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BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial

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BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial

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Abstract:

Introduction: Intubation-related complications are less frequent when intubation is successful on the first attempt. The rate of first attempt success in the ED and ICU is typically less than 90%. The bougie, a semi-rigid introducer that can be placed into the trachea to facilitate a Seldinger-like technique of tracheal intubation and is typically reserved for difficult or failed intubations, might improve first attempt success. Evidence supporting its use, however, is from a single academic emergency department with frequent bougie use. Validation of these findings is needed before widespread implementation.

Methods and Analysis:

The Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial is a prospective, multi-center, non-blinded randomized trial being conducted in 6 EDs and 6 intensive care units in the United States. The trial plans to enroll 1,106 critically-ill adults undergoing orotracheal intubation. Eligible patients are randomized 1:1 to use of a bougie or use of an endotracheal tube with stylet for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is severe hypoxemia, defined as an oxygen saturation less than 80% between induction until two minutes after completion of intubation. Enrollment began on April 29, 2019 and is expected to be completed in 2021.

Ethics and Dissemination:

The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The results will be submitted for publication in a peer-reviewed journal and presented at scientific conferences.

Trial Registration:

This trial was registered with ClinicalTrials.gov (NCT03928925) on April 26, 2019, prior to the enrollment of the first patient on April 29, 2019.

Strengths and Limitations:

- This ongoing pragmatic trial will compare the rate of successful intubation on the first attempt with use of a bougie versus use of an endotracheal tube with stylet for the first intubation attempt of critically ill adults in the ED or ICU.
- Broad eligibility criteria, diverse prior experience with a bougie among operators, and conduct in the ED and ICU at multiple centers will increase the external validity of the findings.
- Patients, clinicians, and investigators are not blinded to study group assignment after randomization.

Introduction:

Tracheal intubation of critically ill adults is frequently performed in the Emergency Department (ED) and Intensive Care Unit (ICU). Successful intubation on the first attempt has been associated with a lower incidence of peri-intubation complications.[1–4] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[5–7]

Emergency tracheal intubation is commonly performed in three discrete steps. First, medications are administered to facilitate optimal intubating conditions (induction). Second, a laryngoscope is inserted into the patient's mouth and a direct or indirect video view of glottic structures is obtained (laryngoscopy). Third, an endotracheal tube is placed in the mouth and advanced past the vocal cords into the trachea (intubation). Two commonly used devices that aid in placing the endotracheal tube include: a stylet (a malleable, aluminum rod preloaded inside the endotracheal tube to facilitate navigation of the upper airway) or a bougie (a thin, plastic introducer passed into the trachea which serves as a guide for passage of the endotracheal tube). When using a stylet, the endotracheal tube and stylet are passed into the trachea together. When using a bougie, the bougie is first passed into the trachea and then the endotracheal tube is advanced over the bougie using a Seldinger-like technique. There is substantial variation between clinicians as to whether they select the stylet or the bougie for the first intubation attempt.[5,8] For some physicians, the bougie is used primarily as a rescue device in the event difficulty is encountered in laryngoscopy or passage of the endotracheal tube with stylet. Other physicians use a bougie routinely on the first attempt at tracheal intubation.[8,9]

To our knowledge, only one prior randomized trial has compared rates of successful intubation on the first attempt outside of the operating room with use of a bougie versus use of endotracheal tube with stylet: the single-center Bougie Use in Emergency Airway Management (BEAM) trial. That study showed a higher rate of successful intubation on the first attempt with use of a bougie (98%) compared to use of an endotracheal tube with stylet (87%) in adult ED patients (absolute difference 11%, 95% CI 7% to 14%).[10] However, it is possible that these findings reflect increased institution-specific comfort with bougie use compared to the endotracheal tube and

stylet – operators reported using a bougie in approximately 80% of intubations before the trial.[8] It is unknown if the results of the BEAM trial will generalize to other settings where operators have less experience using the bougie and have greater experience using an endotracheal tube with stylet during the first attempt at intubation.

Methods and Analysis:

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see SPIRIT checklist in Supplement fig E1 and Fig. 1).[11]

Patient and Public Involvement

We did not involve patients or the public in the design of the study.

Study Design

The BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing use of a bougie to use of an endotracheal tube with stylet for the first attempt at tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The trial was registered prior to initiation of enrollment (ClinicalTrials.gov identifier: NCT03928925). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study sites are listed in the Supplement file, section 7.

Study Population

The inclusion criteria for the trial are:

1. Patient is located in a participating unit of an adult hospital
2. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest, or respiratory arrest)

3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
4. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

The exclusion criteria for the trial are:

1. Patient is pregnant
2. Patient is a prisoner
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
5. Operator feels use of a bougie is required or contraindicated for the care of the patient
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

The original inclusion criteria specified that patients must be at least 18 years old to be eligible. With approval from the central institutional review board at Vanderbilt University Medical Center, trial inclusion and exclusion criteria were amended on January 16, 2020 to allow the enrollment of patients less than 18 years of age. Because the identity and age of critically ill patients presenting to the ED are sometimes unknown (e.g., a patient with cardiac arrest presenting by ambulance without family), this criterion was revised to include patients located in a participating unit of an adult hospital. We anticipate that a small number of patients whose identity and age are unknown, who are judged by treating clinicians to be an adult and enrolled in the trial, will later be determined to be less than 18 years old.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt in permuted blocks of two, four, or six, 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 all inclusion criteria and no exclusion criteria. The operator documents whether they plan to use a video laryngoscope or a direct laryngoscope. The operator then opens the envelope. Patients are considered to be enrolled once the operator opens the envelope to reveal study group assignment. Thus, group assignment is concealed until after documentation of laryngoscope choice and patient enrollment. Patients who are screened and excluded will be reported with trial results using a CONSORT diagram. After enrollment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Training

Before beginning enrollment at a site, operators at each site received a 30-minute in-person lecture and watched a 6-minute training video which demonstrated best-practices for intubation with both a bougie and endotracheal tube with stylet. These materials are available from the authors upon request.

Bougie Group

For patients assigned to the bougie group, operators are instructed to use a bougie on the first attempt at laryngoscopy and tracheal intubation. If the bougie is successfully placed in the trachea, an assistant is instructed to load the endotracheal tube (without a stylet) over the bougie. The operator is instructed to, without removing the laryngoscope from the mouth, advance the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie, the tube is be retracted 2 centimeters, rotated 90° counterclockwise to orient the bevel tip of the tube vertically, and re-advanced into the trachea. With the operator or an assistant manually stabilizing the endotracheal tube, the bougie is withdrawn from the endotracheal tube before ventilation. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

This trial evaluates the use of a straight, semi-rigid bougie. Experts report that less-rigid bougies packaged in a curled position are more difficult to advance through the glottic opening.[12] Participating units use a straight bougie at least 60 cm in length; a Coudé tip is favored but not required. Operators may choose whether and how to bend the bougie prior to intubation.

Endotracheal Tube with Stylet Group

For patients assigned to the endotracheal tube with stylet group, operators are instructed to use an endotracheal tube with stylet on the first attempt at laryngoscopy and tracheal intubation. The shape and curvature of the endotracheal tube with stylet is determined the operator, however a "straight-to-cuff" shape and a distal bend angle of 25° to 35° is encouraged. If there is difficulty passing the endotracheal tube, the operator is instructed to manipulate the tube as needed, including slight retraction and rotation. The stylet remains within the endotracheal tube until the tube is within the trachea. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

Subsequent Attempts at Laryngoscopy and Intubation and Co-Interventions

Study group assignment determines only the device to be used on the first attempt at laryngoscopy and tracheal intubation. All other aspects of the intubation procedure are at the discretion of treating clinicians, including choice of endotracheal tube diameter, patient position, approach to pre-oxygenation, approach to ventilation and oxygenation between induction and intubation, and devices used after the first intubation attempt. For laryngoscopes capable of both video-assisted and direct laryngoscopy, the use of the video screen during intubation is at the discretion of the operator. After the first attempt at laryngoscopy and tracheal intubation, the operator may use any other method of intubation, including use of an endotracheal tube with stylet in the bougie group or use of a bougie in the endotracheal tube with stylet group. In either group, treating clinicians may, at any point, use any device they feel is required to ensure optimal care of the patient regardless of study group assignment. The approach to the

initial attempt at laryngoscopy and intubation and any co-interventions are prospectively collected and will be reported.

Co-enrollment in other randomized trials is permitted as the use of randomization facilitates balance between study arms, reduces the likelihood of any systematic effects on intubation success rates, and allows for evaluation of the main effects in this trial.

Data Collection

An observer, not directly involved with the intubation procedure, collects data for key peri-procedural outcomes, including successful intubation on the first attempt, time between induction and successful intubation, arterial oxygen saturation and systolic blood pressure at induction, and the lowest values for arterial oxygen saturation and systolic blood pressure between induction and 2 minutes following intubation. The background of trained observers depends on local context and may include either clinical professionals (e.g., physicians or nurses) or research study personnel. All observers received training on study procedures and data element definitions.

Immediately after the procedure, operators complete a paper data collection form to document the approach to oxygen administration and use of ventilation for pre-oxygenation and between induction and laryngoscopy, laryngoscope used, Cormack-Lehane grade of glottic view[13], laryngoscope video screen use (if applicable), reason for the failure to intubate on the first attempt (if applicable), subsequent intubation methods, difficult airway characteristics (cervical collar, glottic view obscured by body fluids, facial trauma), and complications of intubation (cardiac arrest, heart rate < 40 beats per minute, esophageal intubation, airway trauma, witnessed aspiration). Operators record their specialty and training level and self-report the number of prior intubations, overall and with a bougie, at the time of each study intubation.

Study personnel review the medical record to collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes. The following variables are collected:

1. Baseline: Age, gender, height, weight, race, ethnicity, APACHE II score, most recent pre-procedural Glasgow Coma Score, active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, whether

the primary diagnosis was trauma-related, indication for intubation, non-invasive positive pressure ventilation and high flow nasal cannula use, vasopressor use in the hour preceding enrollment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate >2mmol/L in the absence of hypovolemia) at the time of enrollment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrollment, and whether or not this was a reintubation (defined as a patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).

2. Peri-procedural: type and dose of neuromuscular blocker; laryngoscope device used, blade shape and size for first attempt; total number of intubation attempts; presence of any of the following difficult airway characteristics: vomiting, witnessed aspiration, upper gastrointestinal hemorrhage, epistaxis or oral bleeding, upper airway mass, infection, or trauma, head and neck radiation, obesity (body mass index > 30 kg/m^2), limited neck mobility, limited mouth opening, history of obstructive sleep apnea, or other.
3. 0-48 hours: Cardiac arrest within 1 hour of intubation, presence or absence of pneumothorax on first chest film obtained within 48 hours after intubation; systolic blood pressure, oxygen saturation, FiO_2, and positive end expiratory pressure delivered at 24 hours after enrollment.
4. In-Hospital Outcomes: Ventilator-free days, ICU-free days, and 28 day in-hospital mortality.

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: (1) a single insertion of a laryngoscope blade into the mouth and (2) EITHER a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth OR a single insertion of an endotracheal tube with stylet into the mouth.

The primary outcome is collected by a trained observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie, and endotracheal tube into the patient's mouth. If data from the independent observer about the primary outcome are missing, the operator's self-report of successful intubation on the first attempt will be used. If documentation of successful intubation on the first attempt are discordant between the independent observer and the operator, data from the independent observer will take precedence.

Secondary Outcome

The secondary outcome is the incidence of severe hypoxemia, defined as an oxygen saturation less than 80% during the time interval from induction to two minutes after completion of tracheal intubation.

Exploratory Outcomes

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing the bougie
- Number of attempts at passing the endotracheal tube
- Duration of intubation: The start of the procedure will be defined as either the time of first sedative administration or, among patients who do not receive a sedative, the time of initiation of laryngoscopy. The end of the procedure will be defined as the time of the final placement of an endotracheal tube within the trachea.
- Whether the video laryngoscope screen was viewed, among intubations where the operator used a video laryngoscope.
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Operator-reported aspiration during the procedure
    - Airway trauma (injury to oropharyngeal, glottic, or thoracic airway structures)
- Cardiac arrest within 1 hour following intubation

- Incidence of peri-intubation cardiovascular collapse, defined as one or more of:
    - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
    - New or increased vasopressor between induction and 2 minutes following intubation
    - Cardiac arrest within 1 hour of intubation
    - Death within 1 hour of intubation
- ICU-free days in the first 28 days (see Supplementary file, section 3)
- Ventilator free days in the first 28 days (see Supplementary file, section 2)
- All-cause, in-hospital mortality at 28 days

Sample Size Estimation

There is no established minimum clinically important difference in successful intubation on the first attempt. A prior single-center randomized trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial was performed in an ED where the majority of first intubation attempts utilized a bougie, we anticipated a potentially smaller difference between groups in this multicenter trial conducted in a broader range of clinical settings with a broader range of operators. Therefore, the current trial was designed to detect a 6% absolute difference between groups in the proportion of patients who experience successful intubation on the first attempt. For two inexpensive interventions already routinely available and utilized in practice, the minimally clinically significant difference that would be expected to change practice is unknown. However, an absolute difference of 6% in successful intubation on the first attempt is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.[7,10,14] Assuming 84% of patients in the endotracheal tube with stylet group experience successful intubation on the first laryngoscopy attempt, detecting a 6% absolute increase in successful intubation on the first attempt with 80% power at a two-sided alpha level of 0.05 would require enrollment of 1,050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enroll a total of 1,106 patients (553 per group).

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of 4 clinical trials experts with backgrounds in critical care medicine, anesthesia, and emergency medicine has overseen the design of the trial and is monitoring its conduct. The DSMB reviewed a single interim analysis, prepared by the study biostatistician, on February 4th, 2020, at the anticipated halfway point of the trial after enrollment of 553 patients, and recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was pre-specified as a P-value of 0.001 or less for the difference in the incidence of the primary outcome between groups tested, using a chi-square test. 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 recommended stopping boundary for safety was a $P < 0.025$ comparing the incidence of esophageal intubation and separately the incidence of airway trauma between groups, using a chi-square test. 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.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[15] Continuous variables will be reported as mean ± standard deviation or median and interquartile range; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. We will also present absolute between-group differences with associated 95% confidence intervals. A two-sided p-value of < 0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment for multiplicity will be made. For secondary and exploratory analyses, emphasis will be placed on the magnitude of differences between groups rather than statistical significance.

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 bougie group and patients randomized to the endotracheal tube with stylet group, using a chi-square test.

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 and operator as random effects, and fixed effects of study group and the following pre-specified baseline covariates: age, sex, race, body-mass index, operator experience quantified as the operator's total number of prior intubations, and location of intubation (ED vs ICU). We will then construct a model with the following additional factors that may be interpreted as baseline covariates but which are unable to be assessed until after randomization: use of a video vs direct laryngoscope; presence of ≥ 1 difficult airway characteristic (obesity, body fluids obscuring glottic view, cervical immobilization, or facial trauma) and Cormack-Lehane grade 2, 3, or 4 laryngeal view. 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 variables modify the effect of bougie vs endotracheal tube with stylet use on the primary outcome using a formal test of interaction between group assignment and effect modifier in the above models. Because this study is not formally designed or powered to test for interaction, a less conservative P value for the interaction term will be used, with values less than 0.10 considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Operator Experience at the time of each enrollment
    a. Total number of previous intubations performed by operator

b. Number of previous intubations performed by operator using a bougie
c. Proportion of previous intubations performed by the operator that were performed using a bougie

2. Location (ED vs ICU)
3. Indication for intubation (trauma vs medical)
4. Difficult airway, defined as one or more of the following difficult airway characteristics: obesity (body mass index > 40 kg/m^2), cervical immobilization, or facial trauma.
5. Time period (before the COVID pandemic vs during or after the COVID pandemic)

In addition to the variables above, which can be assessed prior to enrollment, we will perform exploratory analyses examining additional potential effect modifiers that are intended to represent baseline variables, but which are collected after enrollment, and therefore have the potential to be affected by study group assignment. These include:

1. Laryngoscope type (Direct laryngoscope [without video capability] vs video laryngoscope [with video capability])
2. Presence body fluids obscuring glottic view (Yes vs No)
3. Cormack Lehane grade of view (1 vs 2-4).

Sensitivity Analyses of the Primary Outcome

To assess the robustness of the findings, we will repeat the main analysis of the primary outcome in several alternatives to the overall intention-to-treat population. First, we will repeat the main analysis of the primary outcome among only those patients for whom a non-hyperangulated laryngoscope blade was used on the first attempt at intubation. Second, operators may choose to deviate from the assigned device for the safety of the patient after obtaining a laryngeal view. To address this, we will repeat the main analysis of the primary outcome for all patients, but will assign failure to the first intubation attempt for patients in whom the operator crossed over from the assigned device to the non-assigned device. Third, we will repeat the main analysis of the primary outcome, including only cases in which primary outcome data from the independent

observer is complete (i.e., excluding cases in which the operator's self-report of whether there was successful intubation on the first attempt defined the primary outcome for that patient). Fourth, because prior intubating experience may influence success with both devices, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 10 total prior intubations. Fifth, because prior experience with using a bougie may influence successful intubation in the bougie group, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 5 prior intubations while using a bougie. Sixth, we will perform a sensitivity analysis that defines successful intubation on the first attempt as successful tracheal intubation during the first insertion of the laryngoscope blade, regardless of the number of insertions of a bougie or endotracheal tube.

Analysis of the Secondary Outcome

For the secondary outcome, severe hypoxemia (lowest oxygen saturation < 80%), we will perform an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet 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 bougie to patients randomized to the endotracheal tube with stylet. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with a chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Handling of Missing Data

We anticipate that no 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 BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, prospective, multi-center, non-blinded randomized clinical trial comparing use of a bougie to use of an endotracheal tube with stylet for tracheal intubation of critically ill adults in the ED and ICU. Patient enrollment began on 29 April 2019.

Pause in Enrollment

Over the first 10 months of enrollment, four patients were enrolled and subsequently found to be prisoners. On February 28, 2020, we paused enrollment to evaluate and improve enrollment procedures with a goal of preventing the enrollment of ineligible patients. The decision was made to extend the pause in enrollment during the early stages of the COVID-19 pandemic when enrollment was felt to be infeasible. Enrollment was resumed on August 24, 2020 with introduction of a new pre-procedural "time out" which requires the verbal recitation of eligibility criteria prior to enrollment to prevent subsequent enrollments of ineligible patients.

Ethics and Dissemination

Waiver of Informed Consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive intubation using either a bougie or an endotracheal tube with stylet 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 BOUGIE trial, the patient's treating clinician must believe that either a bougie or an endotracheal tube with stylet 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 provider who thinks either approach is safe

and reasonable for the patient was expected to pose no more than minimal additional risk.

The investigators also determined that obtaining informed consent for participation in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of an informed consent document for the intubation procedure in clinical care, the risks and benefits of the procedure are infrequently discussed and the informed consent document for the procedure in clinical care is infrequently completed before the procedure due to its time-sensitive nature, the impairments induced by the patients' critical illness, and the frequent absence of surrogate decision makers.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from all institutional review boards overseeing the trial. This is consistent with previous randomized trials comparing alternative approaches to tracheal intubation commonly used in clinical care.[7,10,16–21]

Information for Patients and Families

Information regarding the study is made available to patients and families by at least one of the following mechanisms, with the choice between the mechanisms determined by the local context assessment of the site IRB and site principal investigators: (1) a patient and family notification sheet provided to each patient and family following enrollment, informing the patient of their enrollment and describing the study; (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns; or (3) a patient and family information sheet provided to each patient and family on admission as part of an "admission packet" containing general study information and contact information for the research team for additional questions or concerns.

Protocol Changes

Any further amendments to the protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See Supplemental file, section 5 for more 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.

Conclusion

In the interest of allowing for a clearer and more objective interpretation of the trial results, this description of the trial protocol delineates the BOUGIE trial methods and analysis prior to the conclusion of enrollment.

	STUDY PERIOD						
	Eligibility Screen	**Randomize & Allocate**	**Peri-Procedural**				**Final Outcome Assessment**
TIMEPOINT	***Decision to perform TI***	**Prior to TI**	***Induction***	***TI***	***0-2 min post-TI***	**0-48 hrs post-TI**	***Discharge or 30 days after enrollment***
ENROLLMENT:		X					
Eligibility screen	X						
Allocation		X					
INTERVENTIONS:							
Bougie				X			
Endotracheal tube with stylet				X			
Screening for contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-procedural variables		X	X	X	X		
Clinical Outcomes						X	X

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments. TI, Tracheal Intubation; Induction, administration of a sedative or neuromuscular blocking agent

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***Denotes an author listed on the byline.
**Denotes an author not listed on the byline due to space considerations.
*Denotes a collaborator

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Supplementary file to:

Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan

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	5
	2b	All items from the World Health Organization Trial Registration Data Set	1-5
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2-3

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1,2, 16
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	7-8
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	8
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)	8
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	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	11-12

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
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	13-15
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)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	9-10
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	9-10

Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	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	12-14
	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	12-14
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	12-14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-20

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	16, Supplement section 4
	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	16
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 4
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplement section 4

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplement section 5
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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 17-18

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplement 17-18
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	4
	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 18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized 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.

2. 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.

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. Data and Safety Monitoring Board Charter

DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for

Bougie or Stylet In Patients Undergoing Intubation Emergently: BOUGIE

BOUGIE STEERING COMMITTEE

Protocol Co-Chairs	Brian Driver MD Assistant Professor of Emergency Medicine Hennepin County Medical Center and University of Minnesota Matthew Prekker MD, MPH Assistant Professor of Emergency Medicine and Pulmonary and Critical Care Medicine Hennepin County Medical Center and University of Minnesota
Coordinating Center	Vanderbilt University Medical Center Director: Jonathan D. Casey MD ED Site Director: Wesley H. Self, MD, MPH ICU Site Director: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler MD, MSc

Charter, Data and Safety Monitoring Board for

"Bougie or Stylet In Patients Undergoing Intubation Emergently: BOUGIE"

November 2018

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for "Bougie or Stylet In Patients Undergoing Intubation Emergently: The BOUGIE Trial"

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the BOUGIE Trial Steering committee and is assembled to provide recommendations about starting, continuing, and stopping the trial. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Performance of individual centers
- Participant safety
- Notification of and referral for adverse events

3. Organization and Interactions

Communication with DSMB members will be primarily through Dr. Casey. It is expected that neither BOUGIE Trial Steering Committee members nor study investigators will communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A. The DSMB consists of four physicians (Dr. Hooper, the DSMB chair, Dr. Lammi, Dr. Hernandez, and Dr. Storrow) who are experienced in the care of

critically ill patients, the conduct of clinical trials, and the process of data and safety monitoring. All three members of the DSMB have formal training to conduct statistical analyses necessary for the planned interim analysis. Dr. Casey or his designee will serve as the Executive Secretary (ES) and be responsible for keeping the minutes during open sessions. The Chair of the DSMB will be responsible for recording the minutes of the closed sessions and for the timely transmission of the final DSMB recommendations to the BOUGIE Trial Steering Committee, who will be responsible for the timely notification of investigators of all DSMB recommendations.

If one of the DSMB members resigns for any reason, a replacement member will be chosen by the chair of the DSMB, in collaboration with the BOUGIE Trial steering committee. If the DSMB chair resigns from the DSMB, one of the remaining DSMB members will be chosen to serve as the chair of the DSMB and a replacement member will be chosen by the BOUGIE Trial Steering Committee.

5. Scheduling, Timing, Content, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter and the study protocol, including the Data Safety Monitoring Plan. Dr. Casey or his designee can conduct this meeting with individual DSMB members or as a group. Enrollment in the study cannot begin until the BOUGIE Trial Steering Committee has accepted the DSMB's recommendation for approval and IRB approval has been obtained. All DSMB members must sign and return the charter to Dr. Casey or his designee to indicate their approval.

Conference calls are to be held twice per year, with additional conference calls scheduled as needed. Depending on the timing of the interim analysis, and at the discretion of the DSMB, the interim analysis may take the place of one of the biannual conference calls. Conference calls will be scheduled by Dr. Casey or his designee in collaboration with the DSMB members.

The DSMB will perform an interim analysis to review 30-day data after the enrollment of 553 subjects; enrollment will continue during the DSMB review. The primary focus of this review will be efficacy and safety. The DSMB will be supplied with raw data for the outcomes required for these analyses (as described below). Dr. Casey or his designee will also provide the DSMB committee with additional summary statistics on baseline characteristics, by group. The DSMB may request any additional data, as needed. The DSMB will also be able to request unblinding for any reason. All DSMB members must be present during this session and all must vote at the end of the session on the continuation of the trial. All serious adverse events thought to be related to study procedures will be reported to the DSMB on an ongoing basis; the study will be stopped for a safety evaluation by the DSMB if they have any concerns based on either the interim data analysis or review of serious adverse events.

The agenda for DSMB meetings and calls will be drafted by Dr. Casey or his designee. Dr. Casey or his designee will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials will be distributed prior to each call.

Before each teleconference Dr. Casey or his designee will ask all DSMB members to state whether they have developed any new conflicts of interest since the last call. If a new conflict is reported, the Chair will determine if the conflict limits the ability of the DSMB member to participate in the discussion. If the Chair reports a new conflict, the BOUGIE Trial Steering Committee will determine if the conflict limits the ability of the Chair to participate in the discussion.

It is expected that all DSMB members will attend every call and respond to electronic mail communications promptly. A quorum of this DSMB will be all three members.

6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, Dr. Casey or his designee will present information to the DSMB on behalf of the study investigators with time for discussion.

- During the **closed sessions**, the DSMB will discuss confidential and/or unblinded data from the study. Steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

Initial summary: Dr. Casey is responsible for ensuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations. The BOUGIE Trial Steering committee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, the BOUGIE Trial Steering Committee will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: As the Executive Secretary, Dr. Casey is responsible for the accuracy and transmission of the formal DSMB minutes within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email.

8. Reports to the DSMB

For each meeting, Dr. Casey will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first meeting what data they wish to review and how it should be presented. Data requests can be modified at subsequent meetings.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the clinical endpoints and safety monitoring plans. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial.

10. Stopping Rules

The DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, at least 30 days after enrollment of 553 patients. Enrollment will continue during this period. One week prior to the meeting for the interim analysis, Dr. Casey or his designee will provide the DSMB with the following blinded data in raw format:

1. Study group assignment of each patient (A vs B)

2. The primary outcome (successful intubation on the first attempt)
3. Esophageal intubation (safety outcome)
4. Airway trauma

For this interim analysis, the DSMB will be asked to perform an efficacy analysis and a safety analysis as described below. At the completion of these analyses, the DSMB will notify the BOUGIE Trial Steering Committee of their recommendation for the trial to be stopped or continued to completion. If the trial is not stopped, the DSMB will not make the steering committee members or any of the investigators aware of the results of any of their analyses. At the interim analysis or at any other time where the DSMB is deciding if the trial should be stopped or continued, all members of the DSMB must agree that the trial should be stopped or continued.

11. Efficacy and Safety Stopping Rule

The **stopping boundary for efficacy** will be met if the P-value using a chi-square test for the difference between groups in the primary outcome of successful intubation on the first attempt is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The **stopping boundary for safety** will be met if the P-value using a chi-square test for the difference between groups in the either of the safety outcomes, esophageal intubation, or airway trauma, is 0.025 or less.

If requested by the DSMB, the DSMB will be provided with blinded data on all outcomes collected by the trial to use in their review of trial safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, unblind the study assignments, or request modifications of the study protocol as required to protect patient safety.

Appendix A: DSMB members and titles

Michael Hooper, MD, MSc (DSMB Chair)

Associate Dean for Clinical Education, Associate Professor

Allergy, Pulmonary and Critical Care Medicine

Eastern Virginia Medical School

Expertise: Critical care, clinical trials, data and safety monitoring

Matthew Lammi, MD, MSc

Associate Professor of Medicine

Section of Pulmonary/Critical Care and Allergy/Immunology

LSU School of Medicine New Orleans

Expertise: Critical care, clinical trials, biostatistics

Alan B. Storrow, MD

Associate Professor

Department of Emergency Medicine

Associate Director of Research

Center for Emergency Care Research and Innovation (CERI)

Expertise: Emergency medicine, clinical research, quality improvement, patient safety

Antonio Hernandez, MD

Associate Professor

Department of Anesthesiology

Vanderbilt University Medical Center

Expertise: Critical care, intubation, clinical research

5. 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 and approval 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.

6. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication, will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities or other private healthcare information (PHI), is collected. All subjects are assigned a unique study ID number for tracking. 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. Site Characteristics

Table S1

	VUMC ICUs	VUMC ED	LSU UMCNO MICU	Ochsner MICU	UAB MICU	UAB ED
Patient Notification Strategy	Information Sheet	Information Sheet	Information Sheet	Information Sheet	Notification Sheet	Notification Sheet
IRB Process	Central*	Central*	Central	Central	Central	Central
	WFU MC ED	**U of CO ED**	**DHMC ED**	**UW-Harborview ICU**	**Lincoln Medical Center**	
Patient Notification Strategy	Information Sheet	Notification Sheet	Notification Sheet	Information Sheet		
IRB Oversight	Central	Central	Central	Central	Local	

VUMC is Vanderbilt University Medical Center in Nashville, TN; LSU is Louisiana State University Medical Center New Orleans, in New Orleans, LA; Oschner is Ochsner Medical Center, in New Orleans, LA; UAB is University of Alabama at Birmingham in Birmingham, AL; WFU is Wake Forest University Medical Center in Winston-Salem, NC; U of CO is University of Colorado in Aurora, CO; DHMC is Denver Health Medical Center in Denver, CO; UW-Harborview is University of Washington in Seattle, WA; Lincoln Medical Center is Lincoln Medical Center in Bronx, NY.

ED, emergency department; ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; IRB is institutional review board. “Notification sheet” is a patient and family notification packet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study. “Information Sheet” is a patient and family information sheet containing general information about the study and contact information for the research team displayed in at least three publicly-visible locations within the study unit. *The Vanderbilt IRB served as central IRB for sites utilizing a central IRB process.

8. List of BOUGIE Investigators

Vanderbilt University Medical Center— Matthew W. Semler, MD, MSc***; Wesley H. Self, MD, MPH***; Christopher G Hughes, MD, MS***; Janna S. Landsperger, MSN***; Li Wang, MS***; Christopher J. Lindsell PhD***; Todd W. Rice, MD, MSc***; Jonathan D. Casey, MD, MSc***; Christopher S. Gray, RN**; Kevin High, RN, MPH**; Andrea Fletcher, RN**; Sally Dye, RN**; Bradley Lloyd, RRT-ACCS*; Bret D. Alvis, MD*.

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Ochsner Health System New Orleans— Derek J Vonderhaar, MD***.

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Lincoln Medical Center— Jason R West, MD***.

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Louisiana State University School of Medicine—David R Janz, MD, MSc***.

Hennepin County Medical Center— Brian E Driver, MD***; Matthew E Prekker, MD MPH***; Jamie Stang, BS**; Paige DeVries, BS**; Alexandra Schick, MD**.

***Denotes an author listed on the byline.
**Denotes an author not listed on the byline due to space considerations.
*Denotes a collaborator

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BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial

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Secondary Subject Heading:	Intensive care, Anaesthesia
Keywords:	Adult intensive & critical care < ANAESTHETICS, Adult intensive & critical care < INTENSIVE & CRITICAL CARE, INTENSIVE & CRITICAL CARE

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BOugie or stylet in patients UnderGoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan for a randomized clinical trial

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for the BOUGIE Investigators# and the Pragmatic Critical Care Research Group.

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Abstract:

Introduction: Intubation-related complications are less frequent when intubation is successful on the first attempt. The rate of first attempt success in the ED and ICU is typically less than 90%. The bougie, a semi-rigid introducer that can be placed into the trachea to facilitate a Seldinger-like technique of tracheal intubation and is typically reserved for difficult or failed intubations, might improve first attempt success. Evidence supporting its use, however, is from a single academic emergency department with frequent bougie use. Validation of these findings is needed before widespread implementation.

Methods and Analysis:

The Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE) trial is a prospective, multi-center, non-blinded randomized trial being conducted in 6 EDs and 6 intensive care units in the United States. The trial plans to enroll 1,106 critically-ill adults undergoing orotracheal intubation. Eligible patients are randomized 1:1 to use of a bougie or use of an endotracheal tube with stylet for the first intubation attempt. The primary outcome is successful intubation on the first attempt. The secondary outcome is severe hypoxemia, defined as an oxygen saturation less than 80% between induction until two minutes after completion of intubation. Enrollment began on April 29, 2019 and is expected to be completed in 2021.

Ethics and Dissemination:

The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The results will be submitted for publication in a peer-reviewed journal and presented at scientific conferences.

Trial Registration:

This trial was registered with ClinicalTrials.gov (NCT03928925) on April 26, 2019, prior to the enrollment of the first patient on April 29, 2019.

Strengths and limitations of this study:

- This protocol provides a detailed description of the largest pragmatic trial of bougie use in emergency airway management to be conducted to date.
- Broad eligibility criteria, diverse prior experience with a bougie among operators, and conduct in the ED and ICU at multiple centers will increase the external validity of the findings.
- Patients, clinicians, and investigators are not blinded to study group assignment after randomization.

Introduction:

Tracheal intubation of critically ill adults is frequently performed in the Emergency Department (ED) and Intensive Care Unit (ICU). Successful intubation on the first attempt has been associated with a lower incidence of peri-intubation complications.[1–4] However, less than 90% of patients are intubated on the first attempt in most settings outside of the operating room, highlighting an opportunity for improvement.[5–7]

Emergency tracheal intubation is commonly performed in three discrete steps. First, medications are administered to facilitate optimal intubating conditions (induction). Second, a laryngoscope is inserted into the patient's mouth and a direct or indirect video view of glottic structures is obtained (laryngoscopy). Third, an endotracheal tube is placed in the mouth and advanced past the vocal cords into the trachea (intubation). Two commonly used devices that aid in placing the endotracheal tube include: a stylet (a malleable, aluminum rod preloaded inside the endotracheal tube to facilitate navigation of the upper airway) or a bougie (a thin, plastic introducer passed into the trachea which serves as a guide for passage of the endotracheal tube). When using a stylet, the endotracheal tube and stylet are passed into the trachea together. When using a bougie, the bougie is first passed into the trachea and then the endotracheal tube is advanced over the bougie using a Seldinger-like technique. There is substantial variation between clinicians as to whether they select the stylet or the bougie for the first intubation attempt.[5,8] For some physicians, the bougie is used primarily as a rescue device in the event difficulty is encountered in laryngoscopy or passage of the endotracheal tube with stylet. Other physicians use a bougie routinely on the first attempt at tracheal intubation.[8,9]

To our knowledge, only one prior randomized trial has compared rates of successful intubation on the first attempt outside of the operating room with use of a bougie versus use of endotracheal tube with stylet: the single-center Bougie Use in Emergency Airway Management (BEAM) trial. That study showed a higher rate of successful intubation on the first attempt with use of a bougie (98%) compared to use of an endotracheal tube with stylet (87%) in adult ED patients (absolute difference 11%, 95% CI 7% to 14%).[10] However, it is possible that these findings reflect increased institution-specific comfort with bougie use compared to the endotracheal tube and

stylet – operators reported using a bougie in approximately 80% of intubations before the trial.[8] It is unknown if the results of the BEAM trial will generalize to other settings where operators have less experience using the bougie and have greater experience using an endotracheal tube with stylet during the first attempt at intubation.

Methods and Analysis:

This manuscript was written in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (see table 1 and online supplementary file 1, section 1).[11]

Patient and Public Involvement

We did not involve patients or the public in the design of the study.

Study Design

The BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, multicenter, unblinded, parallel-group, randomized trial comparing use of a bougie to use of an endotracheal tube with stylet for the first attempt at tracheal intubation among critically ill adults in the ED and ICU. The primary outcome is successful intubation on the first attempt. The trial protocol was approved with waiver of informed consent by the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at an enrolling site. The trial was registered prior to initiation of enrollment (ClinicalTrials.gov identifier: NCT03928925). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial. Study sites and investigators are listed in the online supplementary file, sections 2 and 3.

Study Population

The inclusion criteria for the trial are:

1. Patient is located in a participating unit of an adult hospital

2. Planned procedure is tracheal intubation with sedative administration (or tracheal intubation without sedative administration in patients with decreased level of consciousness, cardiac arrest, or respiratory arrest)
3. Planned operator is a clinician expected to routinely perform tracheal intubation in the participating unit
4. Planned laryngoscopy device is a non-hyperangulated laryngoscope blade

The exclusion criteria for the trial are:

1. Patient is pregnant
2. Patient is a prisoner
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels an approach to intubation other than use of a bougie or use of an endotracheal tube with stylet would be best for the care of the patient
5. Operator feels use of a bougie is required or contraindicated for the care of the patient
6. Operator feels use of an endotracheal tube with stylet is required or contraindicated for the care of the patient

The original inclusion criteria specified that patients must be at least 18 years old to be eligible. With approval from the central institutional review board at Vanderbilt University Medical Center, trial inclusion and exclusion criteria were amended on January 16, 2020 to allow the enrollment of patients less than 18 years of age. Because the identity and age of critically ill patients presenting to the ED are sometimes unknown (e.g., a patient with cardiac arrest presenting by ambulance without family), this criterion was revised to include patients located in a participating unit of an adult hospital. We anticipate that a small number of patients whose identity and age are unknown, who are judged by treating clinicians to be an adult and enrolled in the trial, will later be determined to be less than 18 years old.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to undergo intubation using a bougie or using an endotracheal tube with stylet for the first attempt in permuted blocks of two, four, or six, 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 all inclusion criteria and no exclusion criteria. The operator documents whether they plan to use a video laryngoscope or a direct laryngoscope by checking a box on the front of the envelope. The operator then opens the envelope. Patients are considered to be enrolled once the operator opens the envelope to reveal study group assignment. Thus, group assignment is concealed until after documentation of laryngoscope choice and patient enrollment. Patients who are screened and excluded will be reported with trial results using a CONSORT diagram. After enrollment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Training

Before beginning enrollment at a site, operators at each site received a 30-minute in-person lecture and watched a 6-minute training video which demonstrated best-practices for intubation with both a bougie and endotracheal tube with stylet. These materials are available from the authors upon request.

Bougie Group

For patients assigned to the bougie group, operators are instructed to use a bougie on the first attempt at laryngoscopy and tracheal intubation. If the bougie is successfully placed in the trachea, an assistant is instructed to load the endotracheal tube (without a stylet) over the bougie. The operator is instructed to, without removing the laryngoscope from the mouth, advance the tube through the vocal cords to the desired depth in the trachea. If resistance is encountered when passing the endotracheal tube over the bougie, the tube is be retracted 2 centimeters, rotated 90° counterclockwise to orient the bevel tip of the tube vertically, and re-advanced into the trachea. With the

operator or an assistant manually stabilizing the endotracheal tube, the bougie is withdrawn from the endotracheal tube before ventilation. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

This trial evaluates the use of a straight, semi-rigid bougie. Experts report that less-rigid bougies packaged in a curled position are more difficult to advance through the glottic opening.[12] Participating units use a straight bougie at least 60 cm in length; a Coudé tip is favored but not required. Operators may choose whether and how to bend the bougie prior to intubation.

Endotracheal Tube with Stylet Group

For patients assigned to the endotracheal tube with stylet group, operators are instructed to use an endotracheal tube with stylet on the first attempt at laryngoscopy and tracheal intubation. The shape and curvature of the endotracheal tube with stylet is determined the operator, however a “straight-to-cuff” shape and a distal bend angle of 25° to 35° is encouraged. If there is difficulty passing the endotracheal tube, the operator is instructed to manipulate the tube as needed, including slight retraction and rotation. The stylet remains within the endotracheal tube until the tube is within the trachea. Confirmation of correct endotracheal tube placement is deferred to clinicians; detection of end-tidal carbon dioxide is the standard of care at participating institutions.

Subsequent Attempts at Laryngoscopy and Intubation and Co-Interventions

Study group assignment determines only the device to be used on the first attempt at laryngoscopy and tracheal intubation. All other aspects of the intubation procedure are at the discretion of treating clinicians, including choice of endotracheal tube diameter, patient position, approach to pre-oxygenation, approach to ventilation and oxygenation between induction and intubation, and devices used after the first intubation attempt. For laryngoscopes capable of both video-assisted and direct laryngoscopy, the use of the video screen during intubation is at the discretion of the operator. After the first attempt at laryngoscopy and tracheal intubation, the operator may use any other method of intubation, including use of an endotracheal tube with stylet in the bougie

group or use of a bougie in the endotracheal tube with stylet group. In either group, treating clinicians may, at any point, use any device they feel is required to ensure optimal care of the patient regardless of study group assignment. The approach to the initial attempt at laryngoscopy and intubation and any co-interventions are prospectively collected and will be reported.

Co-enrollment in other randomized trials is permitted as the use of randomization facilitates balance between study arms, reduces the likelihood of any systematic effects on intubation success rates, and allows for evaluation of the main effects in this trial.

Data Collection

An observer, not directly involved with the intubation procedure, collects data for key peri-procedural outcomes, including successful intubation on the first attempt, time between induction and successful intubation, arterial oxygen saturation and systolic blood pressure at induction, and the lowest values for arterial oxygen saturation and systolic blood pressure between induction and 2 minutes following intubation. The background of trained observers depends on local context and may include either clinical professionals (e.g., physicians or nurses) or research study personnel. All observers received training on study procedures and data element definitions.

Immediately after the procedure, operators complete a paper data collection form to document the approach to oxygen administration and use of ventilation for pre-oxygenation and between induction and laryngoscopy, laryngoscope used, Cormack-Lehane grade of glottic view[13], laryngoscope video screen use (if applicable), reason for the failure to intubate on the first attempt (if applicable), subsequent intubation methods, difficult airway characteristics (cervical collar, glottic view obscured by body fluids, facial trauma), and complications of intubation (cardiac arrest, heart rate < 40 beats per minute, esophageal intubation, airway trauma, witnessed aspiration). Operators record their specialty and training level and self-report the number of prior intubations, overall and with a bougie, at the time of each study intubation.

Study personnel review the medical record to collect data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes. The following variables are collected:

1. Baseline: Age, gender, height, weight, race, ethnicity, APACHE II score, most recent pre-procedural Glasgow Coma Score, active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, whether the primary diagnosis was trauma-related, indication for intubation, non-invasive positive pressure ventilation and high flow nasal cannula use, vasopressor use in the hour preceding enrollment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate >2mmol/L in the absence of hypovolemia) at the time of enrollment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrollment, and whether or not this was a reintubation (defined as a patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).
2. Peri-procedural: type and dose of neuromuscular blocker; laryngoscope device used, blade shape and size for first attempt; total number of intubation attempts; presence of any of the following difficult airway characteristics: vomiting, witnessed aspiration, upper gastrointestinal hemorrhage, epistaxis or oral bleeding, upper airway mass, infection, or trauma, head and neck radiation, obesity (body mass index > 30 kg/m^2), limited neck mobility, limited mouth opening, history of obstructive sleep apnea, or other.
3. 0-48 hours: Cardiac arrest within 1 hour of intubation, presence or absence of pneumothorax on first chest film obtained within 48 hours after intubation; systolic blood pressure, oxygen saturation, FiO_2, and positive end expiratory pressure delivered at 24 hours after enrollment.
4. In-Hospital Outcomes: Ventilator-free days, ICU-free days, and 28 day in-hospital mortality.

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: (1) a single insertion of a laryngoscope blade into the mouth and (2) EITHER

a single insertion of a bougie into the mouth followed by a single insertion of an endotracheal tube into the mouth OR a single insertion of an endotracheal tube with stylet into the mouth.

The primary outcome is collected by a trained observer using a structured data collection form that records the number of insertions of the laryngoscope blade, bougie, and endotracheal tube into the patient's mouth. If data from the independent observer about the primary outcome are missing, the operator's self-report of successful intubation on the first attempt will be used. If documentation of successful intubation on the first attempt are discordant between the independent observer and the operator, data from the independent observer will take precedence.

Secondary Outcome

The secondary outcome is the incidence of severe hypoxemia, defined as an oxygen saturation less than 80% during the time interval from induction to two minutes after completion of tracheal intubation.

Exploratory Outcomes

- Cormack-Lehane grade of glottic view
- Number of laryngoscopy attempts
- Number of attempts at passing the bougie
- Number of attempts at passing the endotracheal tube
- Duration of intubation: The start of the procedure will be defined as either the time of first sedative administration or, among patients who do not receive a sedative, the time of initiation of laryngoscopy. The end of the procedure will be defined as the time of the final placement of an endotracheal tube within the trachea.
- Whether the video laryngoscope screen was viewed, among intubations where the operator used a video laryngoscope.
- Incidence of mechanical intubation complications, including:
    - Esophageal intubation
    - Operator-reported aspiration during the procedure

- Airway trauma (injury to oropharyngeal, glottic, or thoracic airway structures)
- Cardiac arrest within 1 hour following intubation
- Incidence of peri-intubation cardiovascular collapse, defined as one or more of:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes following intubation
  - New or increased vasopressor between induction and 2 minutes following intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation
- ICU-free days in the first 28 days (see online supplementary file, section 4)
- Ventilator free days in the first 28 days (see online supplementary file, section 5)
- All-cause, in-hospital mortality at 28 days

Sample Size Estimation

There is no established minimum clinically important difference in successful intubation on the first attempt. A prior single-center randomized trial reported an absolute difference of 11% in successful intubation on the first attempt between the bougie and endotracheal tube with stylet groups. Because this trial was performed in an ED where the majority of first intubation attempts utilized a bougie, we anticipated a potentially smaller difference between groups in this multicenter trial conducted in a broader range of clinical settings with a broader range of operators. Therefore, the current trial was designed to detect a 6% absolute difference between groups in the proportion of patients who experience successful intubation on the first attempt. For two inexpensive interventions already routinely available and utilized in practice, the minimally clinically significant difference that would be expected to change practice is unknown. However, an absolute difference of 6% in successful intubation on the first attempt is similar to or smaller than the difference considered to be clinically meaningful in the design of prior airway management trials.[7,10,14] Assuming 84% of patients in the endotracheal tube with stylet group experience successful intubation on the first laryngoscopy attempt, detecting a 6% absolute increase in successful intubation on the first attempt with 80%

power at a two-sided alpha level of 0.05 would require enrollment of 1,050 patients (525 per group). Anticipating missing data for 5% of patients or less, we will plan to enroll a total of 1,106 patients (553 per group).

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of 4 clinical trials experts with backgrounds in critical care medicine, anesthesia, and emergency medicine has overseen the design of the trial and is monitoring its conduct. The DSMB reviewed a single interim analysis, prepared by the study biostatistician, on February 4th, 2020, at the anticipated halfway point of the trial after enrollment of 553 patients, and recommended continuing the trial to completion without alteration. The stopping boundary for efficacy was pre-specified as a P-value of 0.001 or less for the difference in the incidence of the primary outcome between groups tested, using a chi-square test. 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 recommended stopping boundary for safety was a $P < 0.025$ comparing the incidence of esophageal intubation and separately the incidence of airway trauma between groups, using a chi-square test. 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. The DSMB charter is available in the online supplementary file, section 6. Patient privacy and data storage details are listed in the online supplementary file, section 7.

Statistical Analysis Principles

Analyses will be conducted following reproducible research principles using R (R Foundation for Statistical Computing, Vienna, Austria).[15] Continuous variables will be reported as mean ± standard deviation or median and interquartile range; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Wilcoxon rank sum test for continuous variables and the chi-square test for categorical variables. We will also present absolute between-group differences with associated 95% confidence intervals. A two-sided p-value of < 0.05 will be used to indicate statistical significance; with just one primary outcome, no adjustment

for multiplicity will be made. For secondary and exploratory analyses, emphasis will be placed on the magnitude of differences between groups rather than statistical significance.

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 bougie group and patients randomized to the endotracheal tube with stylet group, using a chi-square test.

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 and operator as random effects, and fixed effects of study group and the following pre-specified baseline covariates: age, sex, race, body-mass index, operator experience quantified as the operator's total number of prior intubations, and location of intubation (ED vs ICU). We will then construct a model with the following additional factors that may be interpreted as baseline covariates but which are unable to be assessed until after randomization: use of a video vs direct laryngoscope; presence of ≥ 1 difficult airway characteristic (obesity, body fluids obscuring glottic view, cervical immobilization, or facial trauma) and Cormack-Lehane grade 2, 3, or 4 laryngeal view. 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 variables modify the effect of bougie vs endotracheal tube with stylet use on the primary outcome using a formal test of interaction between group assignment and effect modifier in the above models. Because this study is not formally designed or powered to test for interaction, a less conservative P value for the interaction term will be used, with values less than 0.10

considered suggestive of a potential interaction and values less than 0.05 considered to confirm an interaction. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. Operator Experience at the time of each enrollment
    a. Total number of previous intubations performed by operator
    b. Number of previous intubations performed by operator using a bougie
    c. Proportion of previous intubations performed by the operator that were performed using a bougie
2. Location (ED vs ICU)
3. Indication for intubation (trauma vs medical)
4. Difficult airway, defined as one or more of the following difficult airway characteristics: obesity (body mass index > 30 kg/m^2), cervical immobilization, or facial trauma.
5. Time period (before the COVID pandemic vs during or after the COVID pandemic)

In addition to the variables above, which can be assessed prior to enrollment, we will perform exploratory analyses examining additional potential effect modifiers that are intended to represent baseline variables, but which are collected after enrollment, and therefore have the potential to be affected by study group assignment. These include:

1. Laryngoscope type (Direct laryngoscope [without video capability] vs video laryngoscope [with video capability])
2. Presence body fluids obscuring glottic view (Yes vs No)
3. Cormack Lehane grade of view (1 vs 2-4).

Sensitivity Analyses of the Primary Outcome

To assess the robustness of the findings, we will repeat the main analysis of the primary outcome in several alternatives to the overall intention-to-treat population. First, we will repeat the main analysis of the primary outcome among only those patients for whom a non-hyperangulated laryngoscope blade was used on the first attempt at intubation. Second, operators may choose to deviate from the assigned device for the safety of the

patient after obtaining a laryngeal view. To address this, we will repeat the main analysis of the primary outcome for all patients, but will assign failure to the first intubation attempt for patients in whom the operator crossed over from the assigned device to the non-assigned device. Third, we will repeat the main analysis of the primary outcome, including only cases in which primary outcome data from the independent observer is complete (i.e., excluding cases in which the operator's self-report of whether there was successful intubation on the first attempt defined the primary outcome for that patient). Fourth, because prior intubating experience may influence success with both devices, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 10 total prior intubations. Fifth, because prior experience with using a bougie may influence successful intubation in the bougie group, we will repeat the main analysis of the primary outcome, excluding cases where the operator had ≤ 5 prior intubations while using a bougie. Sixth, we will perform a sensitivity analysis that defines successful intubation on the first attempt as successful tracheal intubation during the first insertion of the laryngoscope blade, regardless of the number of insertions of a bougie or endotracheal tube.

Analysis of the Secondary Outcome

For the secondary outcome, severe hypoxemia (lowest oxygen saturation < 80%), we will perform an unadjusted, intention-to-treat comparison of patients randomized to the bougie group versus patients randomized to the endotracheal tube with stylet 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 bougie to patients randomized to the endotracheal tube with stylet. Continuous outcomes will be compared with the Wilcoxon rank sum test and categorical variables with a chi-square test. Between-group differences in continuous and categorical variables and the associated 95% confidence intervals will be presented.

Handling of Missing Data

We anticipate that no 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 BOugie or Stylet In Patients UnderGoing Intubation Emergently (BOUGIE) trial is a pragmatic, prospective, multi-center, non-blinded randomized clinical trial comparing use of a bougie to use of an endotracheal tube with stylet for tracheal intubation of critically ill adults in the ED and ICU. Patient enrollment began on 29 April 2019.

Pause in Enrollment

Over the first 10 months of enrollment, four patients were enrolled and subsequently found to be prisoners. On February 28, 2020, we paused enrollment to evaluate and improve enrollment procedures with a goal of preventing the enrollment of ineligible patients. The decision was made to extend the pause in enrollment during the early stages of the COVID-19 pandemic when enrollment was felt to be infeasible. Enrollment was resumed on August 24, 2020 with introduction of a new pre-procedural "time out" which requires the verbal recitation of eligibility criteria prior to enrollment to prevent subsequent enrollments of ineligible patients.

Ethics and Dissemination

Waiver of Informed Consent

Critically ill patients undergoing tracheal intubation in the ED or ICU are at significant risk for morbidity and mortality from their underlying illness. Most patients undergoing tracheal intubation in routine clinical care receive intubation using either a bougie or an endotracheal tube with stylet 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 BOUGIE trial, the

patient's treating clinician must believe that either a bougie or an endotracheal tube with stylet 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 provider who thinks either approach is safe and reasonable for the patient was expected to pose no more than minimal additional risk.

The investigators also determined that obtaining informed consent for participation in the study would be impracticable. Tracheal intubation of acutely ill patients is a time-sensitive procedure. Despite the availability of an informed consent document for the intubation procedure in clinical care, the risks and benefits of the procedure are infrequently discussed and the informed consent document for the procedure in clinical care is infrequently completed before the procedure due to its time-sensitive nature, the impairments induced by the patients' critical illness, and the frequent absence of surrogate decision makers.

Because the study was expected to pose minimal risk and prospective informed consent was considered to be impracticable, a waiver of informed consent was requested and granted from the single institutional review board at Vanderbilt University Medical Center (reference number 182123). This is consistent with previous randomized trials comparing alternative approaches to tracheal intubation commonly used in clinical care.[7,10,16–21]

Information for Patients and Families

Information regarding the study is made available to patients and families by at least one of the following mechanisms, with the choice between the mechanisms determined by the local context assessment of the site IRB and site principal investigators: (1) a patient and family notification sheet provided to each patient and family following enrollment, informing the patient of their enrollment and describing the study; (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns; or (3) a patient and family information sheet provided to each patient and family on admission as part of

an “admission packet” containing general study information and contact information for the research team for additional questions or concerns.

Protocol Changes

Any further amendments to the protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See the online supplementary file, section 8 for more 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.

	STUDY PERIOD						
	Eligibility Screen	**Randomize & Allocate**	**Peri-Procedural**				**Final Outcome Assessment**
TIMEPOINT	***Decision to perform TI***	**Prior to TI**	***Induction***	***TI***	***0-2 min post-TI***	**0-48 hrs post-TI**	***Discharge or 30 days after enrollment***
ENROLLMENT:		X					
Eligibility screen	X						
Allocation		X					
INTERVENTIONS:							
Bougie				X			
Endotracheal tube with stylet				X			
Screening for contraindications	X	X	X	X			
ASSESSMENTS:							
Baseline Variables	X	X					
Peri-procedural variables		X	X	X	X		
Clinical Outcomes						X	X

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrollment, interventions, and assessments. TI, Tracheal Intubation; Induction, administration of a sedative or neuromuscular blocking agent

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Supplementary file to:

Bougie or Stylet In Patients Undergoing Intubation Emergently (BOUGIE): protocol and statistical analysis plan

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	5
	2b	All items from the World Health Organization Trial Registration Data Set	1-5
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	2-3
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2-3

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1,2, 16
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	7-8
	6b	Explanation for choice of comparators	7-8
Objectives	7	Specific objectives or hypotheses	8
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)	8
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	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	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)	11-12

	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
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	13-15
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)	Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	9-10
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	9-10

Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	9-10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	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	12-14
	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	12-14
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	12-14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16-20

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	16, Supplement section 6
	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	16
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 6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplement section 6

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	8
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplement section 8
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
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 7

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	3
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplement section 7
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	4
	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 7
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized 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.

2. Site Characteristics

Table S1

	VUMC ICUs	VUMC ED	LSU UMCNO MICU	Ochsner MICU	UAB MICU	UAB ED
Patient Notification Strategy	Information Sheet	Information Sheet	Information Sheet	Information Sheet	Notification Sheet	Notification Sheet
IRB Process	Central*	Central*	Central	Central	Central	Central
	WFU MC ED	**U of CO ED**	**DHMC ED**	**UW-Harborview ICU**	**Lincoln Medical Center**	
Patient Notification Strategy	Information Sheet	Notification Sheet	Notification Sheet	Information Sheet	Notification sheet	
IRB Oversight	Central	Central	Central	Central	Local	

VUMC is Vanderbilt University Medical Center in Nashville, TN; LSU is Louisiana State University Medical Center New Orleans, in New Orleans, LA; Oschner is Ochsner Medical Center, in New Orleans, LA; UAB is University of Alabama at Birmingham in Birmingham, AL; WFU is Wake Forest University Medical Center in Winston-Salem, NC; U of CO is University of Colorado in Aurora, CO; DHMC is Denver Health Medical Center in Denver, CO; UW-Harborview is University of Washington in Seattle, WA; Lincoln Medical Center is Lincoln Medical Center in Bronx, NY.

ED, emergency department; ICU, intensive care unit; MICU, medical ICU; SICU, surgical ICU; IRB is institutional review board. “Notification sheet” is a patient and family notification packet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study. “Information Sheet” is a patient and family information sheet containing general information about the study and contact information for the research team displayed in at least three publicly-visible locations within the study unit. *The Vanderbilt IRB served as central IRB for sites utilizing a central IRB process.

3. List of BOUGIE Investigators

Vanderbilt University Medical Center— Matthew W. Semler, MD, MSc***; Wesley H. Self, MD, MPH***; Christopher G Hughes, MD, MS***; Janna S. Landsperger, MSN***; Li Wang, MS***; Christopher J. Lindsell PhD***; Todd W. Rice, MD, MSc***; Jonathan D. Casey, MD, MSc***; Christopher S. Gray, RN**; Kevin High, RN, MPH**; Andrea Fletcher, RN**; Sally Dye, RN**; Bradley Lloyd, RRT-ACCS*; Bret D. Alvis, MD*.

University of Colorado School of Medicine— Adit A Ginde, MD, MPH***; Michelle P Howell, RN, BSN***; Robert Mitchell, RRT**; Justin Oeth, RN, MSN**; Anthony Defebio*; Jennifer Friedel*; Feysel Mohamed*; Karina Nava*; Angela Otoo*; Christian Perez*; Cori Withers*.

University of Alabama at Birmingham Medical Center— Sheetal Gandotra, MD***; David B Page, MD***; Micah R Whitson, MD***; Derek W. Russell, MD***; Swati Gulati, MBBS, MS***; Sarah W. Robison, MD**; Michael C. Kurz, MD, MS**; Anna Altz-Stamm RN, BSN, CCRN*; Cristina Bardita, MD, PhD*; Mary Clay Boone RN, BSN*; Joe W. Chiles III, MD*; Kristina Collins RN, BSN*; Abby Drescher RN, BSN*; Kevin G. Dsouza, MD*; Janna Dunn, RN, ADN*; Stacy Ejem, MD*; Josh Gautney, MD*; Nicole Harris, RN, ADN*; Savannah Herder, RN, BSN*; Tamer Hudali, MD, MPH*; R. Chad Wade, MD*; Rutwij Joshi, MBBS*; Daniel Kelmenson, MD*; Anne Merrill Mason RN, BSN*; Scott R. Merriman, MD*; Takudzwa Mkorombindo, MD*; Megan Moore, RN, MSN*; Jada Nowak, RN, BSN*; Kate O'Connor, DO*; Sheylan D. Patel, MD*; G. Bruno Pereira, MD, PhD*; Lisa Sarratt RN, BSN*; Tabitha Stewart RN, BSN*; William S. Stigler, MD*; Kadambari Vijaykumar, MBBS*; Gina White RN, BSN*; Stephanie C. Demasi, MD*; Laura E. Goyack, MD*.

Denver Health Medical Center— Stacy A Trent, MD, MPH***; Carol L. Lyle, MPH, PA-C**; Alicia K. Cupelo, MSW**.

Wake Forest School of Medicine— Lane M Smith, MD, PhD***; John P Gaillard, MD***; Kevin W. Gibbs, MD***; Erika L.W. Rice, DO**; Nathaniel D. Westphal, MD**; Kristy K. Ford, MD*; Trevor S. Mattox, MD*.

Ochsner Health System New Orleans— Derek J Vonderhaar, MD***.

University of Washington Harborview Medical Center— Aaron M. Joffe, DO***; Itay Bentov, MD, PhD***; Steven H Mitchell, MD***; Andrew J Latimer, MD***; Christopher Barnes**; Andrew M. Walters**; Tak Watase, MD MBA*.

Lincoln Medical Center— Jason R West, MD***.

University of Iowa Hospitals and Clinics— Kevin Doerschug, MD***; Vikas Koppurapu, MD**.

Duke University School of Medicine— Vijay Krishnamoorthy, MD, PhD*; Raquel R Bartz, MD*; William C Fox, MD*; John Whittle, MBBS, MD*.

Louisiana State University School of Medicine—David R Janz, MD, MSc***.

Hennepin County Medical Center— Brian E Driver, MD***; Matthew E Prekker, MD MPH***; Jamie Stang, BS**; Paige DeVries, BS**; Alexandra Schick, MD**.

***Denotes an author listed on the byline.
**Denotes an author not listed on the byline due to space considerations.
*Denotes a collaborator

4. 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.

5. 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.

6. Data and Safety Monitoring Board Charter

DATA AND SAFETY MONITORING BOARD CHARTER

Charter, Data and Safety Monitoring Board for

Bougie or Stylet In Patients Undergoing Intubation Emergently: BOUGIE

BOUGIE STEERING COMMITTEE

Protocol Co-Chairs	Brian Driver MD
	Assistant Professor of Emergency Medicine
	Hennepin County Medical Center and University of Minnesota
	Matthew Prekker MD, MPH
	Assistant Professor of Emergency Medicine and Pulmonary and Critical Care Medicine
	Hennepin County Medical Center and University of Minnesota
Coordinating Center	Vanderbilt University Medical Center
	Director: Jonathan D. Casey MD
	ED Site Director: Wesley H. Self, MD, MPH
	ICU Site Director: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG)
	Steering Committee Chair: Matthew W. Semler MD, MSc

Charter, Data and Safety Monitoring Board for

"Bougie or Stylet In Patients Undergoing Intubation Emergently: BOUGIE"

November 2018

1. Introduction

This Charter is for the Data and Safety Monitoring Board (DSMB) for "Bougie or Stylet In Patients Undergoing Intubation Emergently: The BOUGIE Trial"

The Charter is intended to be a living document. The DSMB may wish to review it at regular intervals to determine whether any changes in procedure are needed.

2. Responsibilities of the DSMB

The DSMB is responsible for safeguarding the interests of study participants, assessing the safety and efficacy of study procedures, and for monitoring the overall conduct of the study.

The DSMB is an independent group advisory to the BOUGIE Trial Steering committee and is assembled to provide recommendations about starting, continuing, and stopping the trial. In addition, the DSMB is asked to make recommendations, as appropriate, to the investigators about:

- Benefit/risk ratio of procedures and participant burden
- Selection, recruitment, and retention of participants
- Adherence to protocol requirements
- Completeness, quality, and analysis of measurements
- Amendments to the study protocol
- Performance of individual centers
- Participant safety
- Notification of and referral for adverse events

3. Organization and Interactions

Communication with DSMB members will be primarily through Dr. Casey. It is expected that neither BOUGIE Trial Steering Committee members nor study investigators will communicate with DSMB members about the study directly, except when making presentations or responding to questions at DSMB meetings or during conference calls.

4. DSMB Members

DSMB members and their expertise are listed in Appendix A. The DSMB consists of four physicians (Dr. Hooper, the DSMB chair, Dr. Lammi, Dr. Hernandez, and Dr. Storrow) who are experienced in the care of

critically ill patients, the conduct of clinical trials, and the process of data and safety monitoring. All three members of the DSMB have formal training to conduct statistical analyses necessary for the planned interim analysis. Dr. Casey or his designee will serve as the Executive Secretary (ES) and be responsible for keeping the minutes during open sessions. The Chair of the DSMB will be responsible for recording the minutes of the closed sessions and for the timely transmission of the final DSMB recommendations to the BOUGIE Trial Steering Committee, who will be responsible for the timely notification of investigators of all DSMB recommendations.

If one of the DSMB members resigns for any reason, a replacement member will be chosen by the chair of the DSMB, in collaboration with the BOUGIE Trial steering committee. If the DSMB chair resigns from the DSMB, one of the remaining DSMB members will be chosen to serve as the chair of the DSMB and a replacement member will be chosen by the BOUGIE Trial Steering Committee.

5. Scheduling, Timing, Content, and Organization of Meetings

DSMB meetings will be held by teleconference. The purpose of the first meeting is to review and discuss this Charter and the study protocol, including the Data Safety Monitoring Plan. Dr. Casey or his designee can conduct this meeting with individual DSMB members or as a group. Enrollment in the study cannot begin until the BOUGIE Trial Steering Committee has accepted the DSMB's recommendation for approval and IRB approval has been obtained. All DSMB members must sign and return the charter to Dr. Casey or his designee to indicate their approval.

Conference calls are to be held twice per year, with additional conference calls scheduled as needed. Depending on the timing of the interim analysis, and at the discretion of the DSMB, the interim analysis may take the place of one of the biannual conference calls. Conference calls will be scheduled by Dr. Casey or his designee in collaboration with the DSMB members.

The DSMB will perform an interim analysis to review 30-day data after the enrollment of 553 subjects; enrollment will continue during the DSMB review. The primary focus of this review will be efficacy and safety. The DSMB will be supplied with raw data for the outcomes required for these analyses (as described below). Dr. Casey or his designee will also provide the DSMB committee with additional summary statistics on baseline characteristics, by group. The DSMB may request any additional data, as needed. The DSMB will also be able to request unblinding for any reason. All DSMB members must be present during this session and all must vote at the end of the session on the continuation of the trial. All serious adverse events thought to be related to study procedures will be reported to the DSMB on an ongoing basis; the study will be stopped for a safety evaluation by the DSMB if they have any concerns based on either the interim data analysis or review of serious adverse events.

The agenda for DSMB meetings and calls will be drafted by Dr. Casey or his designee. Dr. Casey or his designee will finalize the agenda after consultation with the DSMB Chair. The agenda and meeting materials will be distributed prior to each call.

Before each teleconference Dr. Casey or his designee will ask all DSMB members to state whether they have developed any new conflicts of interest since the last call. If a new conflict is reported, the Chair will determine if the conflict limits the ability of the DSMB member to participate in the discussion. If the Chair reports a new conflict, the BOUGIE Trial Steering Committee will determine if the conflict limits the ability of the Chair to participate in the discussion.

It is expected that all DSMB members will attend every call and respond to electronic mail communications promptly. A quorum of this DSMB will be all three members.

6. Discussion of Confidential Material

DSMB meetings and calls will be organized into open, closed, and executive sessions.

- During the **open sessions**, Dr. Casey or his designee will present information to the DSMB on behalf of the study investigators with time for discussion.

- During the **closed sessions**, the DSMB will discuss confidential and/or unblinded data from the study. Steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the closed session.

- The DSMB may elect to hold an **executive session** in which only the DSMB are present in order to discuss study issues independently. Voting on recommendations will follow Roberts' Rules of Order (**Robert's Rules of Order Newly Revised (10th Edition) RONR** by Henry M. Robert III, William J. Evans (Editor), Daniel H. Honemann (Editor), Thomas J. Balch (Editor), Sarah Corbin Robert, Henry M. Robert III, General Henry M. Robert). If the executive session occurs on a conference call, steps will be taken to ensure that only the appropriate participants are on the call, and to invite others to re-join the call only at the conclusion of the executive session.

At the conclusion of the closed and executive sessions, the participants will be re-convened so that the DSMB Chair can provide a summary of the DSMB's recommendations. This provides an opportunity for study investigators to ask questions to clarify the recommendations. The meeting is then adjourned.

7. Reports of DSMB Deliberations

- Initial summary: Dr. Casey is responsible for ensuring the accuracy and transmission of a brief summary of the DSMB's discussion and recommendations. The BOUGIE Trial Steering committee will review this summary and approve or disapprove the recommendation(s), or request additional information. The recommendations will then be sent to the clinical investigators.

- Action plan: If the DSMB's recommendations require significant changes or follow-up, the BOUGIE Trial Steering Committee will prepare an action plan outlining the steps required to implement the recommendations.

- Formal minutes: As the Executive Secretary, Dr. Casey is responsible for the accuracy and transmission of the formal DSMB minutes within 30 days of the meeting or call. These minutes are prepared accordingly to summarize the key points of the discussion and debate, requests for additional information, response of the investigators to previous recommendations, and the recommendations from the current meeting. The DSMB Chair may sign the minutes or indicate approval electronically via email.

8. Reports to the DSMB

For each meeting, Dr. Casey will prepare summary reports and tables to facilitate the oversight role of the DSMB. The DSMB will discuss at the first meeting what data they wish to review and how it should be presented. Data requests can be modified at subsequent meetings.

9. Statistical Monitoring Guidelines

At the first meeting, review of the protocol will include review of the clinical endpoints and safety monitoring plans. The DSMB should discuss the adequacy of that plan. The DSMB should discuss the statistical monitoring procedures they propose to follow to guide their recommendations about termination or continuation of the trial.

10. Stopping Rules

The DSMB will conduct a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, at least 30 days after enrollment of 553 patients. Enrollment will continue during this period. One week prior to the meeting for the interim analysis, Dr. Casey or his designee will provide the DSMB with the following blinded data in raw format:

1. Study group assignment of each patient (A vs B)

2. The primary outcome (successful intubation on the first attempt)
3. Esophageal intubation (safety outcome)
4. Airway trauma

For this interim analysis, the DSMB will be asked to perform an efficacy analysis and a safety analysis as described below. At the completion of these analyses, the DSMB will notify the BOUGIE Trial Steering Committee of their recommendation for the trial to be stopped or continued to completion. If the trial is not stopped, the DSMB will not make the steering committee members or any of the investigators aware of the results of any of their analyses. At the interim analysis or at any other time where the DSMB is deciding if the trial should be stopped or continued, all members of the DSMB must agree that the trial should be stopped or continued.

11. Efficacy and Safety Stopping Rule

The **stopping boundary for efficacy** will be met if the P-value using a chi-square test for the difference between groups in the primary outcome of successful intubation on the first attempt is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The **stopping boundary for safety** will be met if the P-value using a chi-square test for the difference between groups in the either of the safety outcomes, esophageal intubation, or airway trauma, is 0.025 or less.

If requested by the DSMB, the DSMB will be provided with blinded data on all outcomes collected by the trial to use in their review of trial safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, unblind the study assignments, or request modifications of the study protocol as required to protect patient safety.

Appendix A: DSMB members and titles

Michael Hooper, MD, MSc (DSMB Chair)

Associate Dean for Clinical Education, Associate Professor

Allergy, Pulmonary and Critical Care Medicine

Eastern Virginia Medical School

Expertise: Critical care, clinical trials, data and safety monitoring

Matthew Lammi, MD, MSc

Associate Professor of Medicine

Section of Pulmonary/Critical Care and Allergy/Immunology

LSU School of Medicine New Orleans

Expertise: Critical care, clinical trials, biostatistics

Alan B. Storrow, MD

Associate Professor

Department of Emergency Medicine

Associate Director of Research

Center for Emergency Care Research and Innovation (CERI)

Expertise: Emergency medicine, clinical research, quality improvement, patient safety

Antonio Hernandez, MD

Associate Professor

Department of Anesthesiology

Vanderbilt University Medical Center

Expertise: Critical care, intubation, clinical research

7. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication, will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities or other private healthcare information (PHI), is collected. All subjects are assigned a unique study ID number for tracking. 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.

8. 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 and approval 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.