would be needed to justify routine use of a video laryngoscope rather than a direct laryngoscope in the ED and ICU is uncertain. The current trial is 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 used in the design of prior airway management trials and is considered by airway management experts to be clinically meaningful.[21,28,38,39] Assuming (1) an incidence of successful intubation on the first attempt of 80% in the direct laryngoscope group, (2) 90% statistical power, (3) a two-sided alpha of 0.05, and (4) enrollment at 16 sites with an intra-cluster correlation for the primary outcome of 0.05, we calculated that detecting a 5% absolute increase in the incidence of successful intubation on the first attempt would require enrollment of 1,920 patients (960 per group). Anticipating missing data for up to 4% of enrolled patients, we will plan to enroll a total of 2,000 patients (1,000 per group).

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of experts with backgrounds in emergency medicine, pulmonary and critical care medicine, anesthesiology, bioethics, and biostatistics has overseen the design of the trial and is monitoring its conduct. The DSMB will review a single interim analysis prepared by the study biostatistician at the anticipated halfway point of the trial, after enrollment of 1,000 patients. The stopping boundary for efficacy was pre-specified as a P-value of 0.001 or less, using a chi-square test, for the difference in the incidence of the primary outcome between groups. This conservative Haybittle–Peto boundary was selected to allow the final analysis to be performed using an unchanged level of significance ($P < 0.05$). The DSMB retains the authority to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol to protect patient safety. Trial safety monitoring and handling of adverse

events are described in detail in the supplementary file, section 5. Patient privacy and data storage details are listed in the supplementary file, section 6.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[40] We will present summary tabulations by treatment group. For categorical variables, the number and proportion of patients will be presented. For continuous variables, the mean and standard deviation or median and interquartile range will be presented, as appropriate.

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[41] and the European Medicines Agency[42], each will be tested using a two-sided P value with a significance level of 0.05. The primary analysis will occur in an intent-to-treat fashion among all patients randomized, excluding only those patients whose data was withdrawn from the study. 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*[43], and no corrections for multiple comparisons will be performed.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted, intention-to-treat comparison of successful intubation on the first attempt between patients randomized to the video laryngoscope group and patients randomized to the direct laryngoscope group, using a chi-square test. The difference in proportions, the associated 95% confidence interval, and a p value for the primary outcome will be presented.

Secondary Analyses of the Primary Outcome

Multivariable modeling to account for covariates

To account for relevant covariates, we will develop a generalized linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group and the following pre-specified baseline covariates: age, sex, body-mass index, operator experience quantified as the operator's total number of prior intubations, and location of intubation (ED vs ICU). All continuous variables will be modeled assuming a nonlinear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect Modification

We will examine whether pre-specified baseline variables modify the effect of study group assignment (video laryngoscope vs direct laryngoscope) on the primary outcome using a formal test of statistical interaction in a generalized linear mixed effects model with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group, the pre-specified proposed effect modifier, and the interaction between the two. For categorical variables, we will present the odds ratio and 95% confidence intervals within each pre-specified 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[44], we have prespecified the following limited number of baseline variables as potential effect modifiers and the hypothesized direction of effect modification for each:

1. Patient location (ED vs ICU). We hypothesize that patient location will not modify the effect of study group assignment on the primary outcome.
2. Traumatic injury (Yes vs No). We hypothesize that traumatic injury will modify the effect of study group assignment on the primary outcome, with a greater increase in the

incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients with traumatic injury compared to patients without traumatic injury.

3. Body mass index (kg/m^2). We hypothesize that body mass index will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients with higher body mass index as compared to patients with lower body mass index. This hypothesis of effect modification is supported by a non-significant trend toward effect modification in a meta-analysis of multiple prior randomized trials.[9]
4. Operator's pre-enrollment assessment of the anticipated difficulty of intubation (Easy; Moderate; Difficult; Not Recorded). We hypothesize that the operator's pre-enrollment assessment will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients assessed as Difficult or Moderate compared to Easy. This hypothesis of effect modification is supported by significant effect modification in a meta-analysis of multiple prior randomized trials.[9]
5. Operator experience at the time of enrollment.
    1. Total number of previous intubations performed by operator. We hypothesize that the total number of previous intubations performed by the operator will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among operators with fewer previous intubations compared to operators with a greater number of previous intubations. This hypothesis of effect modification is supported by significant

effect modification observed in a prior randomized trial among critically ill adults, but differs from a meta-analysis including trials of intubation in the operating room that did not observe effect modification based on the operator's prior experience.[9,28]

2. Proportion of previous intubations performed by the operator using a direct laryngoscope. We hypothesize that the proportion of previous intubations performed by the operator using a direct laryngoscope will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among operators with a lower proportion of previous intubations performed by the operator using a direct laryngoscope compared to operators with a higher proportion of previous intubations performed by the operator using a direct laryngoscope.

We will also perform an effect modification analysis for the primary outcome that includes a three-way interaction between study group, total number of previous intubations performed by the operator, and proportion of previous intubations performed by the operator using a direct laryngoscope.

Sensitivity Analyses of the Primary Outcome

We will assess the robustness of the findings of the primary analysis in a number of sensitivity analyses. First, because operators may choose to deviate from the assigned laryngoscope for the safety of the patient, we will repeat the primary analysis, but will consider patients for whom the operator crossed over on the first attempt from the assigned laryngoscope type to the non-assigned laryngoscope type not to have experienced successful intubation on the first attempt. Second, we will repeat the primary analysis among only patients

for whom data on the primary outcome from the independent observer is available (i.e., excluding cases in which operator self-report was the sole source of information for the primary outcome). Third, because the operator's prior experience with each type of laryngoscope may affect the likelihood of success with a video laryngoscope compared with a direct laryngoscope, we will repeat the primary analysis among only cases in which the proportion of prior intubations the operator has performed using a direct laryngoscope is between 0.25 and 0.75.

Analysis of the Secondary Outcome

For the secondary outcome, severe complications occurring between induction and 2 minutes following intubation, we will perform an unadjusted, intention-to-treat comparison of patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group, using a chi-square test.

Analyses of Exploratory Outcomes

For all pre-specified exploratory outcomes, we will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group. We will calculate absolute risk differences or differences in medians between groups with the associated 95% confidence intervals.

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.

Trial status

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a prospective, multi-center, non-blinded randomized clinical trial comparing use of a video laryngoscope to use of a direct laryngoscope for the first attempt at tracheal intubation of critically ill adults in the ED and ICU. Patient enrollment began on 16 March 2022 and is being conducted in 6 EDs and 10 ICUs in the United States.

Ethics and Dissemination

Waiver of Informed Consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care are intubated using either a video laryngoscope or a direct laryngoscope on the first attempt. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrollment in the DEVICE trial, the patient's treating clinician must believe that either a video laryngoscope or a direct laryngoscope would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a clinician who thinks either approach is safe and reasonable for the patient is expected to pose no more than minimal additional risk.

Obtaining informed consent for participation in the study would be impracticable. The majority of patients undergoing emergency tracheal intubation lack decisional capacity due to their underlying critical illness and surrogate decision makers are frequently absent. Further, emergency tracheal intubation is a time-sensitive procedure with only minutes between the decision to perform intubation and the completion of the procedure. Meaningful informed consent could not be executed in this brief window and attempting to obtain informed consent

would lead to potentially deleterious and unethical delays in intubation which would increase the risk of hypoxemia, hypotension, and periprocedural cardiac arrest.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, a waiver of informed consent was requested from and approved by the single institutional review board at Vanderbilt University Medical Center (reference number 211272). This is consistent with previous randomized trials comparing alternative approaches to tracheal intubation commonly used in clinical care.[28,38,39,45–50] This approach was approved by the US Department of Defense (DoD) Defense Health Agency Human Research Protection Office (EIRB# 944893).

Information for Patients and Families

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

Protocol Changes

Any further amendments to the protocol will be recorded on ClinicalTrials.gov as per SPIRIT guidelines. See the supplementary file, section 7, for details on how protocol changes will be handled.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal and will be presented at one or more scientific conferences.

Authors' Contributions

Approved the final version of this manuscript and critical revision of the manuscript for important intellectual content: all authors. Study concept and design: MEP, BED, SAT, SGS, BJL, DRG, WHS, TWR, AAG, JDC, MWS. Acquisition of data: all authors. Drafting of the manuscript and study supervision: MEP, BED, SAT, JDC, MWS.

Competing Interests

Matthew W. Semler was supported by the National Heart Lung and Blood Institute (K23HL143053). Jonathan D. Casey was supported by the National Heart Lung and Blood Institute (K23HL153584-01). John P. Gaillard received support from the CHEST Foundation for instruction and travel. Todd W. Rice was supported in part by the National Institutes of Health and received consulting payments from Cumberland Pharmaceuticals, Inc. and Cytovale, Inc., and served on a data safety and monitoring board for Sanofi, Inc. All other authors have no competing interests.

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Figure Legend

Figure 1. Schedule of enrollment, interventions, and assessments in the DEVICE trial. TI, tracheal intubation.

	STUDY PERIOD						
	Eligibility Screen	Randomize & Allocate	Peri-Procedural				Final Outcome Assessment
TIMEPOINT	Decision to perform TI	Prior to TI	Induction	TI	0-2 min after TI	0-48 hrs after TI	Discharge or 28 days after enrollment
ENROLLMENT:							
Eligibility Screen	X						
Allocation		X					
INTERVENTIONS:							
Video Laryngoscope				X			
Direct Laryngoscope				X			
Screening for Contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-Procedural Variables		X	X	X	X		
Clinical Outcomes						X	X

Supplementary file to:

DirEct Versus VIdeo LaryngosCopE (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial

Table of Contents

1. 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	6
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, Supplement section 2
	5b	Name and contact information for the trial sponsor	29
	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	29
	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)	11, 18, 29
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	8-10
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	10
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)	11
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	5, 23
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	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)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	16-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	30

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	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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 enrol participants or assign interventions	11-12
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	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	13-18
	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	13, 16, 19

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	35
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	19-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21, 23
	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)	23
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	18
	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	18
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 5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23-24
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 7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23-25

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Supplement section 6_____
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 6_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____29_____
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	__Supplement section 6_____
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	____n/a_____
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	___10, 25_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	____n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Supplement section 6_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	____n/a_____
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	____n/a_____

*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.

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3. Definition of ICU-Free Days (ICU-FDs)

ICU-FDs are defined as the number of days, between enrollment and 28 days after enrollment, in which the patient is alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit. Patients who are never discharged from the intensive care unit receive a value of 0. Patients who die before day 28 receive a value of 0. For patients who return to an ICU and are subsequently discharged prior to day 28, ICU-free days are counted from the date of final ICU discharge. All data are censored hospital discharge or 28 days, whichever comes first.

4. Definition of Ventilator-Free Days (VFDs)

VFDs are defined as the number of days, between enrollment and 28 days after enrollment, during which the patient is alive and with unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFDs are 0. If a patient is discharged while receiving assisted ventilation, VFDs are 0. All data is censored hospital discharge or 28 days, whichever comes first.

5. 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.

5.1. 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.

5.2. 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.

5.3. 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.

5.4. 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.

5.5. 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.

6. Patient Privacy and Data Storage

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 or other private healthcare information (PHI), is collected. All subjects are assigned a unique study ID number for tracking purposes. Data collected from the medical record is entered into the secure online database REDCap. The PHI required to accurately collect clinical and outcomes data is available only to investigators at the site at which the subject is enrolled, and this data is shared only in completely de-identified form with the coordinating center via the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are 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. The de-identified dataset housed in REDCap will be accessed by the coordinating center for reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, all PHI at local centers will be expunged and only the de-identified version of the database will be retained. Potential future use of de-identified data generated in the course of this study by the coordinating center and other participating sites is allowed and will be governed by mutual data sharing use agreements.

7. Plan for Communication of Protocol Changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, 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 relevant IRBs for 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 change, will be included in the supplementary material for publication.

BMJ Open

DirEct Versus VIdeo LaryngosCopE (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial in critically ill adults undergoing emergency tracheal intubation

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DirEct Versus VIdeo LaryngosCopE (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial in critically ill adults undergoing emergency tracheal intubation

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Abstract:

Introduction:

Among critically ill patients undergoing orotracheal intubation in the emergency department (ED) or intensive care unit (ICU), failure to visualize the vocal cords and intubate the trachea on the first attempt is associated with an increased risk of complications. Two types of laryngoscopes are commonly available: direct laryngoscopes and video laryngoscopes. For critically ill adults undergoing emergency tracheal intubation, it remains uncertain whether use of a video laryngoscope increases the incidence of successful intubation on the first attempt compared with use of a direct laryngoscope.

Methods and Analysis:

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a prospective, multi-center, non-blinded, randomized trial being conducted in 6 EDs and 10 ICUs in the United States. The trial plans to enroll up to 2,000 critically ill adults undergoing orotracheal intubation with a laryngoscope. Eligible patients are randomized 1:1 to the use of a video laryngoscope or a direct laryngoscope for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is the incidence of severe complications between induction and 2 minutes after intubation, defined as the occurrence of one or more of the following: severe hypoxemia (lowest oxygen saturation < 80%); severe hypotension (systolic blood pressure < 65 mm Hg or new or increased vasopressor administration); cardiac arrest; or death. Enrollment began on March 16, 2022 and is expected to be completed in 2023.

Ethics and Dissemination:

The trial protocol was approved with waiver of informed consent by the single institutional review board at Vanderbilt University Medical Center and the Human Research Protection

Office of the Department of Defense. The results will be presented at scientific conferences and submitted for publication in a peer-reviewed journal.

Trial Registration

ClinicalTrials.gov registration (NCT05239195) on February 14, 2022, prior to the enrollment of the first patient.

Strengths and Limitations of this Study

- This protocol describes in detail the design and methods for a large, pragmatic trial of laryngoscope type for the emergency tracheal intubation of critically ill adults.
- Conduct in the emergency departments and intensive care units of multiple centers among operators with diverse prior experience with tracheal intubation, as well as broad patient eligibility criteria, will increase the external validity of trial results.
- Patients, clinicians, and investigators are not blinded to the study group assignment after randomization.

Introduction

Tracheal intubation is a common procedure in the emergency department (ED) and intensive care unit (ICU). Among critically ill patients undergoing tracheal intubation, failure to intubate the trachea on the first attempt is associated with increased risk of complications, including hypoxemia, hypotension, aspiration, and cardiac arrest.[1,2]

Emergency tracheal intubation is typically performed in three discrete steps. First, the patient is administered medications to facilitate optimal intubating conditions (rapid sequence induction). Second, a clinician inserts a laryngoscope into the patient's mouth to visualize the vocal cords (laryngoscopy). Third, an endotracheal tube is inserted into the mouth, alongside the laryngoscope, and the tube is advanced past the vocal cords into the trachea (intubation).

The direct laryngoscope, the traditional instrument consisting of a battery-containing handle attached to a blade with a light source, has been used to visualize the vocal cords for tracheal intubation for over 100 years and remains the most commonly used device for the intubation of critically ill adults in the ED or ICU.[2–5] The operator uses the direct laryngoscope to displace the tongue and elevate the epiglottis to facilitate intubation of the trachea under direct visualization. Obtaining an adequate view of the larynx with a direct laryngoscope can be challenging, especially for inexperienced operators. Once a view of the larynx is obtained, passage of the endotracheal tube follows the operator's direct line-of-sight through the mouth to the vocal cords.

Over the last two decades, video laryngoscopes have provided an alternative to direct laryngoscopes for visualizing the vocal cords to facilitate tracheal intubation.[6,7] A camera embedded near the tip of the video laryngoscope blade transmits an image of the vocal cords to a screen that the operator can view during the procedure.[8] Because the camera is located near the tip of the laryngoscope blade, obtaining a view of the larynx may be easier with a video laryngoscope compared with a direct laryngoscope. However, because this view can be obtained without generating a direct line-of-sight through the mouth to the vocal cords, the

process of passing an endotracheal tube may be more difficult when using a video laryngoscope. When considering both aspects of tracheal intubation, visualizing the vocal cords and passing the endotracheal tube, it remains uncertain whether use of a video laryngoscope increases the incidence of successful intubation on the first attempt.

Among elective tracheal intubations in the operating room, use of video laryngoscope probably increases the incidence of successful intubation on the first attempt and decreases complications compared to use of a direct laryngoscope, supported with moderate certainty in the existing anesthesiology literature.[9] Extrapolating the results of randomized clinical trials conducted in the operating room to non-operating room settings is problematic because of factors related to the patient, the operator, and the environment.[10,11] Because tracheal intubation of critically ill adults outside of the operating room is common, complications of intubation in the ED and ICU are common, and use of a video laryngoscope during intubation in the ED and ICU has increased significantly over time,[9,12] understanding the effects of use of a video laryngoscope vs direct laryngoscope on successful intubation on the first attempt in these settings is a priority.

Previous trials randomizing patients to use of a video laryngoscope or a direct laryngoscope during emergency tracheal intubation in prehospital[13–18], ED[19–25], and ICU settings[26–32] have been small and heterogeneous and have generally suggested that while a video laryngoscope improves the view of the larynx and reduces the incidence of esophageal intubation, it may not affect the incidence of successful intubation on the first attempt. Findings were similar in the largest such trial to date, a 371-patient, multicenter, randomized clinical trial in French medical ICUs in which use of video laryngoscope failed to improve successful intubation on the first attempt (68% vs. 70%; p = 0.60) and was associated with a greater incidence of severe peri-procedural complications in post-hoc analyses.[33]

The sample size of these prior trials did not provide sufficient statistical power to definitively rule out a clinically important effect of use of a video laryngoscope vs direct

laryngoscope on successful intubation on the first laryngoscopy attempt or the incidence of complications. To compare the effectiveness of these two commonly used devices during this important emergency procedure, a large trial conducted across a wide variety of clinical settings, operator specialties, and levels of operator experience is required. Therefore, we designed the DirEct Versus VIdeo LaryngosCopE (DEVICE) trial to test the hypothesis that, among critically ill adults undergoing emergency tracheal intubation in the ED or ICU, use of a video laryngoscope will increase the incidence of successful intubation on the first attempt compared with use of a direct laryngoscope.

Methods and Analysis

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Figure 1; supplementary file, section 1).[34]

Patient and Public Involvement

Materials used to communicate details of the study with patients and family members were developed with input from the Vanderbilt Community Advisory Council. Study authors will disseminate the results of this study online and via social media in forms suitable for public understanding.

Study Design

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing use of a video laryngoscope to use of a direct laryngoscope for the first attempt at emergency tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. An

independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study institutions and investigators are listed in the supplementary file, section 2.

Study Population

The inclusion criteria for this study are:

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.

The exclusion criteria for the study are:

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.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo intubation using a video laryngoscope or using a direct laryngoscope for the first attempt in permuted blocks of variable size, stratified by study site. Study-group assignments are generated using a computerized randomization sequence, placed in sequentially numbered opaque envelopes, and distributed to enrolling sites. Before opening the envelope, the operator determines that the patient meets eligibility criteria, records the predicted difficulty of intubation (“easy”, “moderate”, or “difficult”) and selects the blade shape the operator plans to use if the patient is randomized to the video laryngoscope group (“hyperangulated” or “non-hyperangulated / standard geometry”). The

operator or delegate then opens the envelope. Patients are enrolled once the envelope is opened to reveal the study group assignment. After enrollment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Video Laryngoscope Group

For patients assigned to the video laryngoscope group, operators are instructed to use a video laryngoscope on the first laryngoscopy attempt. A video laryngoscope is defined as a laryngoscope with a camera and a video screen. Trial protocol does not dictate the brand of video laryngoscope or the geometry of the laryngoscope blade (e.g. hyperangulated vs. non-hyperangulated), but these details will be recorded. Operators are encouraged, but not required, to view the video screen during laryngoscopy ("indirect laryngoscopy") and tracheal intubation.

Direct Laryngoscope Group

For patients assigned to the direct laryngoscope group, operators are instructed to use a direct laryngoscope on the first laryngoscopy attempt. A direct laryngoscope is defined as a laryngoscope without a camera and a video screen. Trial protocol does not dictate the brand of direct laryngoscope or the geometry of the laryngoscope blade (e.g. curved [Macintosh] vs. straight [Miller]), but these details will be recorded.

Co-Interventions and Subsequent Attempts at Laryngoscopy and Intubation

Study group assignment determines only the type of laryngoscope (video vs direct) used on the first laryngoscopy attempt. If determined to be required to ensure optimal care of the patient, treating clinicians may use any device at any time, regardless of study group assignment. Cases in which clinicians use a laryngoscope discordant with randomized assignment on the first intubation attempt will be documented and tracked. All aspects of the

intubation procedure, except the type of laryngoscope used on the first attempt, are at the discretion of treating clinicians, including selection of sedative and neuromuscular blocking medications, patient positioning, approach to pre-oxygenation, use of a bougie or a stylet, and endotracheal tube size. Best practices in tracheal intubation will be encouraged according to clinical protocols at the study sites. The trial intervention ends after the first attempt at laryngoscopy. If the first attempt is unsuccessful, the operator may use any method of intubation on subsequent intubation attempts, including use of a direct laryngoscope in the video laryngoscope group or use of a video laryngoscope in the direct laryngoscope group. The type of laryngoscope used during the initial and final laryngoscopy attempt will be collected and reported.

Data Collection

A trained observer, not directly involved with the intubation procedure, collects data for key peri-procedural outcomes. These outcomes include successful intubation on the first attempt, time interval between laryngoscopy and successful intubation, the oxygen saturation and systolic blood pressure at induction, the lowest oxygen saturation and systolic blood pressure between induction and 2 minutes after successful intubation, and new or increased vasopressor administration between induction and 2 minutes after successful intubation. Observers may be clinical personnel on the enrolling unit (e.g., physician, nurse, or pharmacist) or research study personnel.

Immediately following the intubation procedure, the operator completes a paper data collection form to record the approach to preoxygenation, oxygenation and ventilation between induction and laryngoscopy, the brand of laryngoscope used, the blade shape, the Cormack-Lehane grade of laryngeal view[35], use of the video screen to visualize the larynx (if applicable), use of a bougie or a stylet, reasons for failure to intubate on the first attempt (if applicable), intubation approaches on subsequent attempts, difficult airway characteristics observed before

or during the procedure (facial trauma, small mouth opening, limited neck mobility, cervical collar, large neck, obesity, fluids obscuring view of vocal cords, upper airway obstruction or edema), and complications of intubation (witnessed pulmonary aspiration, esophageal intubation, injury to airways, injury to teeth, cardiac arrest between induction and 2 minutes following intubation). The diagnosis of esophageal intubation is made by the operator based on the presence of any clinical sign including visual inspection, capnography, or absence of breath sounds or chest rise. Operators also record their specialty, training level, and estimates of the number of previous intubations they have performed and the number of previous intubations they have performed using a direct laryngoscope.

Study personnel at each site review the medical record to collect data on baseline patient characteristics, pre- and post-laryngoscopy management, and clinical outcomes at 28 days after enrollment.

The following variables are collected:

1. Baseline: Age, sex, height, weight, race, ethnicity, Acute Physiology and Chronic Health Evaluation II (APACHE II) score[36], active medical problems at the time of enrollment, comorbidities, indication for intubation, vasopressor receipt in the hour prior to enrollment, highest FIO_2 in the hour prior to enrollment, lowest SpO_2/FIO_2 (or PaO_2/FIO_2) ratio in the hour prior to enrollment, pre-procedural Glasgow Coma Scale (GCS) score[37], oxygen delivery device at enrollment, assessment of the likelihood of a difficult intubation, presence of difficult airway characteristics (limited mouth opening, small mandible, large tongue, short neck, large neck circumference, limited anatomic neck mobility, cervical immobilization due to trauma, obesity), operator's level of training and specialty, operator's prior intubation experience.
2. Peri-procedural: Lowest SpO_2 from enrollment to induction, approach to and duration of pre-oxygenation, time of sedative administration, sedative agent and dose administered,

neuromuscular blocking agent and dose administered, SpO_2 and systolic blood pressure at the time of induction, approach to oxygen administration and ventilation between induction and the first attempt at laryngoscopy, time of start of first laryngoscopy attempt, laryngoscope used on first attempt (model, blade size, blade shape), use of video screen (if applicable) on the first laryngoscopy attempt, best Cormack-Lehane grade of view[35] on the first laryngoscopy attempt, presence of body fluid obstructing view of the larynx, presence of upper airway obstruction or edema, number of intubation attempts (number of times the laryngoscope entered the mouth, number of times the bougie entered mouth [if applicable], number of times the endotracheal tube entered the mouth), reason for failure of the first intubation attempt (if applicable), procedural adjustments made for the final intubation attempt, esophageal intubation, injury to teeth, operator-reported pulmonary aspiration between induction and intubation, time of successful tracheal intubation, endotracheal tube size, lowest SpO_2 from induction until 2 minutes after intubation, lowest systolic blood pressure from induction until 2 minutes after intubation, new or increased vasopressor administration 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.

3. 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, positive end-expiratory pressure (PEEP) at 24 hours after induction, systolic blood pressure at 24 hours after induction.
4. In-Hospital Outcomes: Ventilator-free days in the first 28 days, ICU-free days in the first 28 days, and in-hospital mortality at 28 days. Definitions for ICU-free days and ventilator-free days are provided in the supplementary file, sections 3 and 4.

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 following 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 into the mouth.

Data for the assessment of the primary outcome are collected by a trained independent observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie (if used), and endotracheal tube into the patient's mouth. In the event that data from the independent observer are missing, data from the operator's self-report of successful intubation on the first attempt will be used.

Secondary Outcome

The secondary outcome is the incidence of severe complications occurring between induction and 2 minutes following successful intubation. Severe complications are defined as one or more of the following:

- Severe hypoxemia (lowest oxygen saturation measured by pulse oximetry < 80%);
- Severe hypotension (systolic blood pressure < 65 mm Hg or new or increased vasopressor administration);
- Cardiac arrest not resulting in death
- 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.

Exploratory Outcomes

Exploratory procedural outcomes are as follows:

- Duration of laryngoscopy and tracheal intubation. This is 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 endotracheal tube
- Successful intubation on the first attempt without a severe complication
- Reason for failure to intubate the trachea on the first attempt, which include:
    - 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 a change in patient condition (e.g. worsened hypoxemia, hypotension, bradycardia, vomiting, bleeding)
    - Technical failure of the laryngoscope (e.g. battery, light source, camera, screen)
    - Other
- Operator-reported aspiration

Exploratory safety outcomes are as follows:

- Esophageal intubation
- Injury to the teeth

Exploratory clinical outcomes are as follows:

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

Sample Size Estimation

The minimum clinically important difference in successful intubation on the first attempt that would be needed to justify routine use of a video laryngoscope rather than a direct laryngoscope in the ED and ICU is uncertain. The current trial is 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 used in the design of prior airway management trials and is considered by airway management experts to be clinically meaningful.[21,28,38,39] Assuming (1) an incidence of successful intubation on the first attempt of 80% in the direct laryngoscope group, (2) 90% statistical power, (3) a two-sided alpha of 0.05, and (4) enrollment at 16 sites with an intra-cluster correlation for the primary outcome of 0.05, we calculated that detecting a 5% absolute increase in the incidence of successful intubation on the first attempt would require enrollment of 1,920 patients (960 per group). Anticipating missing data for up to 4% of enrolled patients, we will plan to enroll a total of 2,000 patients (1,000 per group).

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of experts with backgrounds in emergency medicine, pulmonary and critical care medicine, anesthesiology, bioethics, and biostatistics has overseen the design of the trial and is monitoring its conduct. The DSMB will review a single interim analysis prepared by the study biostatistician at the anticipated halfway point of the trial, after enrollment of 1,000 patients. The stopping boundary for efficacy was pre-specified as a P-value of 0.001 or less, using a chi-square test, for the difference in the incidence of the primary outcome between groups. This conservative Haybittle–Peto boundary was selected to allow the final analysis to be performed using an unchanged level of significance ($P < 0.05$). The DSMB retains the authority to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol to protect patient safety. Trial safety monitoring and handling of adverse

events are described in detail in the supplementary file, section 5. Patient privacy and data storage details are listed in the supplementary file, section 6.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[40] We will present summary tabulations by treatment group. For categorical variables, the number and proportion of patients will be presented. For continuous variables, the mean and standard deviation or median and interquartile range will be presented, as appropriate.

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[41] and the European Medicines Agency[42], each will be tested using a two-sided P value with a significance level of 0.05 with contextual information provided via effect size and 95% confidence intervals. The primary analysis will occur in an intent-to-treat fashion among all patients randomized, excluding only those patients whose data was withdrawn from the study. 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*[43], and no corrections for multiple comparisons will be performed.

Main Analysis of the Primary Outcome

The main analysis will be an unadjusted, intention-to-treat comparison of successful intubation on the first attempt between patients randomized to the video laryngoscope group and patients randomized to the direct laryngoscope group, using a chi-square test. The difference in proportions, the associated 95% confidence interval, and a p value for the primary outcome will be presented.

Secondary Analyses of the Primary Outcome

Multivariable modeling to account for covariates

To account for relevant covariates, we will develop a generalized linear mixed effects model using a logit link function with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group and the following pre-specified baseline covariates: age, sex, body-mass index, operator experience quantified as the operator's total number of prior intubations, and location of intubation (ED vs ICU). All continuous variables will be modeled assuming a nonlinear relationship to the outcome using restricted cubic splines with between 3 and 5 knots.

Effect Modification

We will examine whether pre-specified baseline variables modify the effect of study group assignment (video laryngoscope vs direct laryngoscope) on the primary outcome using a formal test of statistical interaction in a generalized linear mixed effects model with the primary outcome as the dependent variable, study site as a random effect, and fixed effects of study group, the pre-specified proposed effect modifier, and the interaction between the two. For categorical variables, we will present the odds ratio and 95% confidence intervals within each pre-specified 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[44], we have prespecified the following limited number of baseline variables as potential effect modifiers and the hypothesized direction of effect modification for each:

1. Patient location (ED vs ICU). We hypothesize that patient location will not modify the effect of study group assignment on the primary outcome.
2. Traumatic injury (Yes vs No). We hypothesize that traumatic injury will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients with traumatic injury compared to patients without traumatic injury.
3. Body mass index (kg/m^2). We hypothesize that body mass index will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients with higher body mass index as compared to patients with lower body mass index. This hypothesis of effect modification is supported by a non-significant trend toward effect modification in a meta-analysis of multiple prior randomized trials.[9]

4. Operator's pre-enrollment assessment of the anticipated difficulty of intubation (Easy; Moderate; Difficult; Not Recorded). We hypothesize that the operator's pre-enrollment assessment will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among patients assessed as Difficult or Moderate compared to Easy. This hypothesis of effect modification is supported by significant effect modification in a meta-analysis of multiple prior randomized trials.[9]
5. Operator experience at the time of enrollment.
    1. Total number of previous intubations performed by operator. We hypothesize that the total number of previous intubations performed by the operator will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among operators with fewer previous intubations compared to operators with a greater number of previous intubations. This hypothesis of effect modification is supported by significant effect modification observed in a prior randomized trial among critically ill adults, but differs from a meta-analysis including trials of intubation in the operating room that did not observe effect modification based on the operator's prior experience.[9,28]
    2. Proportion of previous intubations performed by the operator using a direct laryngoscope. We hypothesize that the proportion of previous intubations performed by the operator using a direct laryngoscope will modify the effect of study group assignment on the primary outcome, with a greater increase in the incidence of successful intubation on the first attempt with use of a video laryngoscope compared with a direct laryngoscope among operators with a lower

proportion of previous intubations performed by the operator using a direct laryngoscope compared to operators with a higher proportion of previous intubations performed by the operator using a direct laryngoscope.

We will also perform an effect modification analysis for the primary outcome that includes a three-way interaction between study group, total number of previous intubations performed by the operator, and proportion of previous intubations performed by the operator using a direct laryngoscope.

Sensitivity Analyses of the Primary Outcome

We will assess the robustness of the findings of the primary analysis in a number of sensitivity analyses. First, because operators may choose to deviate from the assigned laryngoscope for the safety of the patient, we will repeat the primary analysis, but will consider patients for whom the operator crossed over on the first attempt from the assigned laryngoscope type to the non-assigned laryngoscope type not to have experienced successful intubation on the first attempt. Second, we will repeat the primary analysis among only patients for whom data on the primary outcome from the independent observer is available (i.e., excluding cases in which operator self-report was the sole source of information for the primary outcome). Third, because the operator's prior experience with each type of laryngoscope may affect the likelihood of success with a video laryngoscope compared with a direct laryngoscope, we will repeat the primary analysis among only cases in which the proportion of prior intubations the operator has performed using a direct laryngoscope is between 0.25 and 0.75.

Analysis of the Secondary Outcome

For the secondary outcome, severe complications occurring between induction and 2 minutes following intubation, we will perform an unadjusted, intention-to-treat comparison of

patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group, using a chi-square test.

Analyses of Exploratory Outcomes

For all pre-specified exploratory outcomes, we will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the video laryngoscope group versus patients randomized to the direct laryngoscope group. We will calculate absolute risk differences or differences in medians between groups with the associated 95% confidence intervals.

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.

Trial status

The DirEct Versus VIdeo LaryngosCopE (DEVICE) trial is a prospective, multi-center, non-blinded randomized clinical trial comparing use of a video laryngoscope to use of a direct laryngoscope for the first attempt at tracheal intubation of critically ill adults in the ED and ICU. Patient enrollment began on 16 March 2022 and is being conducted in 6 EDs and 10 ICUs in the United States.

Ethics and Dissemination

Waiver of Informed Consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care are intubated using either a video laryngoscope or a direct laryngoscope on the first attempt. Any benefits or risks of these two approaches are experienced by patients undergoing tracheal intubation in clinical care, outside the context of research. As a requirement for enrollment in the DEVICE trial, the patient's treating clinician must believe that either a video laryngoscope or a direct laryngoscope would be a safe and reasonable approach for the patient (otherwise the patient is excluded). Therefore, making the decision between the two approaches randomly (by study group assignment) rather than by a clinician who thinks either approach is safe and reasonable for the patient is expected to pose no more than minimal additional risk.

Obtaining informed consent for participation in the study would be impracticable. The majority of patients undergoing emergency tracheal intubation lack decisional capacity due to their underlying critical illness and surrogate decision makers are frequently absent. Further, emergency tracheal intubation is a time-sensitive procedure with only minutes between the decision to perform intubation and the completion of the procedure. Meaningful informed consent could not be executed in this brief window and attempting to obtain informed consent would lead to potentially deleterious and unethical delays in intubation which would increase the risk of hypoxemia, hypotension, and periprocedural cardiac arrest.

Because the study involves minimal incremental risk, the study would not adversely affect the welfare or privacy rights of the participant, and obtaining informed consent would be impracticable, a waiver of informed consent was requested from and approved by the single institutional review board at Vanderbilt University Medical Center (reference number 211272). This is consistent with previous randomized trials comparing alternative approaches to tracheal

intubation commonly used in clinical care.[28,38,39,45–50] This approach was approved by the United States Department of Defense (DoD) Defense Health Agency Human Research Protection Office (EIRB# 944893). Institutional review boards at participating sites reviewed the protocol, addressed any local contextual factors with the site principal investigator, and ceded responsibility for ethics approval and study oversight to the single IRB.

Information for Patients and Families

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

Protocol Changes

Any further amendments to the protocol will be recorded on ClinicalTrials.gov as per SPIRIT guidelines. See the supplementary file, section 7, for details on how protocol changes will be handled.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal and will be presented at one or more scientific conferences.

Authors' Contributions

Study concept and design: MEP, BED, SAT, SGS, BJL, DRJ, WHS, TWR, AAG, JDC, MWS. Acquisition of data: MEP, BED, SAT, DRA, KPS, DWR, SG, JPG, KWG, AJL, MRW, SAG, DJV, JPW, SJH, ISD, CRB, VK, JJB, BDL, SWR, JAP, SHM, DBP, HDW, AE, CGH, AJ, JTH, AAG, JDC, MWS. Drafting of the manuscript and study supervision: MEP, BED, SAT, JDC, MWS. Approved the final version of this manuscript and critical revision of the manuscript for important intellectual content: MEP, BED, SAT, DRA, KPS, DWR, SG, JPG, KWG, AJL, MRW, SAG, DJV, JPW, SJH, ISD, CRB, VK, JJB, BDL, SWR, JAP, SHM, DBP, HDW, AE, CGH, AJ, JTH, SGS, BJL, BI, LW, JPR, KNW, DRJ, WHS, TWR, AAG, JDC, MWS.

Competing Interests

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approval of the manuscript. The views expressed are those of the authors and do not reflect the official views or policy of the Department of Defense or its components.

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Figure Legend

Figure 1. Schedule of enrollment, interventions, and assessments in the DEVICE trial. TI, tracheal intubation.

	STUDY PERIOD						
	Eligibility Screen	Randomize & Allocate	Peri-Procedural				Final Outcome Assessment
TIMEPOINT	Decision to perform TI	Prior to TI	Induction	TI	0-2 min after TI	0-48 hrs after TI	Discharge or 28 days after enrollment
ENROLLMENT:							
Eligibility Screen	X						
Allocation		X					
INTERVENTIONS:							
Video Laryngoscope				X			
Direct Laryngoscope				X			
Screening for Contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-Procedural Variables		X	X	X	X		
Clinical Outcomes						X	X

Supplementary file to:

DirEct Versus VIdeo LaryngosCopE (DEVICE): Protocol and statistical analysis plan for a randomized clinical trial

Table of Contents

1. 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	6
	2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	3	Date and version identifier	n/a
Funding	4	Sources and types of financial, material, and other support	29
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-2, Supplement section 2
	5b	Name and contact information for the trial sponsor	29
	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	29
	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)	11, 18, 29
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	8-10
	6b	Explanation for choice of comparators	8
Objectives	7	Specific objectives or hypotheses	10
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)	11
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	5, 23
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	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)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13-14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	13
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	16-18
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	30

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	18
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	n/a
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 enrol participants or assign interventions	11-12
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	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
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	13-18
	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	13, 16, 19

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	35
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	19-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21, 23
	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)	23
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	18
	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	18
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 5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	18-19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	23-24
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 7
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	23-25

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__Supplement section 6_____
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 6_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____29_____
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	__Supplement section 6_____
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	_____n/a_____
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	___10, 25_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_____n/a_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__Supplement section 6_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_____n/a_____
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	_____n/a_____

*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.

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3. Definition of ICU-Free Days (ICU-FDs)

ICU-FDs are defined as the number of days, between enrollment and 28 days after enrollment, in which the patient is alive and not admitted to an intensive care unit service after the patient's final discharge from the intensive care unit. Patients who are never discharged from the intensive care unit receive a value of 0. Patients who die before day 28 receive a value of 0. For patients who return to an ICU and are subsequently discharged prior to day 28, ICU-free days are counted from the date of final ICU discharge. All data are censored hospital discharge or 28 days, whichever comes first.

4. Definition of Ventilator-Free Days (VFDs)

VFDs are defined as the number of days, between enrollment and 28 days after enrollment, during which the patient is alive and with unassisted breathing and remains free of assisted breathing. If a patient returns to assisted breathing and subsequently achieves unassisted breathing prior to day 28, VFD will be counted from the end of the last period of assisted breathing to day 28. If the patient is receiving assisted ventilation at day 28 or dies prior to day 28, VFDs are 0. If a patient is discharged while receiving assisted ventilation, VFDs are 0. All data is censored hospital discharge or 28 days, whichever comes first.

5. 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.

5.1. 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.

5.2. 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.

5.3. 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.

5.4. 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.

5.5. 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.

6. Patient Privacy and Data Storage

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 or other private healthcare information (PHI), is collected. All subjects are assigned a unique study ID number for tracking purposes. Data collected from the medical record is entered into the secure online database REDCap. The PHI required to accurately collect clinical and outcomes data is available only to investigators at the site at which the subject is enrolled, and this data is shared only in completely de-identified form with the coordinating center via the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are 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. The de-identified dataset housed in REDCap will be accessed by the coordinating center for reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, all PHI at local centers will be expunged and only the de-identified version of the database will be retained. Potential future use of de-identified data generated in the course of this study by the coordinating center and other participating sites is allowed and will be governed by mutual data sharing use agreements.

7. Plan for Communication of Protocol Changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, 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 relevant IRBs for 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 change, will be included in the supplementary material for publication.