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Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

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Complete List of Authors:	Russell, Derek ; University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy, & Critical Care Medicine; Department of Veterans Affairs, Veterans Integrated Service Network 7 Casey, Jonathan; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Gibbs, Kevin ; Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease Dargin, James; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine Vonderhaar, Derek ; Ochsner Health System, Department of Pulmonary and Critical Care Medicine Joffe, AM; University of Washington, Department of Anesthesiology and Pain Medicine Ghamande, Shekhar; Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine Khan, Akram; Oregon Health & Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine Dutta, Simanta; Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease Landsperger, Janna; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Robison, Sarah; University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy, & Critical Care Medicine Bentov, Itay; University of Washington, Department of Anesthesiology and Pain Medicine Wozniak, Joanne; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine Stempek, Susan; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine White, Heath; Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine Krol, Olivia; Oregon Health & Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine Prekker, Matthew; Hennepin County Medical Center, Department of

	Emergency Medicine; Hennepin County Medical Center, Department of Medicine, Division of Pulmonary/Critical Care Medicine Driver, Brian; Hennepin County Medical Center, Department of Emergency Medicine Brewer, Joseph; University of Mississippi Medical Center, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine Wang, Li; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Lindsell, Christopher; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Self, Wesley; Vanderbilt University School of Medicine, Department of Emergency Medicine Rice, Todd; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Semler, Matthew; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Janz, David; Louisiana State University School of Medicine in New Orleans, Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology
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Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

Derek W. Russell*, MD[1]; Jonathan D. Casey*, MD, MSc[2]; Kevin W. Gibbs, MD[3]; James M. Dargin, MD[4]; Derek J. Vonderhaar MD[5]; Aaron M. Joffe, DO[6]; Shekhar Ghamande, MD[7]; Akram Khan, MD[8]; Simanta Dutta, MD[3]; Janna S. Landsperger, MS, PA-C[2]; Sarah W. Robison, MD[1]; Itay Bentov, MD, PhD[6]; Joanne M. Wozniak, PA-C[4]; Susan Stempek, PA-C[4], Heath D. White, DO, MS[7]; Olivia F. Krol, BS[8]; Matthew E. Prekker, MD[10,11]; Brian E. Driver, MD[10]; Joseph M. Brewer, DO[12]; Li Wang, MS[2]; Christopher J. Lindsell PhD[2]; Wesley H. Self, MD, MPH[14]; Todd W. Rice, MD, MSc[2]; Matthew W. Semler**, MD, MSc[2]; David R. Janz**, MD, MSc[12] for the PREPARE II Investigators# and the Pragmatic Critical Care Research Group.

Affiliations:
[1]University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; Birmingham Veteran's Affairs Medical Center, Pulmonary Section; [2] Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine; [3]Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease; [4]Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine; [5]Ochsner Health System New Orleans, Department of Pulmonary and Critical Care Medicine; [6]University of Washington, Department of Anesthesiology and Pain Medicine; [7]Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine; [8]Oregon Health and Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine; [9]University of Washington School of Medicine, Department of Medicine, Division of Pulmonary/Critical Care; [10]Hennepin County Medical Center, Department of Emergency Medicine; [11]Hennepin County Medical Center, Department of Medicine, Division of Pulmonary/Critical Care Medicine;[12]University of Mississippi Medical Center, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine; [13]Louisiana State University School of Medicine New Orleans, Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology; [14]Vanderbilt University School of Medicine, Department of Emergency Medicine.

*Authors contributed equally
**Authors contributed equally
#See below for a full list of the PREPARE II Investigators

Corresponding Author:
Derek W. Russell, MD

Email:
dwrussell@uabmc.edu

Address:
Lyons Harrison Research Building Room 321
701 19th St. S
Birmingham, AL 35294

Telephone:
205-996-1496

Fax:
205-996-4699

Author contributions: All study authors approved the final version of this manuscript. Study concept and design: D.W.R., J.D.C., M.W.S., D.R.J., C.J.L., L.W., W.H.S., and T.W.R.; Acquisition of data: D.W.R, J.D.C, K.W.G., J.D., D.J.V., A.M.J., S.G., A.K., S.D., J.S.L., S.R., I.B., J.W., H.W., O.F.K., M.E.P., B.E.D., J.M.B., K.M.D, J.W., K.G., K.W.G., S.G., A.K., W.H.S., S.S., K.D., C.B., A.M.W., A.C.A., T.L., S.N., M.K.J., T.W.R., M.W.S. and D.R.J.; Drafting of the manuscript: D.W.R., J.D.C., D.R.J., M.W.S.; Critical revision of the manuscript for important intellectual content: D.W.R, J.D.C, K.W.G., J.D., D.J.V., A.M.J., S.G., A.K., S.D., J.S.L., S.R., I.B., J.W., H.W., O.F.K., M.E.P., B.E.D., J.M.B., K.M.D, J.W., K.G., K.W.G., S.G., A.K., W.H.S., S.S., K.D., C.B., A.M.W., A.C.A., T.L., S.N., M.K.J., C.J.L., L.W., T.W.R., M.W.S. and D.R.J.; Study supervision: D.R.J. and M.W.S.

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Abstract:

Introduction: Cardiovascular collapse is a common complication during tracheal intubation of critically ill adults. Whether administration of an intravenous fluid bolus prevents cardiovascular collapse during tracheal intubation remains uncertain. A prior randomized trial found fluid bolus administration to be ineffective overall but suggested potential benefit for patients receiving positive pressure ventilation during tracheal intubation.

Methods and Analysis:

The PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) trial is a prospective, multi-center, non-blinded randomized trial being conducted in 13 academic intensive care units in the United States. The trial will randomize 1,065 critically ill adults undergoing tracheal intubation with planned use of positive pressure ventilation (non-invasive ventilation or bag-mask ventilation) between induction and laryngoscopy to receive 500 mL of intravenous crystalloid or no intravenous fluid bolus. The primary outcome is cardiovascular collapse, defined as any of: SBP <65 mm Hg, new or increased vasopressor administration between induction and 2 minutes after intubation, or cardiac arrest or death between induction and 1 hour after intubation. The primary analysis will be an unadjusted, intention-to-treat comparison of the primary outcome between patients randomized to fluid bolus administration and patients randomized to no fluid bolus administration using a Chi-square test. The sole secondary outcome is 28-day in-

hospital mortality. Enrolment began on February 1, 2019 and is expected to conclude in June, 2020.

Ethics and Dissemination:

The trial was approved by either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site (details in **Supplemental file 1, Item 2**). 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 (NCT03787732) on December 25, 2018, prior to the enrolment of the first patient.

Strengths and Limitations:

- This ongoing pragmatic trial will examine the effect of a 500 mL intravenous fluid bolus on the incidence of cardiovascular collapse among critically ill adults undergoing tracheal intubation with positive-pressure ventilation.
- Broad eligibility criteria and enrolment at multiple centers will increase the external validity of the findings.
- Blinding is impractical due to the nature of this study intervention.
- The trial is not designed to examine the effects of fluid composition or volume of fluid administered.

Introduction:

Tracheal intubation is common in the care of critically ill patients but is associated with a high incidence of complications[1-3]. Cardiovascular collapse is a composite of life-threatening haemodynamic complications of tracheal intubation comprised of post-intubation hypotension[4-6], administration of vasopressors to treat hypotension, cardiac arrest, and death. Cardiovascular collapse occurs in 20-30% of critically ill patients undergoing tracheal intubation[7 8], and is associated with increased in-hospital mortality[5 6 9].

Some airway management experts recommend the intravenous administration of a fluid bolus beginning prior to induction (i.e., the administration of procedural drugs such as anaesthetics) to prevent cardiovascular collapse during tracheal intubation[4 10]. A fluid bolus could address the haemodynamic perturbations induced by induction and tracheal intubation, which include vasodilatory effects of induction medications, increased venous capacitance due to decreased circulating catecholamines, and decreased venous return secondary to positive pressure applied to the thoracic cavity. However, the only reported trial to examine administration of a pre-intubation fluid bolus, the PrePARE (Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation) trial, reported that a pre-intubation fluid bolus had no effect on the overall rate of cardiovascular collapse[8]. The receipt of positive pressure ventilation, however, appeared to modify the effect of a fluid bolus administration on cardiovascular collapse in the PrePARE trial. Patients receiving positive pressure ventilation appeared to have a lower rate cardiovascular collapse in the fluid bolus group compared to the no fluid bolus group, both among patients

receiving non-invasive ventilation for pre-oxygenation (RR 0.51; 95% confidence interval [CI], 0.24-1.09; P value for interaction = 0.032) and among patients receiving bag-mask ventilation between induction and laryngoscopy (RR 0.61; 95% CI, 0.33-1.13; P value for interaction = 0.008)[8].

Provision of positive pressure ventilation with a bag-mask device between induction and laryngoscopy has been shown to decrease the incidence of severe hypoxaemia during tracheal intubation of intensive care unit (ICU) patients (relative risk, 0.48; 95%, CI, 0.30 to 0.77)[11]. These results, and others examining use of non-invasive ventilation for pre-oxygenation during ICU intubations[12], suggest that positive pressure ventilation should be provided during tracheal intubation for most critically ill patients[10]. This increases the importance of investigating the finding from the PrePARE trial that a pre-induction fluid bolus might prevent cardiovascular collapse among patients receiving positive pressure ventilation. We designed the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) trial to examine the hypothesis that administration of a fluid bolus beginning prior to induction will decrease the incidence of cardiovascular collapse among critically ill adults undergoing tracheal intubation with positive pressure ventilation between induction and laryngoscopy.

Methods and Analysis:

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

Table 1	STUDY PERIOD							
	Enrollment	Allocation	On-Study					On-Study
TIMEPOINT	Decision to perform TI	Between decision to intubate and Induction	Sedative & NMB	TI	2 minutes post-TI	1 hour post TI	24 hours post-TI	Discharge or 28 days after enrollment
ENROLMENT:	X							
Eligibility screen	X							
Allocation		X						
INTERVENTIONS:								
Fluid Bolus Initiation		X						
Screening for contraindications	X	X						
No New Fluid Bolus		X						
Screening for contraindications	X	X						
ASSESSMENTS:								
Baseline Variables	X	X						
Peri-procedural variables		X	X	X	X			
Clinical Outcomes						X	X	X

Baseline variables obtained from medical record include: demographic characteristics, APACHEII score, and presence of sepsis/septic shock. Peri-procedural data collected by independent, trained observer includes the following: whether fluids were infusing prior to enrollment, receipt of the study intervention, the volume of study crystalloid infused (induction and 2 minutes after procedure), use of prophylactic vasopressor (or prophylactically increased vasopressor dose), addition of new vasopressor (or increased vasopressor dose), and systolic blood pressure (at baseline and nadir from induction to 2 minutes after procedure). Peri-procedural data collected by operator includes: sedation drugs used (and doses), oxygenation/ventilation modality between induction and laryngoscopy, and procedural complications. Clinical outcomes include: vital status (overall in-hospital death, cardiac arrest death within 1 hour of TI), number of ventilator-free days to 28 days, and number of ICU-free days to 28 days. TI: tracheal intubation. NMB: neuromuscular blockade.

Patient and Public Involvement

Materials used to communicate about the study with patients and family members were developed with input from the Vanderbilt Community Advisory Council.

Study authors will disseminate the results of this study online and via social media in forms suitable for public understanding.

Study Design

The PREPARE II trial is a pragmatic, multi-center, un-blinded, parallel group, randomized trial. Among critically ill adults undergoing tracheal intubation undergoing positive pressure ventilation between induction and laryngoscopy, PREPARE II compares incidence of cardiovascular collapse between patients administered intravenous administration of a 500 mL fluid bolus and those receiving no fluid bolus administration. The trial protocol was approved with waiver of informed consent by either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site. The trial was registered prior to initiation of enrolment (ClinicalTrials.gov identifier: NCT03787732). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial.

Study Sites

PREPARE II is being conducted in 13 intensive care units at academic medical centers across the United States. Site characteristics are listed in **Supplementary file 1, Item 2**.

Population

The trial includes adults (age ≥ 18 years) located in a participating ICU for whom the treating clinicians have determined that tracheal intubation is required and for whom

the planned procedural approach includes an operator who routinely performs tracheal intubation in the participating unit, administration of sedation (with or without neuromuscular blockade), and positive-pressure ventilation between induction and laryngoscopy. The trial excludes pregnant women, prisoners, and patients for whom the treating clinicians feel that the urgency of the intubation precludes safe performance of study procedures or feel that fluid bolus administration is either required or contraindicated.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to intravenous fluid bolus administration or no fluid bolus administration in permuted blocks of two, four, or six, stratified according to study site. Study-group assignments (see **Supplementary file 1, Item 3; Figure S1**) are placed in sequentially numbered opaque envelopes and remain concealed until after enrolment. After enrolment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Fluid Bolus Group

For patients who are assigned to the fluid bolus group, intravenous infusion of 500 mL of a crystalloid solution of the operator's choosing is initiated after randomization and prior to induction. The fluid bolus is infused from above the level of the intravenous or intra-osseous access and allowed to infuse by gravity, manual pressure, or bag pressure. The fluid bolus is discontinued after 500 mL have infused.

For patients assigned to the fluids bolus group who are already receiving a fluid infusion, administration of 500mL of fluids between randomization and induction is achieved with either an additional bolus or increasing the rate of the existing infusion.

No Fluid Bolus Group

For patients who are assigned to the no fluid bolus group, intravenous fluid administration is not initiated between randomization and induction. Intravenous fluid infusions initiated prior to randomization are not altered.

Co-Interventions

Regardless of study group assignment, treating clinicians determine the timing of induction and tracheal intubation. Treating clinicians may stop infusion of a fluid bolus, increase or decrease the rate of infusion, or add a new fluid bolus at any time if felt to be required for the optimal care of the patient. Study group assignment determines only the initiation of intravenous fluid bolus administered between randomization and induction. **Figure 1** depicts the timeline of study procedures in the context of the tracheal intubation procedure.

Because the study enrols only patients for whom treating clinicians plan to administer positive-pressure ventilation between induction and laryngoscopy, most patients receive either non-invasive ventilation or bag-mask ventilation between induction and laryngoscopy. Instances in which positive-pressure ventilation between induction and laryngoscopy is not administered are recorded, along with the reason that

positive-pressure ventilation was not administered (e.g., emesis arising between randomization and induction).

Treating clinicians determine the decision to intubate, modality and timing of pre-oxygenation, choice, dose, and timing of medications for induction and neuromuscular blockade, decision to administer vasopressors before or after induction, choice of laryngoscope, use of cricoid pressure, method of positive pressure ventilation (non-invasive ventilation or bag-mask ventilation) between induction and laryngoscopy, decision to administer intravenous fluid for the treatment of hypotension, and use of additional airway management equipment and personnel. Data on these co-interventions is prospectively collected.

In some participating units, patients may be co-enrolled in a randomized trial comparing use of bougie versus use of an endotracheal tube with stylet on the first attempt at tracheal intubation (ClinicalTrials.gov, NCT03928925). An interaction between the interventions evaluated in these trials in not anticipated and the results will be reported separately.

Data Collection

Data collection for this study is described in detail in **Supplementary file 1, Item 4** and **Table 1** provides further detail on data collection procedures.

Primary Outcome

The primary outcome is cardiovascular collapse, defined as the occurrence of one or more of the following: Systolic blood pressure (SBP) < 65 mmHg between

induction and 2 minutes after intubation; new or increased vasopressor administration between induction and 2 minutes after intubation; cardiac arrest between induction and 1 hour after intubation; or death between induction and 1 hour after intubation.

Cardiovascular collapse is a commonly used endpoint in airway management research[4 8]. Cardiovascular collapse is considered a "reasonably likely surrogate endpoint" for short-term mortality because a strong mechanistic rationale links severe hypotension and cardiac arrest to short-term mortality and interventions that prevent cardiovascular collapse might reasonably be expected to prevent short-term mortality[17]. Cardiovascular collapse was the primary outcome of the recently completed PrePARE trial[8], on which the design of the PREPARE II trial was based. In the PrePARE trial, the absolute risk of in-hospital mortality was 16.7% (95% CI 3.4% to 30.0%) higher among patients who experienced cardiovascular collapse during intubation compared with patients who did not[8].

Secondary Outcome

The sole secondary outcome is 28-day all-cause in-hospital mortality (**Supplementary file 1, Item 5**). Short-term mortality is a commonly used patient-centered clinical endpoint for randomized trials in intensive care medicine and may be mechanistically associated with the primary outcome of cardiovascular collapse.

Exploratory Clinical Outcomes

- Each individual component of the composite primary endpoint:
  - SBP < 65 mmHg between induction and 2 minutes after intubation

- new or increased vasopressor administration between induction and 2 minutes after intubation
- cardiac arrest between induction and 1 hour after intubation
- death between induction and 1 hour after intubation.

- Lowest SBP between induction and 2 minutes after intubation
- Change in SBP from induction to lowest SBP between induction and 2 minutes after intubation
- Ventilator-free days to 28 days (defined in **Supplementary file 1, Item 6**)
- ICU-free days to 28 days (defined in **Supplementary file 1, Item 7**)

Exploratory Safety Outcomes

- Lowest arterial oxygen saturation between induction and 2 minutes after intubation
- Incidence of hypoxaemia (oxygen saturation < 90%) between induction and 2 minutes after intubation
- Incidence of severe hypoxaemia (oxygen saturation < 80%) between induction and 2 minutes after intubation
- Oxygen saturation at 24 hours after intubation
- Fraction of inspired oxygen at 24 hours after intubation
- Positive end expiratory pressure at 24 hours after intubation
- SBP at 24 hours after intubation

Exploratory Process Measures

- Initiation of an intravenous fluid bolus between induction and 2 minutes after intubation
- Time from induction to successful intubation
- Incidence of successful intubation on the first laryngoscopy attempt
- Number of laryngoscopy attempts
- Cormack-Lehane grade of glottic view on first attempt
- Operator-assessed difficulty of intubation
- Need for additional airway equipment or a second operator

Initial Sample Size Estimation

In a prior randomized trial comparing fluid bolus administration beginning prior to induction versus no fluid bolus administration in the same setting as the current trial, the incidence of cardiovascular collapse was 19.6% in the fluid bolus group and 18.3% in the no fluid bolus group overall. However, among the subgroup of patients assigned to receive positive pressure ventilation with a bag-mask device between induction and laryngoscopy, the incidence of cardiovascular collapse was 16.0% in the fluid bolus group and 26.2% in the no fluid bolus group (10% absolute risk difference and 40% relative risk difference). Assuming more conservative rates of cardiovascular collapse of 16.25% in the fluid bolus group and 25.0% in the no fluid bolus group (8.75% absolute risk difference and 35% relative risk difference), we calculated that enrolling 714 patients would provide 80 percent statistical power at a two-sided alpha level of 0.05. Anticipating less than 5% missing data for the primary outcome, the initial planned enrolment for the trial was 750 patients. The study protocol included a pre-specified

sample size re-estimation following the single interim analysis (see *Sample Size Re-estimation*)

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of experts in clinical trials, critical care medicine, anaesthesia, and emergency medicine is overseeing the design and conduct of the trial. The DSMB conducted a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrolment of 375 patients, on November 12, 2019. Stopping criteria were pre-specified in the study protocol, suggesting termination of the trial at the interim if the P value for the difference between groups in the incidence of the primary outcome (cardiovascular collapse) or secondary outcome (28-day in-hospital mortality) were 0.001 or less using a chi-square test. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) allows the final analysis at the end of the trial to be performed using an unchanged level of significance.

The DSMB also formally evaluated the trial for safety and examined the highest fraction of inspired oxygen, highest positive end expiratory pressure, and lowest arterial oxygen saturation at 24 hours after intubation in each study group. The prespecified early stopping criteria for physiologic outcomes were as follows: if the *P* value for the difference between study groups in any of these three physiologic variables were 0.001 or less using a Mann-Whitney rank-sum test and concordant in direction with the point-estimate for mortality.

At the interim analysis, finding that no stopping criteria had been met and no safety concerns were observed, the DSMB recommended continuing the trial.

Sample Size Re-Estimation

The study protocol specified that, after completion of the interim analysis and the recommendation to continue enrolment, "the DSMB will evaluate the rate of the primary outcome in the no fluid bolus group. If the incidence of the primary outcome in the no fluid bolus group differs from the original estimate of 25.0%, the DSMB may ask that the investigators perform a sample size re-estimation to maintain adequate statistical power to detect the planned relative risk difference in the primary outcome between groups."

After completion of the interim analysis and the recommendation to continue enrolment, the DSMB examined the number of patients that would need to be enrolled in order to maintain 80% statistical power to detect the planned relative risk reduction of 35% in the primary outcome. Based on this information, the DSMB recommended increasing the total sample size from 750 to 1,065 patients. The investigators accepted the DSMB's recommendation, revising the planned sample size for the final trial to 1,065 patients. During the sample size re-estimation, both the study investigators and the DSMB remained blind to all outcomes by study group. No further interim analyses are planned.

Statistical Analysis Principles

R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses. Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions.

Between-group comparisons will be made with the Mann-Whitney rank-sum test for continuous variables, and the chi-square test for categorical variables

Primary Analysis of the Primary Outcome

The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group with regard to the primary outcome of cardiovascular collapse. Between group differences will be tested using an unadjusted chi-square test. A P value < 0.05 will be used to indicate statistical significance for the primary analysis.

Secondary Analyses of the Primary Outcome

To account for potential confounders, we will develop a logistic regression model with cardiovascular collapse (primary outcome) as the dependent variable and independent variables to include study group (fluid bolus group vs no fluid bolus group) and relevant confounders (age, APACHE II score at enrolment, presence of sepsis or septic shock, vasopressor receipt in the hour prior to enrolment, and receipt of intravenous fluid infusion initiated prior to enrolment). We will also develop a logistic regression model accounting for the above variables plus any baseline characteristics that appear on visual review to be potentially imbalanced between the study groups.

Because patients within a specific ICU may be more similar to other patients within the same ICU than to patients in other ICUs, we will fit a generalized linear mixed-effects model with the outcome of cardiovascular collapse, including group assignment as a fixed effect and study unit (stratification variable) as a random effect.

We will repeat the primarily analysis using alternative definitions of cardiovascular collapse, including: (1) using an SBP < 90 mm Hg rather than an SBP <65 mm Hg, (2) using 28-day in-hospital mortality rather than death within 1 hour, and (3) using days from enrolment to in-hospital death (defined in **Supplementary file 1, Item 8**) rather than death within 1 hour.

Interpreting composite endpoints can be challenging when the components have different levels of clinical importance. We will repeat the primary analysis of the primary outcome using a global rank scale. Use of a hierarchical global rank score places greater weight on the objective, patient-centered clinical outcomes (death, cardiac arrest) than on the immediate physiologic outcomes (hypotension and vasopressors). The global rank endpoint will be constructed by comparing each patient with every other patient in the study and assigning a score for each pairwise comparison based on whom fared better. To make the pairwise comparison, we will consider a priority order of endpoints: (1) death within one hour of intubation; (2) cardiac arrest within one hour of intubation; (3) SBP < 65 mmHg between induction and two minutes after intubation; and (4) new or increased vasopressor administration between induction and two minutes after intubation. The scores will be summarized and compared between study groups (fluid bolus group vs no fluid bolus group) using an unadjusted Mann-Whitney U test.

Given the findings of the PrePARE trial subgroup analysis (i.e., that the effect of fluid bolus administration on cardiovascular collapse may be related to the receipt of positive pressure ventilation during intubation)[8], we will repeat the primary analysis excluding patients who did not receive positive pressure during intubation. Because many critical care patients are already receiving intravenous fluid for other indications

when the decision is made to intubate and this may modify the effect of a new fluid bolus, we will repeat the primary analysis excluding patients who were already receiving intravenous fluid at the time of enrolment.

Analysis of Effect Modification for the Primary Outcome

We will examine whether pre-specified baseline variables modify the effect of treatment group on the primary outcome using formal tests of statistical interaction in a logistic regression model. Independent variables will include study group assignment, the potential effect modifier of interest, and the interaction between the two (e.g., study group * presence of sepsis or septic shock). Significance will be determined by the P value for the interaction term, with values less than 0.10 considered to suggest of a potential interaction and values less than 0.05 considered to confirm an interaction. Continuous variables will be analyzed using restricted cubic splines and preferentially displayed as continuous variables with 3-5 knots using a locally weighted regression or partial effects plots. We will use a forest plot to display the effect of covariates. If required for data presentation, continuous variables will be dichotomized for inclusion in a forest plot. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. APACHE II score at enrolment (continuous variable);
2. Presence of sepsis or septic shock at time of enrolment (yes/no);
3. Receipt of vasopressors in the 1 hour prior to enrolment (yes/no);
4. Predicted probability of cardiovascular collapse as calculated by a pre-specified multivariable model (continuous variable);

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

1. Receipt of positive pressure ventilation for pre-oxygenation (via either non-invasive mechanical ventilation or bag-mask ventilation) (yes/no);
2. Choice of sedative medication (etomidate, ketamine, propofol, other);
3. New or increased vasopressor administration prior to or with induction (yes/no);
4. SBP at induction (continuous variable in mm Hg)
5. Oxygen saturation at induction (continuous variable in %)

Finally, to examine our assumption that no interaction will exist between the interventions evaluated in the PREPARE II and BOUGIE trials, among patients co-enrolled to these trials, we will examine whether BOUGIE group assignment modifies the primary outcome. If, contrary to our expectation, an interaction is confirmed (based on criteria listed above for interaction testing), the BOUGIE group assignment will be added to the adjustment model for the primary outcome of cardiovascular collapse.

Analysis of the Secondary Outcome

The sole secondary outcome of 28-day in-hospital mortality will be compared between patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group using an unadjusted chi-squared test.

Analyses of Exploratory Outcomes

All pre-specified exploratory outcomes will be compared between patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test. In a sensitivity analysis using data only from each patient's first tracheal intubation in the PREPARE II dataset, we will compare the fluid group to the no fluid bolus group with regard to in-hospital mortality, ventilator-free days, and ICU-free days.

Handling of Missing Data

Although we have allowed for up to 5% missingness in our power calculation, we do not anticipate that data for the primary outcome of cardiovascular collapse will be missing for any patients. Missing data will not be imputed for the primary or secondary outcome. In adjusted analyses, missing data for covariates may be imputed using a multiple imputation technique.

Corrections for Multiple Testing

We pre-specify a single primary analysis of a single primary outcome, and a single secondary analysis with one outcome. All additional analyses are deemed hypothesis-generating, and no corrections for multiple comparisons will be performed.

Trial Status

The Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II) trial is a pragmatic, prospective, multi-center, non-blinded randomized clinical trial comparing fluid bolus to no fluid bolus during tracheal intubation of critically ill adults. Patient enrolment began on February 1, 2019 and is expected to be completed in June, 2020.

Ethics and Dissemination

Informed Consent

In current clinical practice, initiating an intravenous fluid bolus beginning prior to tracheal intubation and not administering an intravenous fluid bolus beginning prior to tracheal intubation are both common management approaches, with significant variation between providers[18]. All patients eligible for this trial would have either received or not received an intravenous fluid bolus for tracheal intubation as a part of their clinical care, regardless of participation in the trial. To be eligible for the trial, patients' treating clinicians must feel that initiation of a new fluid bolus for tracheal intubation is neither required nor contraindicated for the patient's optimal care. The protocol states that a fluid bolus can be given or withheld for patient safety at any time in the study, regardless of group assignment. For these reasons, the trial is felt to pose minimal incremental risk compared with the clinical care patients would receive outside of the trial.

Tracheal intubation of critically ill adults is commonly an urgent or emergent procedure for which obtaining informed consent for the clinical procedure or informed consent for research is impracticable.

This information was provided to either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site (see **Supplemental file 1, Item 2**), and the trial was approved with a waiver of informed consent.

Information for Patients and Families

Information regarding the study is made available to patients and families through three mechanisms: (1) a patient and family notification sheet provided to each patient and family following enrolment informing the patient of his or her enrolment and describing the study, (2) 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, (3) a patient and family information sheet containing general study information and contact information for the research team provided to each patient and family at the time of admission to the study unit. The mechanism(s) of providing information to patients and families used by each study site was determined by local site investigators and local IRBs and is described in **Supplemental file 1, Item 2**; **Table S1**.

Protocol Changes

Any changes to the trial protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See **Supplemental file 1, Item 9** for more details.

Data Handling

For details of privacy and data handling, see **Supplemental file 1, Item 10**.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at scientific conferences.

Conclusion

We describe, before the conclusion of enrolment or data un-blinding, our trial design and approach to analyzing the data from a large, pragmatic, multicenter trial comparing fluid bolus administration versus no fluid bolus administration with regard to rate of cardiovascular collapse among critically ill adults undergoing tracheal intubation with positive pressure ventilation. This pre-specified framework will enhance the rigor and reproducibility of the final report and will allow readers to better judge the impact of our findings.

Figure Legends

Figure 1: Timeline of tracheal intubation (TI), enrolment, study interventions, and primary/secondary outcome eligibility in an enrolled patient.

List of PREPARE II Investigators

Wake Forest School of Medicine— Kevin W. Gibbs, MD***; Simanta Dutta, MD***; Stephen P Peters MD, PhD*; Muhammad Ali, MBBS*; Rita N. Bakhru, MD, MS*; Scott Bauer, ANP-BC*; Christina R. Bellinger, MD*; Amanda M. Brown, PA-C*; Blair Brown, MD*; Jerri Brown, ADN, RN*; Caitlin Bumgarner, ACGNP*; Wendy Butcher, RN, BSN*; Megan Caudle, ACGNP*; Arjun B. Chatterjee, MD*; David J. Chodos, MD*; Gerardo Corcino, RN, BSN*; Nathan S. Cutler, MD*; Travis L. Dotson, MD*; Daniel C. Files, MD*; Jonathan L Forbes, DO*; John P. Gaillard, MD*; Katherine A. Gershner, DO*; Shannon Ginty, PA-C*; Kiadrick R. Hood, RN, MSN, CMSRN*; April Hazelwood, ADN, RN*; Katherine Hendricks, FNP*; Kelly Jacobus, PA-C*; Jonathan T. Jaffe, MD*; Stacy Kay, ACGNP*; Chad A. Kloefkorn, MD*; Jennifer Krall, MD*; Margo T. Lannan, MD*; Cornelia Lane, ACGNP*; Cynthia Lanning, BSN, RN*; Jessica Lyons, PA-C*; William I. Mariencheck Jr., MD*; Chad R. Marion, DO, PhD*; Matthew A. Maslonka, MD*; Sara McClintock, ACGNP*; Nathaniel M. Meier, MD*; Matthew C. Miles, MD, MEd*; Peter J. Miller, MD*; Sophia Mitchell, PA-C*; Wendy C. Moore, MD*; Katherine Moss, PA-C*; Andrew M. Namen, MD*; Dustin L. Norton, MD*; Stella B. Ogake, MD*; Jill A. Ohar, MD*; Victor E. Ortega, MD, PhD*; Jessica A. Palakshappa, MD, MS*; Rodolfo M. Pascual, MD*; Sandi Pascual, ANP-BC*; Aaron Pickens, MD*; Adam R Schertz, MD*; Matt Strong, ADN, RN*; Alexander O. Sy, MD*; Braghadheeswar Thyagarajan MD*; Amy Townsend, ACGNP*; Russell Worthen, FNP-BC*; Michael Wlodarski, PA-C*; Charles Yarbrough, ADN, RN*; Caroline York, PA-C*; Vanderbilt University Medical Center— Jonathan D. Casey, MD, MSc***; Janna S. Landsperger, MSN***; Li Wang, MS***; Christopher J. Lindsell PhD***; Todd W. Rice, MD, MSc***; Matthew W. Semler, MD, MSc***; Wesley H. Self, MD, MPH**; Bradley Lloyd, RRT-ACCS*; Lahey Hospital and Medical Center— James Dargin, MD***; Joanne Wozniak, PA-C***; Susan Stempek, PA-C***; Christopher Adler, PA-C*; Ahmed Agameya, MD*; Michael Colancecco, DO*; Daniel Fitelson, MD*; Joshua Giaccotto, MD*; Gena Han, DO*; Louise Kane, MD*; Ezra Miller, MD*; Timothy Noland, PA-C*; Jaqueline Price, PA-C*; Joseph Plourde, PA-C*; Emily Adams, PA-C*; Fraser Mackay, MD*; Laura Mahoney, PA-C*; Avignat Patel, MD*; Michael Plourde, PA-C*; Zena Saadeh, PA-C*; Sara Shadchehr, DO*; Sandeep Somalaraju, MD*; Eleanor Summerhill, MD*; Ryan Webster, MD*; Jordan Winnicki, PA-C*; Ekaterina Yavarovich, DO*; University of Alabama at Birmingham Medical Center— Derek W. Russell, MD***; Sarah Robison, MD***; Sheetal Gandotra, MD**; Swati Gulati, MBBS, 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, AND*; 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*; David B. Page, MD*; 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*; Micah R. Whitson, MD*; Ochsner Health System New Orleans— Derek J. Vonderhaar, MD***; Kevin M. Dischert MD**; University of Washington Harborview Medical Center— Aaron M. Joffe, DO***; Itay Bentov, MD, PhD***; Christopher Barnes**; Andrew M. Walters**; Baylor Scott & White Medical Center— Shekhar Ghamande, MD***; Heath D. White, DO, MS***; Alejandro C. Arroliga, MD, MS**; Tasnim Lat, DO**; Oregon Health and Science University School of Medicine— Akram Khan, MD***; Olivia F.

Krol, BS***; Stephanie Nonas, MD**; Milad K. Jouzestani**; Raya Adi*; Chandani Anandkat*; Hanae Benchbani, MD*; Matthew G. Drake, MD*; Makrina N. Kamel, BS*; Ramanpreet Randhawa, MD*; Jessica L. Tsui, MD*; Hennepin County Medical Center—Matthew E. Prekker, MD***; Brian E. Driver, MD***; University of Mississippi Medical Center— Joseph M. Brewer, DO***; Louisiana State University School of Medicine—David R. Janz, MD, MSc***

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

Bibliography:

1. Simpson GD, Ross MJ, McKeown DW, et al. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;108(5):792-9. doi: 10.1093/bja/aer504
2. Martin LD, Mhyre JM, Shanks AM, et al. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-8. doi: 10.1097/ALN.0b013e318201c415
3. Leibowitz AB. Tracheal intubation in the intensive care unit: extremely hazardous even in the best of hands. *Crit Care Med* 2006;34(9):2497-8. doi: 10.1097/01.CCM.0000235993.47514.8F
4. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36(2):248-55. doi: 10.1007/s00134-009-1717-8
5. Green RS, Turgeon AF, McIntyre LA, et al. Postintubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30(5):1055-60. doi: 10.1016/j.jcrc.2015.06.007
6. Ferrada P, Manzano-Nunez R, Lopez-Castilla V, et al. Meta-Analysis of Post-Intubation Hypotension: A Plea to Consider Circulation First in Hypovolemic Patients. *Am Surg* 2019;85(2):167-72.
7. Perbet S, De Jong A, Delmas J, et al. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. *Crit Care* 2015;19:257. doi: 10.1186/s13054-015-0975-9
8. Janz DR, Casey JD, Semler MW, et al. Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial. *Lancet Respir Med* 2019 doi: 10.1016/S2213-2600(19)30246-2
9. Heffner AC, Swords DS, Nussbaum ML, et al. Predictors of the complication of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27(6):587-93. doi: 10.1016/j.jcrc.2012.04.022
10. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* 2018;120(2):323-52. doi: 10.1016/j.bja.2017.10.021
11. Casey JD, Janz DR, Russell DW, et al. Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. *N Engl J Med* 2019;380(9):811-21. doi: 10.1056/NEJMoa1812405

12. Baillard C, Prat G, Jung B, et al. Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. *Br J Anaesth* 2018;120(2):361-67. doi: 10.1016/j.bja.2017.11.067 [published Online First: 2018/02/07]
13. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586
14. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;39(11):1105-11.
15. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818-29.
16. Jennett B, Teasdale G, Braakman R, et al. Predicting outcome in individual patients after severe head injury. *Lancet* 1976;1(7968):1031-4.
17. Cagney DN, Sul J, Huang RY, et al. The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. *Neuro Oncol* 2018;20(9):1162-72. doi: 10.1093/neuonc/nox242
18. Green RS, Fergusson DA, Turgeon AF, et al. Resuscitation Prior to Emergency Endotracheal Intubation: Results of a National Survey. *West J Emerg Med* 2016;17(5):542-8. doi: 10.5811/westjem.2016.6.30503

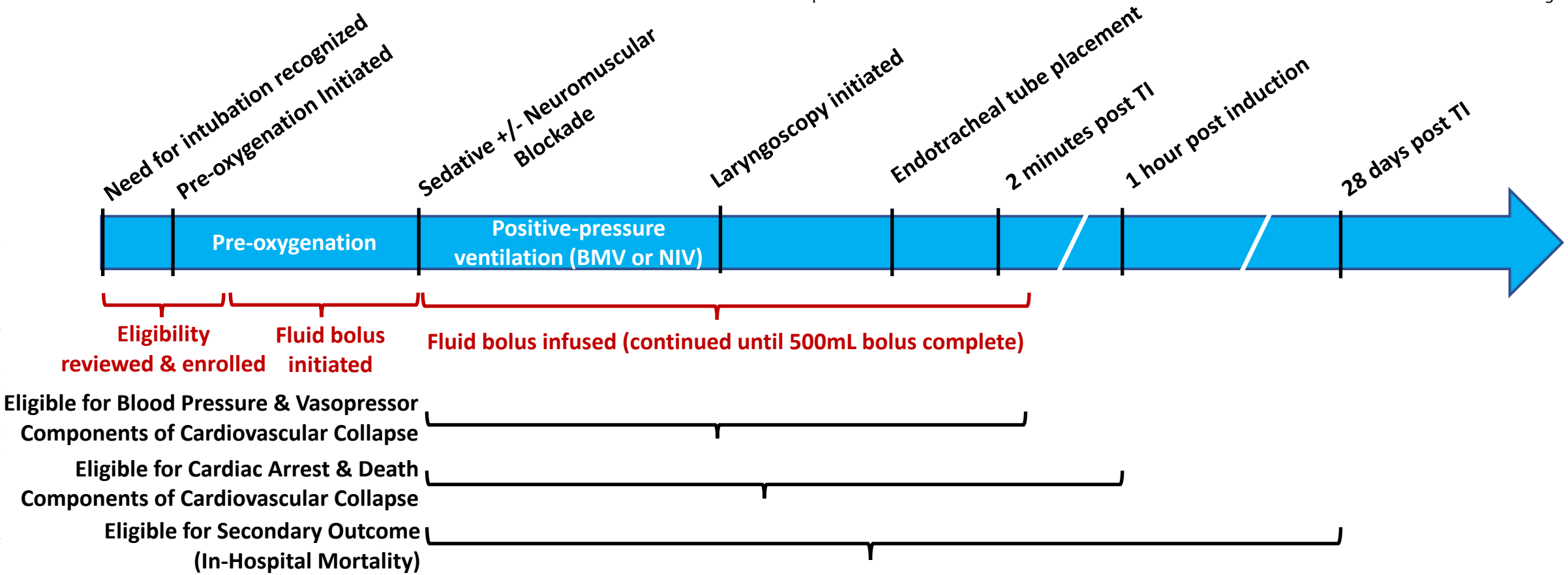

Need for intubation recognized
Pre-oxygenation Initiated
Sedative +/- Neuromuscular Blockade
Laryngoscopy initiated
Endotracheal tube placement
2 minutes post TI
1 hour post induction
28 days post TI
Pre-oxygenation
Positive-pressure ventilation (BMV or NIV)
Eligibility reviewed & enrolled
Fluid bolus initiated
Fluid bolus infused (continued until 500mL bolus complete)
Eligible for Blood Pressure & Vasopressor Components of Cardiovascular Collapse
Eligible for Cardiac Arrest & Death Components of Cardiovascular Collapse
Eligible for Secondary Outcome (In-Hospital Mortality)

Figure 1

Supplementary file to:

Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

Table of Contents

1. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,10-12
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
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

	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, 9,10, 24,
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, 13
	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)	9
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	9,10
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)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12,
	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)	12,13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-14

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-14
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)	Figure 1, 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	15-17
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	10-13
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 (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11,12, Fig. S1
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	11-13

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	12-22, Supplement 15-17
	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, Supplement 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	Supplement 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	18, 22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-23
	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)	18, 22
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, 17
	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	16,17
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	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16,17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25, Supplement 13, 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	23,24
	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 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2

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 14
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 (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5,9, 25
	31b	Authorship eligibility guidelines and any intended use of professional writers	1,2,
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25, Supplement 14
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 MICU	LSU UMCNO MICU	Ochsner MICU	UW Harborview MICU	UW Harborview NICU	UW Harborview TICU	Lahey MICU
Number of Beds	35	20	33	17	30	24	20
Patient Notification Strategy	Information Sheet	Notification Sheet	Information Sheet	Information Sheet	Information Sheet	Information Sheet	Admission Information Sheet
IRB Process	Central*	Central	Central	Central	Central	Central	Local

	UAB MICU	WFU MC MICU	BSW Hospital MICU	OHSU MC MICU	Hennepin MICU	UMMC MICU
Number of Beds	24	42	70	16	28	20
Patient Notification Strategy	Notification Sheet	Information Sheet	Information Sheet	Notification Sheets	Notification and Information Sbeets	Notification Sheet
IRB Oversight	Central	Central	Local	Central	Central	Central

VUMC is Vanderbilt University Medical Center in Nashville, TN; LSU is Louisiana State University Medical Center New Orleans, in New Orleans, LA; Ochsner is Ochsner Medical Center, in New Orleans, LA; UAB is University of Alabama at Birmingham in Birmingham, AL; UW is University of Washington Harborview Medical Center in Seattle, WA; Lahey is Lahey Hospital and Medical Center in Burlington, MA; WFU is Wake Forest University Medical Center in Winston-Salem, NC; BSW is Baylor, Scott & White Medical Center in Temple, TX; OHSU is Oregon Health Sciences University Medical Center in Portland, OR; Hennepin is Hennepin County Medical Center in Minneapolis, MN; UMMC is University of Mississippi Medical Center, in Jackson, MS; MICU is medical intensive care unit; NICU is neurological intensive care unit; TICU is trauma intensive care unit; IRB is institutional review board. “Notification sheet” is a patient and family notification packet provided to each patient and family following enrolment informing the patient of his or her enrolment 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. “Admission Information Sheet” is a patient and family information sheet containing general study information and contact information for the research team provided to each patient and family on admission as part of an packet of materials provided at the time of admission to the study unit. *The Vanderbilt IRB served as central IRB for sites utilizing a central IRB process.

3. Randomization Assignment Forms

A.

NO Fluid Bolus

Do NOT start a new fluid bolus PRIOR to induction (pushing meds)

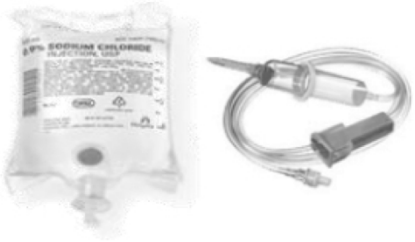
OK to continue any IV fluids already running or ordered

OK to give IV fluids for treatment of cardiovascular collapse
(SBP < 65, new pressor requirement, or cardiac arrest)

B.

Fluid Bolus

1 Obtain 500 ml of crystalloid & gravity IV tubing



2 Hang fluid from top of IV pole, don't use IV pump

3 Start infusion to gravity ASAP
Any IV or IO + squeeze fluid bag

4 Begin procedure whenever ready
(don't need to wait for fluid to finish)

Complete 500 mL infusion

Figure S1: Randomization assignment sheets for subjects randomized to NO Fluid Bolus (A.), and Fluid Bolus (B.) groups.

4. Data Collection:

A trained, independent observer not involved in the performance of the procedure collects data for key peri-procedural outcomes including: whether the patient was already receiving an intravenous fluid infusion at the time of enrolment, whether a new fluid bolus was started between randomization and induction, the volume of new fluid bolus infused from randomization to induction, the administration of new or increased vasopressors prior to or with induction, systolic blood pressure and oxygen saturation at the time of induction, the lowest arterial oxygen saturation and systolic blood pressure from induction to two minutes after tracheal intubation, the administration of a new fluid bolus between induction and two minutes after tracheal intubation, the administration of a new or increased dose of any vasopressor between induction and two minutes after tracheal intubation, the total volume of new fluid bolus infused between induction and two minutes after tracheal intubation, and the number of attempts at tracheal intubation.

Immediately following the procedure, the operator records the following information: sedative choice and dose, subjective difficulty of intubation, modality of pre-oxygenation, modality of oxygenation and ventilation between induction and laryngoscopy, laryngoscopy device used for first attempt, whether video or direct laryngoscopy was used on the first attempt, Cormack-Lehane grade of glottic view on the first attempt[14], difficult airway characteristics present (cervical spine immobilization collar, body fluid obscuring the operator's view of the glottis, or facial trauma), use of a bougie or endotracheal tube with stylet on the first attempt, use of rescue equipment (bougie, stylet, video laryngoscope, direct laryngoscope, laryngeal mask airway, bronchoscope, second proceduralist), and procedural complications (cardiac arrest, bradycardia, esophageal intubation, airway trauma, or witnessed aspiration). Operators also report their specialty and number of previous intubation procedures completed.

Study personnel also collect data on baseline characteristics, pre- and post-intubation management, and clinical outcomes from the medical record. The following information is collected from the medical record:

Baseline: Age, gender, height, weight, race, ethnicity, Acute Physiology and Chronic Health Evaluation (APACHE) II score[15], active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, indication for intubation, most recent pre-procedural Glasgow Coma Score[16], non-invasive ventilator and high flow nasal cannula use in the hour prior to starting pre-oxygenation, vasopressor use in the hour preceding enrolment, 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 enrolment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrolment, and whether or not the intubation was a reintubation (defined as patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).

Peri-procedural: type and dose of neuromuscular blocker; laryngoscope used, shape and size of the laryngoscope blade used for first attempt; total number of attempts; subjective assessment of the difficulty of tracheal intubation reported by the operator (easy, moderate, difficult, unknown);

0-24 hours: Cardiac arrest within 1 hour of intubation; death within 1 hour of intubation; systolic blood pressure, oxygen saturation, FiO_2, and positive end expiratory pressure delivered at 24 hours following intubation.

In-Hospital Outcomes: 28 day in-hospital mortality, days from enrolment to death, ventilator-free days, and ICU-free days – all censored at hospital discharge. See Supplementary file 1, Items 5-8 below for definitions of these terms.

5. Definition of 28-day in-hospital mortality

28-day in-hospital mortality is defined as death from any cause between enrolment and either 28 days from enrolment or discharge from the hospital, whichever comes first.

6. Definition of Ventilator Free Days

Ventilator-free days (VFDs) are defined as the number of days alive and free of invasive mechanical ventilation, from the patient's final extubation to 28 days after enrolment. If a patient returns to invasive mechanical ventilation and is subsequently liberated from invasive mechanical ventilation prior to day 28, the number of VFDs will be counted from the date of the final liberation from invasive mechanical ventilation before day 28. If the patient is receiving invasive mechanical ventilation at day 28 or dies prior to day 28, the number of VFDs will be counted as 0. If a patient is discharged while receiving assisted ventilation, the number of VFDs will be counted as 0. VFDs are counted as 0 in any patients who die before day 28. All data are censored at hospital discharge or 28 days, whichever occurs first (i.e., any liberation from invasive mechanical ventilation after a hospital discharge or after day 28 does not affect VFDs).

7. Definition of ICU-Free Days (ICUFDs)

ICU-FDs are defined as the number of days alive and not admitted to an ICU service, from the patient's final discharge from the ICU service to 28 days after enrolment. If a patient is not discharged from the ICU service by day 28, the number of ICU-FDs will be counted as 0. If a patient is discharged but later admitted again to an ICU service but then is subsequently discharged prior to day 28, ICU-FDs are counted as the number of days from the date of the final ICU discharge to day 28. ICU-FDs are counted as 0 in any patients who die before day 28. All data are censored at hospital discharge or 28 days, whichever comes first (i.e., any readmission to an ICU service after day 28 or after a hospital discharge does not affect VFDs).

8. Definition of "days from enrolment to in-hospital death"

For patients who die prior to hospital discharge, the number of days from enrolment to in-hospital death will be calculated as the number of midnights crossed from the day of enrolment until the day of death. For example, a patient who died on the day of enrolment would have a value for days from extubation to death of "0".

9. Plan for communication of protocol changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, analyses) will be reflected in 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 submitted to the relevant IRBs for tracking and approval

prior to implementation of each 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 provided in the supplementary material for publication.

10. 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. All data available to the coordinating center and investigators at other sites are completely de-identified and contain no PHI. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until. The de-identified dataset housed in REDCap will be accessed by the coordinating center for analyzing and reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. After 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 will be governed by mutual data use agreements.

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Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

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Complete List of Authors:	Russell, Derek ; University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy, & Critical Care Medicine; Department of Veterans Affairs, Veterans Integrated Service Network 7 Casey, Jonathan; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Gibbs, Kevin ; Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease Dargin, James; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine Vonderhaar, Derek ; Ochsner Health System, Department of Pulmonary and Critical Care Medicine Joffe, AM; University of Washington, Department of Anesthesiology and Pain Medicine Ghamande, Shekhar; Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine Khan, Akram; Oregon Health & Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine Dutta, Simanta; Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease Landsperger, Janna; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Robison, Sarah; University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy, & Critical Care Medicine Bentov, Itay; University of Washington, Department of Anesthesiology and Pain Medicine Wozniak, Joanne; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine Stempek, Susan; Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine White, Heath; Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine Krol, Olivia; Oregon Health & Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine Prekker, Matthew; Hennepin County Medical Center, Department of

	Emergency Medicine; Hennepin County Medical Center, Department of Medicine, Division of Pulmonary/Critical Care Medicine Driver, Brian; Hennepin County Medical Center, Department of Emergency Medicine Brewer, Joseph; University of Mississippi Medical Center, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine Wang, Li; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Lindsell, Christopher; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Self, Wesley; Vanderbilt University School of Medicine, Department of Emergency Medicine Rice, Todd; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Semler, Matthew; Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine Janz, David; Louisiana State University School of Medicine in New Orleans, Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology
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Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

Derek W. Russell*, MD[1]; Jonathan D. Casey*, MD, MSc[2]; Kevin W. Gibbs, MD[3]; James M. Dargin, MD[4]; Derek J. Vonderhaar MD[5]; Aaron M. Joffe, DO[6]; Shekhar Ghamande, MD[7]; Akram Khan, MD[8]; Simanta Dutta, MD[3]; Janna S. Landsperger, MS, PA-C[2]; Sarah W. Robison, MD[1]; Itay Bentov, MD, PhD[6]; Joanne M. Wozniak, PA-C[4]; Susan Stempek, PA-C[4], Heath D. White, DO, MS[7]; Olivia F. Krol, BS[8]; Matthew E. Prekker, MD[9,10]; Brian E. Driver, MD[10]; Joseph M. Brewer, DO[11]; Li Wang, MS[2]; Christopher J. Lindsell PhD[2]; Wesley H. Self, MD, MPH[12]; Todd W. Rice, MD, MSc[2]; Matthew W. Semler**, MD, MSc[2]; David R. Janz**, MD, MSc[13] for the PREPARE II Investigators# and the Pragmatic Critical Care Research Group.

Affiliations:
[1]University of Alabama at Birmingham, Department of Medicine, Division of Pulmonary, Allergy and Critical Care Medicine; Birmingham Veteran's Affairs Medical Center, Pulmonary Section; [2] Vanderbilt University School of Medicine, Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine; [3]Wake Forest School of Medicine, Department of Medicine, Section of Pulmonary, Critical Care, Allergy and Immunologic Disease; [4]Lahey Hospital and Medical Center, Department of Medicine, Division of Pulmonary and Critical Care Medicine; [5]Ochsner Health System New Orleans, Department of Pulmonary and Critical Care Medicine; [6]University of Washington, Department of Anesthesiology and Pain Medicine; [7]Baylor Scott & White Medical Center, Department of Medicine, Division of Pulmonary Disease and Critical Care Medicine; [8]Oregon Health and Science University School of Medicine, Department of Medicine, Division of Pulmonary and Critical Care Medicine; [9]Hennepin County Medical Center, Department of Emergency Medicine; [10]Hennepin County Medical Center, Department of Medicine, Division of Pulmonary/Critical Care Medicine;[11]University of Mississippi Medical Center, Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine; [12] Vanderbilt University School of Medicine, Department of Emergency Medicine; [13] Louisiana State University School of Medicine New Orleans, Department of Medicine, Section of Pulmonary/Critical Care Medicine and Allergy/Immunology.

*Authors contributed equally
**Authors contributed equally
#A full list of the PREPARE II Investigators can be found below

Corresponding Author:
Derek W. Russell, MD

Email:
dwrussell@uabmc.edu

Address:
Lyons Harrison Research Building Room 321
701 19th St. S
Birmingham, AL 35294

Telephone:
205-996-1496

Fax:
205-996-4699

Author contributions: All study authors approved the final version of this manuscript. Study concept and design: D.W.R., J.D.C., M.W.S., D.R.J., C.J.L., L.W., W.H.S., and T.W.R.; Acquisition of data: D.W.R, J.D.C, K.W.G., J.D., D.J.V., A.M.J., S.G., A.K., S.D., J.S.L., S.R., I.B., J.W., H.W., O.F.K., M.E.P., B.E.D., J.M.B., K.W.G., S.G., A.K., W.H.S., S.S., T.W.R., M.W.S. D.R.J., and the PREPARE II Investigators; Drafting of the manuscript: D.W.R., J.D.C., D.R.J., M.W.S.; Critical revision of the manuscript for important intellectual content: D.W.R, J.D.C, K.W.G., J.D., D.J.V., A.M.J., S.G., A.K., S.D., J.S.L., S.R., I.B., J.W., H.W., O.F.K., M.E.P., B.E.D., J.M.B., K.W.G., S.G., A.K., W.H.S., S.S., C.J.L., L.W., T.W.R., M.W.S., D.R.J., and the PREPARE II Investigators; Study supervision: D.R.J. and M.W.S.

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Abstract:

Introduction: Cardiovascular collapse is a common complication during tracheal intubation of critically ill adults. Whether administration of an intravenous fluid bolus prevents cardiovascular collapse during tracheal intubation remains uncertain. A prior randomized trial found fluid bolus administration to be ineffective overall but suggested potential benefit for patients receiving positive pressure ventilation during tracheal intubation.

Methods and Analysis:

The PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) trial is a prospective, multi-center, non-blinded randomized trial being conducted in 13 academic intensive care units in the United States. The trial will randomize 1,065 critically ill adults undergoing tracheal intubation with planned use of positive pressure ventilation (non-invasive ventilation or bag-mask ventilation) between induction and laryngoscopy to receive 500 mL of intravenous crystalloid or no intravenous fluid bolus. The primary outcome is cardiovascular collapse, defined as any of: SBP <65 mm Hg, new or increased vasopressor administration between induction and 2 minutes after intubation, or cardiac arrest or death between induction and 1 hour after intubation. The primary analysis will be an unadjusted, intention-to-treat comparison of the primary outcome between patients randomized to fluid bolus administration and patients randomized to no fluid bolus administration using a Chi-square test. The sole secondary outcome is 28-day in-

hospital mortality. Enrolment began on February 1, 2019 and is expected to conclude in June, 2020.

Ethics and Dissemination:

The trial was approved by either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site. 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 (NCT03787732) on December 25, 2018, prior to the enrolment of the first patient.

Strengths and Limitations:

- This multi-center, randomized, controlled trial with target enrolment of 1065 patients will provide the highest quality available evidence for an important question in a commonly encountered clinical scenario.
- Broad eligibility criteria and enrolment at multiple centers will increase the external validity of the findings.
- Blinding is impractical due to the nature of this study intervention.
- The trial is not designed to examine the effects of fluid composition or volume of fluid administered.

Introduction:

Tracheal intubation is common in the care of critically ill patients but is associated with a high incidence of complications[1-3]. Cardiovascular collapse is a composite of life-threatening haemodynamic complications of tracheal intubation comprised of post-intubation hypotension[4-6], administration of vasopressors to treat hypotension, cardiac arrest, and death. Cardiovascular collapse occurs in 20-30% of critically ill patients undergoing tracheal intubation[7 8], and is associated with increased in-hospital mortality[5 6 9].

Some airway management experts recommend the intravenous administration of a fluid bolus beginning prior to induction (i.e., the administration of procedural drugs such as anaesthetics) to prevent cardiovascular collapse during tracheal intubation[4 10]. A fluid bolus could address the haemodynamic perturbations induced by induction and tracheal intubation, which include vasodilatory effects of induction medications, increased venous capacitance due to decreased circulating catecholamines, and decreased venous return secondary to positive pressure applied to the thoracic cavity. However, the only reported trial to examine administration of a pre-intubation fluid bolus, the PrePARE (Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation) trial, reported that a pre-intubation fluid bolus had no effect on the overall rate of cardiovascular collapse[8]. The receipt of positive pressure ventilation, however, appeared to modify the effect of a fluid bolus administration on cardiovascular collapse in the PrePARE trial. Patients receiving positive pressure ventilation appeared to have a lower rate cardiovascular collapse in the fluid bolus group compared to the no fluid bolus group, both among patients

receiving non-invasive ventilation for pre-oxygenation (RR 0.51; 95% confidence interval [CI], 0.24-1.09; P value for interaction = 0.032) and among patients receiving bag-mask ventilation between induction and laryngoscopy (RR 0.61; 95% CI, 0.33-1.13; P value for interaction = 0.008)[8].

Provision of positive pressure ventilation with a bag-mask device between induction and laryngoscopy has been shown to decrease the incidence of severe hypoxaemia during tracheal intubation of intensive care unit (ICU) patients (relative risk, 0.48; 95%, CI, 0.30 to 0.77)[11]. These results, and others examining use of non-invasive ventilation for pre-oxygenation during ICU intubations[12], suggest that positive pressure ventilation should be provided during tracheal intubation for most critically ill patients[10]. This increases the importance of investigating the finding from the PrePARE trial that a pre-induction fluid bolus might prevent cardiovascular collapse among patients receiving positive pressure ventilation. We designed the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) trial to examine the hypothesis that administration of a fluid bolus beginning prior to induction will decrease the incidence of cardiovascular collapse among critically ill adults undergoing tracheal intubation with positive pressure ventilation between induction and laryngoscopy.

Methods and Analysis:

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

	STUDY PERIOD							
	Enrollment	Allocation	On-Study					On-Study
TIMEPOINT	Decision to perform TI	Between decision to intubate and Induction	Sedative & NMB	TI	2 minutes post-TI	1 hour post TI	24 hours post-TI	Discharge or 28 days after enrollment
ENROLMENT:	X							
Eligibility screen	X							
Allocation		X						
INTERVENTIONS:								
Fluid Bolus Initiation		X						
Screening for contraindications	X	X						
No New Fluid Bolus		X						
Screening for contraindications	X	X						
ASSESSMENTS:								
Baseline Variables	X	X						
Peri-procedural variables		X	X	X	X			
Clinical Outcomes						X	X	X

Table 1: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist Baseline variables obtained from medical record include: demographic characteristics, APACHEII score, and presence of sepsis/septic shock. Peri-procedural data collected by independent, trained observer includes the following: whether fluids were infusing prior to enrollment, receipt of the study intervention, the volume of study crystalloid infused (induction and 2 minutes after procedure), use of prophylactic vasopressor (or prophylactically increased vasopressor dose), addition of new vasopressor (or increased vasopressor dose), and systolic blood pressure (at baseline and nadir from induction to 2 minutes after procedure). Peri-procedural data collected by operator includes: sedation drugs used (and doses), oxygenation/ventilation modality between induction and laryngoscopy, and procedural complications. Clinical outcomes include: vital status (overall in-hospital death, cardiac arrest death within 1 hour of TI), number of ventilator-free days to 28 days, and number of ICU-free days to 28 days. TI: tracheal intubation. NMB: neuromuscular blockade.

Patient and Public Involvement

Materials used to communicate about the study with patients and family members were developed with input from the Vanderbilt Community Advisory Council.

Study authors will disseminate the results of this study online and via social media in forms suitable for public understanding.

Study Design

The PREPARE II trial is a pragmatic, multi-center, un-blinded, parallel group, randomized trial. Among critically ill adults undergoing tracheal intubation undergoing positive pressure ventilation between induction and laryngoscopy, PREPARE II compares incidence of cardiovascular collapse between patients administered intravenous administration of a 500 mL fluid bolus and those receiving no fluid bolus administration. The trial protocol was approved with waiver of informed consent by either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site. The trial was registered prior to initiation of enrolment (ClinicalTrials.gov identifier: NCT03787732). An independent data and safety monitoring board (DSMB) is monitoring the progress and safety of the trial.

Study Sites

PREPARE II is being conducted in 13 intensive care units at academic medical centers across the United States. Site characteristics are listed in **Supplementary file 1, section 2**.

Population

In order to maximise the generalisability of this trial, the target population is meant to be broad and encompass all patients in whom the treating clinician judges

there to be clinical equipoise on the use of the intervention. The trial includes adults (age ≥ 18 years) located in a participating ICU for whom the treating clinicians have determined that tracheal intubation is required and for whom the planned procedural approach includes an operator who routinely performs tracheal intubation in the participating unit, administration of sedation (with or without neuromuscular blockade), and positive-pressure ventilation between induction and laryngoscopy. The trial excludes pregnant women and prisoners. In order for clinicians to not feel compelled to provide or withhold an intervention which they feel is wrong for a given patient, the trial also excludes patients for whom the treating clinicians feel (based upon their clinical judgment at the time of enrolment) that the urgency of the intubation precludes safe performance of study procedures or that fluid bolus administration is either required or contraindicated.

Randomization and Treatment Allocation

Patients are randomized in a 1:1 ratio to intravenous fluid bolus administration or no fluid bolus administration in permuted blocks of two, four, or six, stratified according to study site. Study-group assignments (see **Supplementary file 1, section 3; Figure S1**) are placed in sequentially numbered opaque envelopes and remain concealed until after enrolment. After enrolment and randomization, patients, treating clinicians, and study personnel are not blinded to study group assignment.

Study Interventions

Fluid Bolus Group

For patients who are assigned to the fluid bolus group, intravenous infusion of 500 mL of a crystalloid solution of the operator's choosing is initiated after randomization and prior to induction. The fluid bolus is infused from above the level of the intravenous or intra-osseous access and allowed to infuse by gravity, manual pressure, or bag pressure. The fluid bolus is discontinued after 500 mL have infused. For patients assigned to the fluids bolus group who are already receiving a fluid infusion, administration of 500mL of fluids between randomization and induction is achieved with either an additional bolus or increasing the rate of the existing infusion.

No Fluid Bolus Group

For patients who are assigned to the no fluid bolus group, intravenous fluid administration is not initiated between randomization and induction. Intravenous fluid infusions initiated prior to randomization are not altered.

Co-Interventions

Regardless of study group assignment, treating clinicians determine the timing of induction and tracheal intubation. Treating clinicians may stop infusion of a fluid bolus, increase or decrease the rate of infusion, or add a new fluid bolus at any time if felt to be required for the optimal care of the patient. Study group assignment determines only the initiation of intravenous fluid bolus administered between randomization and induction. **Figure 1** depicts the timeline of study procedures in the context of the tracheal intubation procedure.

Because the study enrols only patients for whom treating clinicians plan to administer positive-pressure ventilation between induction and laryngoscopy, most patients receive either non-invasive ventilation or bag-mask ventilation between induction and laryngoscopy. Instances in which positive-pressure ventilation between induction and laryngoscopy is not administered are recorded, along with the reason that positive-pressure ventilation was not administered (e.g., emesis arising between randomization and induction).

Treating clinicians determine the decision to intubate, modality and timing of pre-oxygenation, choice, dose, and timing of medications for induction and neuromuscular blockade, decision to administer vasopressors before or after induction, choice of laryngoscope, use of cricoid pressure, method of positive pressure ventilation (non-invasive ventilation or bag-mask ventilation) between induction and laryngoscopy, decision to administer intravenous fluid for the treatment of hypotension, and use of additional airway management equipment and personnel. Data on these co-interventions is prospectively collected.

In some participating units, patients may be co-enrolled in a randomized trial comparing use of bougie versus use of an endotracheal tube with stylet on the first attempt at tracheal intubation (ClinicalTrials.gov, NCT03928925). An interaction between the interventions evaluated in these trials in not anticipated and the results will be reported separately.

Data Collection

Data collection for this study is described in detail in **Supplementary file 1, Section 4** and **Table 1** provides further detail on data collection procedures.

Primary Outcome

The primary outcome is cardiovascular collapse, defined as the occurrence of one or more of the following: Systolic blood pressure (SBP) < 65 mmHg between induction and 2 minutes after intubation; new or increased vasopressor administration between induction and 2 minutes after intubation; cardiac arrest between induction and 1 hour after intubation; or death between induction and 1 hour after intubation.

Cardiovascular collapse is a commonly used endpoint in airway management research[4 8]. Cardiovascular collapse is considered a "reasonably likely surrogate endpoint" for short-term mortality because a strong mechanistic rationale links severe hypotension and cardiac arrest to short-term mortality and interventions that prevent cardiovascular collapse might reasonably be expected to prevent short-term mortality[14]. Cardiovascular collapse was the primary outcome of the recently completed PrePARE trial[8], on which the design of the PREPARE II trial was based. In the PrePARE trial, the absolute risk of in-hospital mortality was 16.7% (95% CI 3.4% to 30.0%) higher among patients who experienced cardiovascular collapse during intubation compared with patients who did not[8].

Secondary Outcome

The sole secondary outcome is 28-day all-cause in-hospital mortality (**Supplementary file 1, section 5**). Short-term mortality is a commonly used patient-

centered clinical endpoint for randomized trials in intensive care medicine and may be mechanistically associated with the primary outcome of cardiovascular collapse.

Exploratory Clinical Outcomes

- Each individual component of the composite primary endpoint:
  - SBP < 65 mmHg between induction and 2 minutes after intubation
  - new or increased vasopressor administration between induction and 2 minutes after intubation
  - cardiac arrest between induction and 1 hour after intubation
  - death between induction and 1 hour after intubation.
- Lowest SBP between induction and 2 minutes after intubation
- Change in SBP from induction to lowest SBP between induction and 2 minutes after intubation
- Ventilator-free days to 28 days (defined in **Supplementary file 1, section 6**)
- ICU-free days to 28 days (defined in **Supplementary file 1, section 7**)

Exploratory Safety Outcomes

- Lowest arterial oxygen saturation between induction and 2 minutes after intubation
- Incidence of hypoxaemia (oxygen saturation < 90%) between induction and 2 minutes after intubation

- Incidence of severe hypoxaemia (oxygen saturation < 80%) between induction and 2 minutes after intubation
- Oxygen saturation at 24 hours after intubation
- Fraction of inspired oxygen at 24 hours after intubation
- Positive end expiratory pressure at 24 hours after intubation
- SBP at 24 hours after intubation

Exploratory Process Measures

- Initiation of an intravenous fluid bolus between induction and 2 minutes after intubation
- Time from induction to successful intubation
- Incidence of successful intubation on the first laryngoscopy attempt
- Number of laryngoscopy attempts
- Cormack-Lehane grade of glottic view on first attempt
- Operator-assessed difficulty of intubation
- Need for additional airway equipment or a second operator

Initial Sample Size Estimation

In a prior randomized trial comparing fluid bolus administration beginning prior to induction versus no fluid bolus administration in the same setting as the current trial, the incidence of cardiovascular collapse was 19.6% in the fluid bolus group and 18.3% in the no fluid bolus group overall. However, among the subgroup of patients assigned to receive positive pressure ventilation with a bag-mask device between induction and

laryngoscopy, the incidence of cardiovascular collapse was 16.0% in the fluid bolus group and 26.2% in the no fluid bolus group (10% absolute risk difference and 40% relative risk difference). Assuming more conservative rates of cardiovascular collapse of 16.25% in the fluid bolus group and 25.0% in the no fluid bolus group (8.75% absolute risk difference and 35% relative risk difference), we calculated that enrolling 714 patients would provide 80 percent statistical power at a two-sided alpha level of 0.05. Anticipating less than 5% missing data for the primary outcome, the initial planned enrolment for the trial was 750 patients. The study protocol included a pre-specified sample size re-estimation following the single interim analysis (see *Sample Size Re-estimation*)

Data and Safety Monitoring Board (DSMB) and Interim Analysis

A DSMB composed of experts in clinical trials, critical care medicine, anaesthesia, and emergency medicine is overseeing the design and conduct of the trial. The DSMB conducted a single interim analysis for efficacy and safety at the anticipated halfway point of the trial, after enrolment of 375 patients, on November 12, 2019. Stopping criteria were pre-specified in the study protocol, suggesting termination of the trial at the interim if the P value for the difference between groups in the incidence of the primary outcome (cardiovascular collapse) or secondary outcome (28-day in-hospital mortality) were 0.001 or less using a chi-square test. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) allows the final analysis at the end of the trial to be performed using an unchanged level of significance.

The DSMB also formally evaluated the trial for safety and examined the highest fraction of inspired oxygen, highest positive end expiratory pressure, and lowest arterial oxygen saturation at 24 hours after intubation in each study group. The prespecified early stopping criteria for physiologic outcomes were as follows: if the *P* value for the difference between study groups in any of these three physiologic variables were 0.001 or less using a Mann-Whitney rank-sum test and concordant in direction with the point-estimate for mortality.

At the interim analysis, finding that no stopping criteria had been met and no safety concerns were observed, the DSMB recommended continuing the trial.

Sample Size Re-Estimation

The study protocol specified that, after completion of the interim analysis and the recommendation to continue enrolment, "the DSMB will evaluate the rate of the primary outcome in the no fluid bolus group. If the incidence of the primary outcome in the no fluid bolus group differs from the original estimate of 25.0%, the DSMB may ask that the investigators perform a sample size re-estimation to maintain adequate statistical power to detect the planned relative risk difference in the primary outcome between groups."

After completion of the interim analysis and the recommendation to continue enrolment, the DSMB examined the number of patients that would need to be enrolled in order to maintain 80% statistical power to detect the planned relative risk reduction of 35% in the primary outcome. Based on this information, the DSMB recommended increasing the total sample size from 750 to 1,065 patients. The investigators accepted the DSMB's recommendation, revising the planned sample size for the final trial to

1,065 patients. During the sample size re-estimation, both the study investigators and the DSMB remained blind to all outcomes by study group. No further interim analyses are planned.

Statistical Analysis Principles

R version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria) will be used for all analyses. Continuous variables will be reported as mean ± SD or median and IQR; categorical variables will be reported as frequencies and proportions. Between-group comparisons will be made with the Mann-Whitney rank-sum test for continuous variables, and the chi-square test for categorical variables

Primary Analysis of the Primary Outcome

The primary analysis will be an unadjusted, intention-to-treat comparison of patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group with regard to the primary outcome of cardiovascular collapse. Between group differences will be tested using an unadjusted chi-square test. A P value < 0.05 will be used to indicate statistical significance for the primary analysis.

Secondary Analyses of the Primary Outcome

To account for potential confounders, we will develop a logistic regression model with cardiovascular collapse (primary outcome) as the dependent variable and independent variables to include study group (fluid bolus group vs no fluid bolus group) and relevant confounders (age, APACHE II score at enrolment, presence of sepsis or

septic shock, vasopressor receipt in the hour prior to enrolment, and receipt of intravenous fluid infusion initiated prior to enrolment). We will also develop a logistic regression model accounting for the above variables plus any baseline characteristics that appear on visual review to be potentially imbalanced between the study groups.

Because patients within a specific ICU may be more similar to other patients within the same ICU than to patients in other ICUs, we will fit a generalized linear mixed-effects model with the outcome of cardiovascular collapse, including group assignment as a fixed effect and study unit (stratification variable) as a random effect.

We will repeat the primarily analysis using alternative definitions of cardiovascular collapse, including: (1) using an SBP < 90 mm Hg rather than an SBP <65 mm Hg, (2) using 28-day in-hospital mortality rather than death within 1 hour, and (3) using days from enrolment to in-hospital death (defined in **Supplementary file 1, section 8**) rather than death within 1 hour.

Interpreting composite endpoints can be challenging when the components have different levels of clinical importance. We will repeat the primary analysis of the primary outcome using a global rank scale. Use of a hierarchical global rank score places greater weight on the objective, patient-centered clinical outcomes (death, cardiac arrest) than on the immediate physiologic outcomes (hypotension and vasopressors). The global rank endpoint will be constructed by comparing each patient with every other patient in the study and assigning a score for each pairwise comparison based on whom fared better. To make the pairwise comparison, we will consider a priority order of endpoints: (1) death within one hour of intubation; (2) cardiac arrest within one hour of intubation; (3) SBP < 65 mmHg between induction and two minutes after intubation; and

(4) new or increased vasopressor administration between induction and two minutes after intubation. The scores will be summarized and compared between study groups (fluid bolus group vs no fluid bolus group) using an unadjusted Mann-Whitney U test.

Given the findings of the PrePARE trial subgroup analysis (i.e., that the effect of fluid bolus administration on cardiovascular collapse may be related to the receipt of positive pressure ventilation during intubation)[8], we will repeat the primary analysis excluding patients who did not receive positive pressure during intubation. Because many critical care patients are already receiving intravenous fluid for other indications when the decision is made to intubate and this may modify the effect of a new fluid bolus, we will repeat the primary analysis excluding patients who were already receiving intravenous fluid at the time of enrolment.

Analysis of Effect Modification for the Primary Outcome

We will examine whether pre-specified baseline variables modify the effect of treatment group on the primary outcome using formal tests of statistical interaction in a logistic regression model. Independent variables will include study group assignment, the potential effect modifier of interest, and the interaction between the two (e.g., study group * presence of sepsis or septic shock). Significance will be determined by the P value for the interaction term, with values less than 0.10 considered to suggest of a potential interaction and values less than 0.05 considered to confirm an interaction. Continuous variables will be analyzed using restricted cubic splines and preferentially displayed as continuous variables with 3-5 knots using a locally weighted regression or partial effects plots. We will use a forest plot to display the effect of covariates. If

required for data presentation, continuous variables will be dichotomized for inclusion in a forest plot. We will examine whether the following baseline variables modify the effect of study group on the primary outcome:

1. APACHE II score at enrolment (continuous variable);
2. Presence of sepsis or septic shock at time of enrolment (yes/no);
3. Receipt of vasopressors in the 1 hour prior to enrolment (yes/no);
4. Predicted probability of cardiovascular collapse as calculated by a pre-specified multivariable model (continuous variable);

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

1. Receipt of positive pressure ventilation for pre-oxygenation (via either non-invasive mechanical ventilation or bag-mask ventilation) (yes/no);
2. Choice of sedative medication (etomidate, ketamine, propofol, other);
3. New or increased vasopressor administration prior to or with induction (yes/no);
4. SBP at induction (continuous variable in mm Hg)
5. Oxygen saturation at induction (continuous variable in %)

Finally, to examine our assumption that no interaction will exist between the interventions evaluated in the PREPARE II and BOUGIE trials, among patients co-enrolled to these trials, we will examine whether BOUGIE group assignment modifies the primary outcome. If, contrary to our expectation, an interaction is confirmed (based on criteria listed above for interaction testing), the BOUGIE group assignment will be added to the adjustment model for the primary outcome of cardiovascular collapse.

Analysis of the Secondary Outcome

The sole secondary outcome of 28-day in-hospital mortality will be compared between patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group using an unadjusted chi-squared test.

Analyses of Exploratory Outcomes

All pre-specified exploratory outcomes will be compared between patients randomized to the fluid bolus group versus patients randomized to the no fluid bolus group. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test. In a sensitivity analysis using data only from each patient's first tracheal intubation in the PREPARE II dataset, we will compare the fluid group to the no fluid bolus group with regard to in-hospital mortality, ventilator-free days, and ICU-free days.

Handling of Missing Data

Although we have allowed for up to 5% missingness in our power calculation, we do not anticipate that data for the primary outcome of cardiovascular collapse will be

missing for any patients. Missing data will not be imputed for the primary or secondary outcome. In adjusted analyses, missing data for covariates may be imputed using a multiple imputation technique.

Corrections for Multiple Testing

We pre-specify a single primary analysis of a single primary outcome, and a single secondary analysis with one outcome. All additional analyses are deemed hypothesis-generating, and no corrections for multiple comparisons will be performed.

Trial Status

The Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II) trial is a pragmatic, prospective, multi-center, non-blinded randomized clinical trial comparing fluid bolus to no fluid bolus during tracheal intubation of critically ill adults. Patient enrolment began on February 1, 2019 and is expected to be completed in June, 2020.

Ethics and Dissemination

Informed Consent

In current clinical practice, initiating an intravenous fluid bolus beginning prior to tracheal intubation and not administering an intravenous fluid bolus beginning prior to tracheal intubation are both common management approaches, with significant variation between providers[15]. All patients eligible for this trial would have either received or not received an intravenous fluid bolus for tracheal intubation as a part of their clinical care,

regardless of participation in the trial. To be eligible for the trial, patients' treating clinicians must feel that initiation of a new fluid bolus for tracheal intubation is neither required nor contraindicated for the patient's optimal care. The protocol states that a fluid bolus can be given or withheld for patient safety at any time in the study, regardless of group assignment. For these reasons, the trial is felt to pose minimal incremental risk compared with the clinical care patients would receive outside of the trial.

Tracheal intubation of critically ill adults is commonly an urgent or emergent procedure for which obtaining informed consent for the clinical procedure or informed consent for research is impracticable.

This information was provided to either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at each trial site (see **Supplemental file 1, section 2**), and the trial was approved with a waiver of informed consent.

Information for Patients and Families

Information regarding the study is made available to patients and families through three mechanisms: (1) a patient and family notification sheet provided to each patient and family following enrolment informing the patient of his or her enrolment and describing the study, (2) 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, (3) a patient and family information sheet containing general study information and contact information for the

research team provided to each patient and family at the time of admission to the study unit. The mechanism(s) of providing information to patients and families used by each study site was determined by local site investigators and local IRBs and is described in **Supplemental file 1, section 2**; **Table S1**.

Protocol Changes

Any changes to the trial protocol will be recorded on ClinicalTrials.Gov as per SPIRIT guidelines. See **Supplemental file 1, section 9** for more details.

Data Handling

For details of privacy and data handling, see **Supplemental file 1, section 10**.

Dissemination Plan

Trial results will be submitted to a peer-reviewed journal for consideration of publication and will be presented at scientific conferences.

Figure Legends

Figure 1: Timeline of tracheal intubation (TI), enrolment, study interventions, and primary/secondary outcome eligibility in an enrolled patient.

List of PREPARE II Investigators

Wake Forest School of Medicine— Kevin W. Gibbs, MD***; Simanta Dutta, MD***; Stephen P Peters MD, PhD*; Muhammad Ali, MBBS*; Rita N. Bakhru, MD, MS*; Scott Bauer, ANP-BC*; Christina R. Bellinger, MD*; Amanda M. Brown, PA-C*; Blair Brown, MD*; Jerri Brown, ADN, RN*; Caitlin Bumgarner, ACGNP*; Wendy Butcher, RN, BSN*; Megan Caudle, ACGNP*; Arjun B. Chatterjee, MD*; David J. Chodos, MD*; Gerardo Corcino, RN, BSN*;

Nathan S. Cutler, MD*; Travis L. Dotson, MD*; Daniel C. Files, MD*; Jonathan L Forbes, DO*; John P. Gaillard, MD*; Katherine A. Gershner, DO*; Shannon Ginty, PA-C*; Kiadrick R. Hood, RN, MSN, CMSRN*; April Hazelwood, ADN, RN*; Katherine Hendricks, FNP*; Kelly Jacobus, PA-C*; Jonathan T. Jaffe, MD*; Stacy Kay, ACGNP*; Chad A. Kloefkorn, MD*; Jennifer Krall, MD*; Margo T. Lannan, MD*; Cornelia Lane, ACGNP*; Cynthia Lanning, BSN, RN*; Jessica Lyons, PA-C*; William I. Mariencheck Jr., MD*; Chad R. Marion, DO, PhD*; Matthew A. Maslonka, MD*; Sara McClintock, ACGNP*; Nathaniel M. Meier, MD*; Matthew C. Miles, MD, MEd*; Peter J. Miller, MD*; Sophia Mitchell, PA-C*; Wendy C. Moore, MD*; Katherine Moss, PA-C*; Andrew M. Namen, MD*; Dustin L. Norton, MD*; Stella B. Ogake, MD*; Jill A. Ohar, MD*; Victor E. Ortega, MD, PhD*; Jessica A. Palakshappa, MD, MS*; Rodolfo M. Pascual, MD*; Sandi Pascual, ANP-BC*; Aaron Pickens, MD*; Adam R Schertz, MD*; Matt Strong, ADN, RN*; Alexander O. Sy, MD*; Braghadheeswar Thyagarajan MD*; Amy Townsend, ACGNP*; Russell Worthen, FNP-BC*; Michael Wlodarski, PA-C*; Charles Yarbrough, ADN, RN*; Caroline York, PA-C*; Vanderbilt University Medical Center— Jonathan D. Casey, MD, MSc***; Janna S. Landsperger, MSN***; Li Wang, MS***; Christopher J. Lindsell PhD***; Todd W. Rice, MD, MSc***; Matthew W. Semler, MD, MSc***; Wesley H. Self, MD, MPH***; Bradley Lloyd, RRT-ACCS*; Lahey Hospital and Medical Center— James Dargin, MD***; Joanne Wozniak, PA-C***; Susan Stempek, PA-C***; Christopher Adler, PA-C*; Ahmed Agameya, MD*; Michael Colancecco, DO*; Daniel Fitelson, MD*; Joshua Giaccotto, MD*; Gena Han, DO*; Louise Kane, MD*; Ezra Miller, MD*; Timothy Noland, PA-C*; Jaqueline Price, PA-C*; Joseph Plourde, PA-C*; Emily Adams, PA-C*; Fraser Mackay, MD*; Laura Mahoney, PA-C*; Avignat Patel, MD*; Michael Plourde, PA-C*; Zena Saadeh, PA-C*; Sara Shadchehr, DO*; Sandeep Somalaraju, MD*; Eleanor Summerhill, MD*; Ryan Webster, MD*; Jordan Winnicki, PA-C*; Ekaterina Yavarovich, DO*; University of Alabama at Birmingham Medical Center— Derek W. Russell, MD***; Sarah W. Robison, MD***; Sheetal Gandotra, MD**; Swati Gulati, MBBS, 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, AND*; 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*; David B. Page, MD*; 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*; Micah R. Whitson, MD*; Ochsner Health System New Orleans— Derek J. Vonderhaar, MD***; Kevin M. Dischert MD**; University of Washington Harborview Medical Center— Aaron M. Joffe, DO***; Itay Bentov, MD, PhD***; Christopher Barnes**; Andrew M. Walters**; Baylor Scott & White Medical Center— Shekhar Ghamande, MD***; Heath D. White, DO, MS***; Alejandro C. Arroliga, MD, MS**; Tasnim Lat, DO**; Oregon Health and Science University School of Medicine— Akram Khan, MD***; Olivia F. Krol, BS***; Stephanie Nonas, MD**; Milad K. Jouzestani**; Raya Adi*; Chandani Anandkat*; Hanae Benchbani, MD*; Matthew G. Drake, MD*; Makrina N. Kamel, BS*; Ramanpreet Randhawa, MD*; Jessica L. Tsui, MD*; Hennepin County Medical Center— Matthew E. Prekker, MD***; Brian E. Driver, MD***; University of Mississippi Medical Center— Joseph M. Brewer, DO***; Louisiana State University School of Medicine—David R. Janz, MD, MSc***

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

Bibliography:

1. Simpson GD, Ross MJ, McKeown DW, et al. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;108(5):792-9. doi: 10.1093/bja/aer504
2. Martin LD, Mhyre JM, Shanks AM, et al. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114(1):42-8. doi: 10.1097/ALN.0b013e318201c415
3. Leibowitz AB. Tracheal intubation in the intensive care unit: extremely hazardous even in the best of hands. *Crit Care Med* 2006;34(9):2497-8. doi: 10.1097/01.CCM.0000235993.47514.8F
4. Jaber S, Jung B, Corne P, et al. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36(2):248-55. doi: 10.1007/s00134-009-1717-8
5. Green RS, Turgeon AF, McIntyre LA, et al. Postintubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30(5):1055-60. doi: 10.1016/j.jcrc.2015.06.007
6. Ferrada P, Manzano-Nunez R, Lopez-Castilla V, et al. Meta-Analysis of Post-Intubation Hypotension: A Plea to Consider Circulation First in Hypovolemic Patients. *Am Surg* 2019;85(2):167-72.
7. Perbet S, De Jong A, Delmas J, et al. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. *Crit Care* 2015;19:257. doi: 10.1186/s13054-015-0975-9
8. Janz DR, Casey JD, Semler MW, et al. Effect of a fluid bolus on cardiovascular collapse among critically ill adults undergoing tracheal intubation (PrePARE): a randomised controlled trial. *Lancet Respir Med* 2019 doi: 10.1016/S2213-2600(19)30246-2
9. Heffner AC, Swords DS, Nussbaum ML, et al. Predictors of the complication of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27(6):587-93. doi: 10.1016/j.jcrc.2012.04.022
10. Higgs A, McGrath BA, Goddard C, et al. Guidelines for the management of tracheal intubation in critically ill adults. *Br J Anaesth* 2018;120(2):323-52. doi: 10.1016/j.bja.2017.10.021
11. Casey JD, Janz DR, Russell DW, et al. Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults. *N Engl J Med* 2019;380(9):811-21. doi: 10.1056/NEJMoa1812405
12. Baillard C, Prat G, Jung B, et al. Effect of preoxygenation using non-invasive ventilation before intubation on subsequent organ failures in hypoxaemic patients: a randomised clinical trial. *Br J Anaesth* 2018;120(2):361-67. doi: 10.1016/j.bja.2017.11.067 [published Online First: 2018/02/07]
13. Chan AW, Tetzlaff JM, Gotzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586

14. Cagney DN, Sul J, Huang RY, et al. The FDA NIH Biomarkers, EndpointS, and other Tools (BEST) resource in neuro-oncology. *Neuro Oncol* 2018;20(9):1162-72. doi: 10.1093/neuonc/nox242
15. Green RS, Fergusson DA, Turgeon AF, et al. Resuscitation Prior to Emergency Endotracheal Intubation: Results of a National Survey. *West J Emerg Med* 2016;17(5):542-8. doi: 10.5811/westjem.2016.6.30503

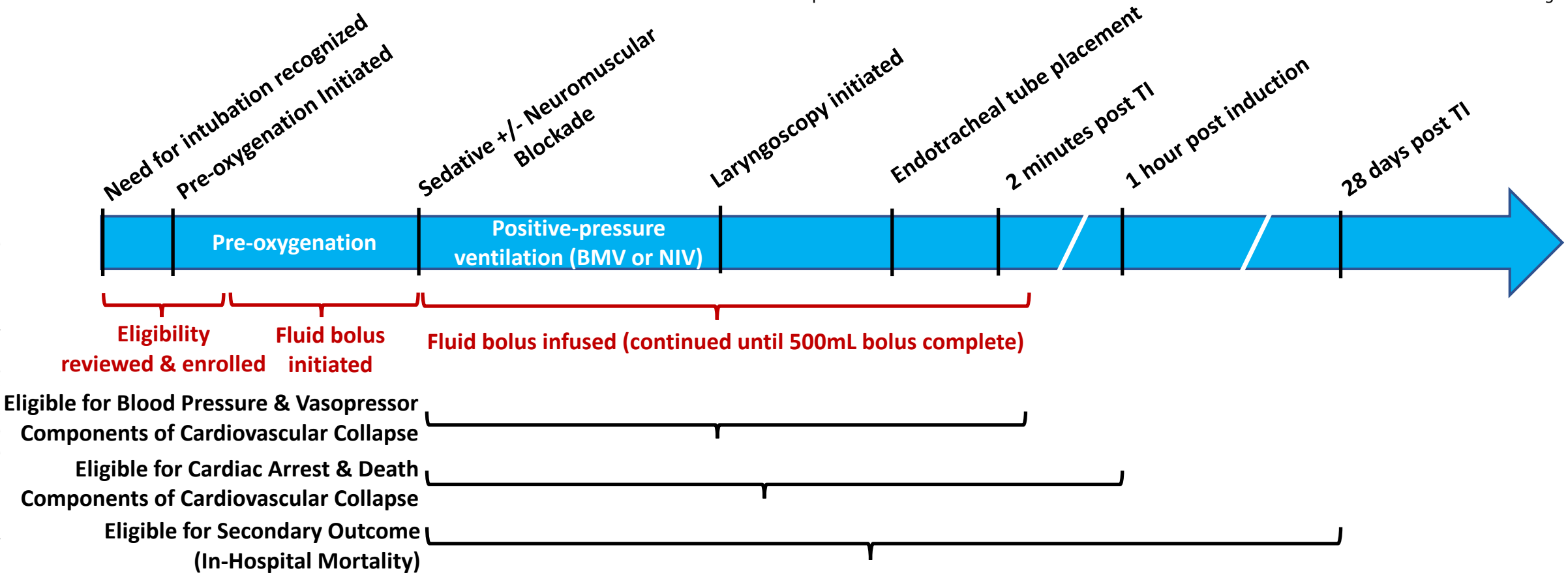
Need for intubation recognized
Pre-oxygenation Initiated
Sedative +/- Neuromuscular Blockade
Laryngoscopy initiated
Endotracheal tube placement
2 minutes post TI
1 hour post induction
28 days post TI
Pre-oxygenation
Positive-pressure ventilation (BMV or NIV)
Eligibility reviewed & enrolled
Fluid bolus initiated
Fluid bolus infused (continued until 500mL bolus complete)
Eligible for Blood Pressure & Vasopressor Components of Cardiovascular Collapse
Eligible for Cardiac Arrest & Death Components of Cardiovascular Collapse
Eligible for Secondary Outcome (In-Hospital Mortality)

Figure 1

Supplementary file to:

Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomized clinical trial

Table of Contents

1. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,10-12
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
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

	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, 9,10, 24,
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, 13
	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)	9
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	9,10
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)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12,
	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)	12,13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-14

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-14
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)	Figure 1, 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	15-17
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	10-13
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 (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11,12, Fig. S1
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	11-13

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	12-22, Supplement 15-17
	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, Supplement 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	Supplement 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	18, 22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-23
	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)	18, 22
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, 17
	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	16,17
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	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16,17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25, Supplement 13, 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	23,24
	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 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2

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 14
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 (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5,9, 25
	31b	Authorship eligibility guidelines and any intended use of professional writers	1,2,
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25, Supplement 14
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 MICU	LSU UMCNO MICU	Ochsner MICU	UW Harborview MICU	UW Harborview NICU	UW Harborview TICU	Lahey MICU
Number of Beds	35	20	33	17	30	24	20
Patient Notification Strategy	Information Sheet	Notification Sheet	Information Sheet	Information Sheet	Information Sheet	Information Sheet	Admission Information Sheet
IRB Process	Central*	Central	Central	Central	Central	Central	Local

	UAB MICU	WFU MC MICU	BSW Hospital MICU	OHSU MC MICU	Hennepin MICU	UMMC MICU
Number of Beds	24	42	70	16	28	20
Patient Notification Strategy	Notification Sheet	Information Sheet	Information Sheet	Notification Sheets	Notification and Information Sbeets	Notification Sheet
IRB Oversight	Central	Central	Local	Central	Central	Central

VUMC is Vanderbilt University Medical Center in Nashville, TN; LSU is Louisiana State University Medical Center New Orleans, in New Orleans, LA; Ochsner is Ochsner Medical Center, in New Orleans, LA; UAB is University of Alabama at Birmingham in Birmingham, AL; UW is University of Washington Harborview Medical Center in Seattle, WA; Lahey is Lahey Hospital and Medical Center in Burlington, MA; WFU is Wake Forest University Medical Center in Winston-Salem, NC; BSW is Baylor, Scott & White Medical Center in Temple, TX; OHSU is Oregon Health Sciences University Medical Center in Portland, OR; Hennepin is Hennepin County Medical Center in Minneapolis, MN; UMMC is University of Mississippi Medical Center, in Jackson, MS; MICU is medical intensive care unit; NICU is neurological intensive care unit; TICU is trauma intensive care unit; IRB is institutional review board. “Notification sheet” is a patient and family notification packet provided to each patient and family following enrolment informing the patient of his or her enrolment 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. “Admission Information Sheet” is a patient and family information sheet containing general study information and contact information for the research team provided to each patient and family on admission as part of an packet of materials provided at the time of admission to the study unit. *The Vanderbilt IRB served as central IRB for sites utilizing a central IRB process.

3. Randomization Assignment Forms

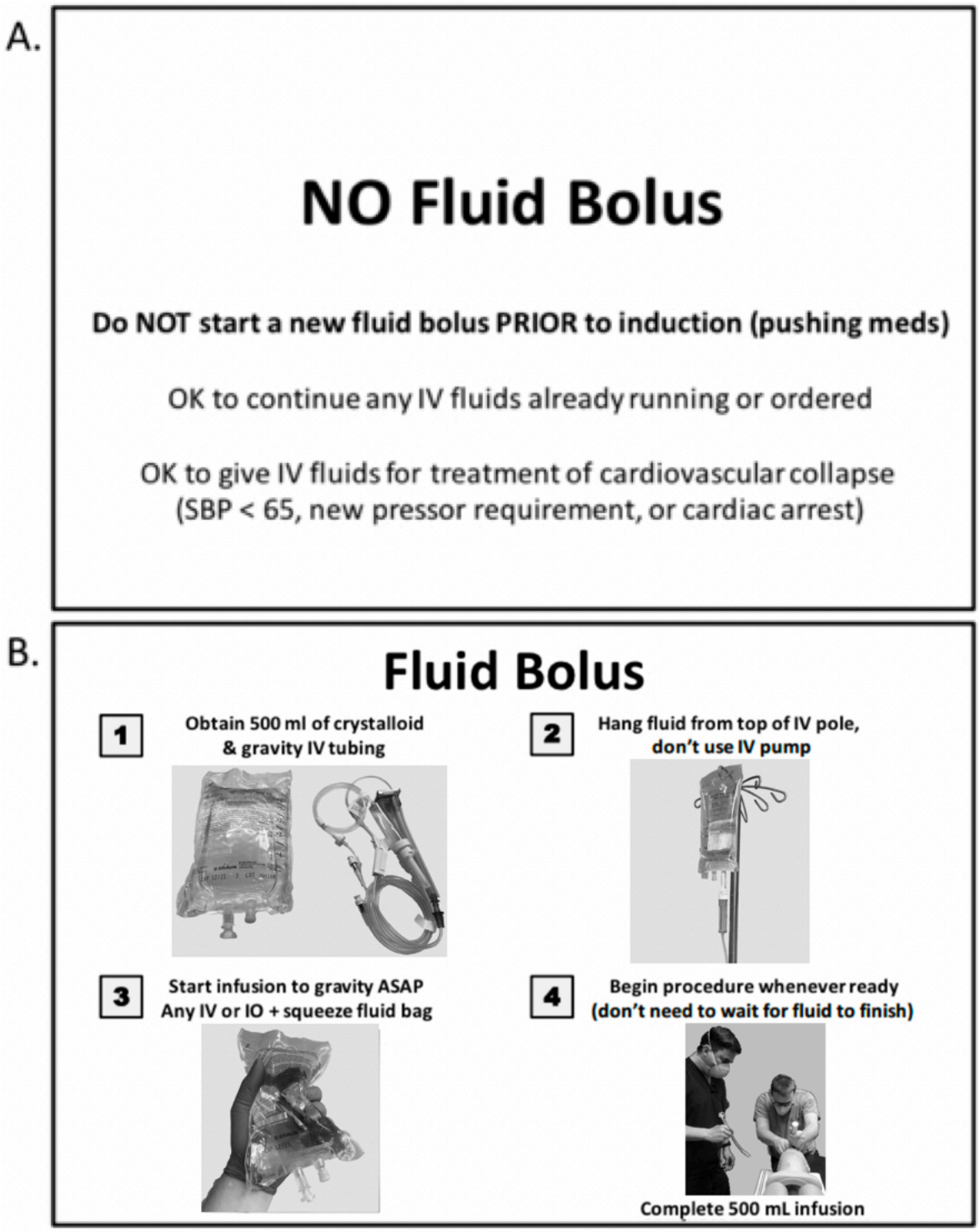

Figure S1: Facsimile of randomization assignment sheets use for subjects randomized to NO Fluid Bolus (A.), and Fluid Bolus (B.) groups. Personnel shown in this figure all consented to the reproduction of their image.

4. Data Collection:

A trained, independent observer not involved in the performance of the procedure collects data for key peri-procedural outcomes including: whether the patient was already receiving an intravenous fluid infusion at the time of enrolment, whether a new fluid bolus was started between randomization and induction, the volume of new fluid bolus infused from randomization to induction, the administration of new or increased vasopressors prior to or with induction, systolic blood pressure and oxygen saturation at the time of induction, the lowest arterial oxygen saturation and systolic blood pressure from induction to two minutes after tracheal intubation, the administration of a new fluid bolus between induction and two minutes after tracheal intubation, the administration of a new or increased dose of any vasopressor between induction and two minutes after tracheal intubation, the total volume of new fluid bolus infused between induction and two minutes after tracheal intubation, and the number of attempts at tracheal intubation.

Immediately following the procedure, the operator records the following information: sedative choice and dose, subjective difficulty of intubation, modality of pre-oxygenation, modality of oxygenation and ventilation between induction and laryngoscopy, laryngoscopy device used for first attempt, whether video or direct laryngoscopy was used on the first attempt, Cormack-Lehane grade of glottic view on the first attempt[1], difficult airway characteristics present (cervical spine immobilization collar, body fluid obscuring the operator's view of the glottis, or facial trauma), use of a bougie or endotracheal tube with stylet on the first attempt, use of rescue equipment (bougie, stylet, video laryngoscope, direct laryngoscope, laryngeal mask airway, bronchoscope, second proceduralist), and procedural complications (cardiac arrest, bradycardia, esophageal intubation, airway trauma, or witnessed aspiration). Operators also report their specialty and number of previous intubation procedures completed.

Study personnel also collect data on baseline characteristics, pre- and post-intubation management, and clinical outcomes from the medical record. The following information is collected from the medical record:

Baseline: Age, gender, height, weight, race, ethnicity, Acute Physiology and Chronic Health Evaluation (APACHE) II score[2], active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, indication for intubation, most recent pre-procedural Glasgow Coma Score[3], non-invasive ventilator and high flow nasal cannula use in the hour prior to starting pre-oxygenation, vasopressor use in the hour preceding enrolment, 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 enrolment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrolment, and whether or not the intubation was a reintubation (defined as patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).

Peri-procedural: type and dose of neuromuscular blocker; laryngoscope used, shape and size of the laryngoscope blade used for first attempt; total number of attempts; subjective assessment of the difficulty of tracheal intubation reported by the operator (easy, moderate, difficult, unknown);

0-24 hours: Cardiac arrest within 1 hour of intubation; death within 1 hour of intubation; systolic blood pressure, oxygen saturation, FiO_2, and positive end expiratory pressure delivered at 24 hours following intubation.

In-Hospital Outcomes: 28 day in-hospital mortality, days from enrolment to death, ventilator-free days, and ICU-free days – all censored at hospital discharge. See **Supplementary file 1, Items 5-8** below for definitions of these terms.

5. Definition of 28-day in-hospital mortality

28-day in-hospital mortality is defined as death from any cause between enrolment and either 28 days from enrolment or discharge from the hospital, whichever comes first.

6. Definition of Ventilator Free Days

Ventilator-free days (VFDs) are defined as the number of days alive and free of invasive mechanical ventilation, from the patient's final extubation to 28 days after enrolment. If a patient returns to invasive mechanical ventilation and is subsequently liberated from invasive mechanical ventilation prior to day 28, the number of VFDs will be counted from the date of the final liberation from invasive mechanical ventilation before day 28. If the patient is receiving invasive mechanical ventilation at day 28 or dies prior to day 28, the number of VFDs will be counted as 0. If a patient is discharged while receiving assisted ventilation, the number of VFDs will be counted as 0. VFDs are counted as 0 in any patients who die before day 28. All data are censored at hospital discharge or 28 days, whichever occurs first (i.e., any liberation from invasive mechanical ventilation after a hospital discharge or after day 28 does not affect VFDs).

7. Definition of ICU-Free Days (ICUFDs)

ICU-FDs are defined as the number of days alive and not admitted to an ICU service, from the patient's final discharge from the ICU service to 28 days after enrolment. If a patient is not discharged from the ICU service by day 28, the number of ICU-FDs will be counted as 0. If a patient is discharged but later admitted again to an ICU service but then is subsequently discharged prior to day 28, ICU-FDs are counted as the number of days from the date of the final ICU discharge to day 28. ICU-FDs are counted as 0 in any patients who die before day 28. All data are censored at hospital discharge or 28 days, whichever comes first (i.e., any readmission to an ICU service after day 28 or after a hospital discharge does not affect VFDs).

8. Definition of "days from enrolment to in-hospital death"

For patients who die prior to hospital discharge, the number of days from enrolment to in-hospital death will be calculated as the number of midnights crossed from the day of enrolment until the day of death. For example, a patient who died on the day of enrolment would have a value for days from extubation to death of "0".

9. Plan for communication of protocol changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, analyses) will be reflected in 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 submitted to the relevant IRBs for tracking and approval

prior to implementation of each 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 provided in the supplementary material for publication.

10. 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. All data available to the coordinating center and investigators at other sites are completely de-identified and contain no PHI. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until. The de-identified dataset housed in REDCap will be accessed by the coordinating center for analyzing and reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. After 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 will be governed by mutual data use agreements.

11. References:

1. Cormack RS, Lehane J. Difficult tracheal intubation in obstetrics. *Anaesthesia* 1984;39(11):1105-11.
2. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med* 1985;13(10):818-29.
3. Jennett B, Teasdale G, Braakman R, et al. Predicting outcome in individual patients after severe head injury. *Lancet* 1976;1(7968):1031-4.