Online Supplementary Material

Study Protocol and Statistical Analysis Plan

Title: PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II)

Manuscript: Effect of fluid bolus administration on cardiovascular collapse among critically ill patients undergoing tracheal intubation: a randomized clinical trial

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

This Supplementary Appendix contains the following items:

(1) Original Study Protocol [dated July 4, 2018]
(2) Final Study Protocol [dated December 20, 2019]
(3) Summary of changes to Study Protocol
(4) Original Statistical Analysis Plan [completed December 26, 2019; submitted January 7, 2020]
(5) Description of Final Statistical Analysis Plan [submitted May 26, 2020; published September 18, 2020]
(6) Statistical Analysis Plan Revision Sequence

(1) Original Study Protocol

Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II)

Title	Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation
Acronym	PREPARE II
Version	Version 1.0
Date	July 4, 2018
Protocol Chair	Derek W. Russell, MD Assistant Professor of Medicine Pulmonary and Critical Care Medicine University of Alabama at Birmingham
Protocol Co-Chair	David R. Janz, MD, MSc Assistant Professor of Medicine Section of Pulmonary/Critical Care & Allergy/Immunology Louisiana State University
Coordinating Center	Vanderbilt University Medical Center DCC Chair: Jonathan D. Casey, MD CCC Chair: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler, MD, MSc
Sponsor	Arthur and Lisa Wheeler Critical Care Research Grant

Table of Contents

PREPARE II Investigators

Lahey Medical Center - James Dargin, Joanne Wozniak**,** Susan Stempek

Lincoln Medical Center - Jason West**,** Nicholas Caputo

Louisiana State University - David R. Janz, Derek J. Vonderhar

Ochsner Health System: Derek J. Vonderhaar, Jairo I. Santanilla, Kevin M. Dischert

University of Alabama at Birmingham –Derek W. Russell, Swati Gulati, Sarah Robison, William S. Stigler

University of Washington - Aaron Joffe;

Vanderbilt University Medical Center - Jonathan D. Casey**,** Matthew W. Semler**,** Michael G. Lester**,** Todd W. Rice**,** Wesley H. Self

Trial Summary

Title: Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II)

Study Sites: Intensive care units (ICUs) and emergency departments (EDs) at Lahey Medical Center, Lincoln Medical Center, Louisiana State University, Ochsner Health System, University of Alabama at Birmingham, University of Washington, and Vanderbilt University Medical Center.

Background: Severe complications are common during endotracheal intubation of critically ill patients. Nearly one in five patients undergoing intubation in the intensive care unit experiences cardiovascular collapse, defined as severe hypotension, vasopressor administration, cardiac arrest or death. Cardiovascular collapse during intubation is associated with increased resource utilization and decreased survival. Administration of 500 mL of intravenous crystalloid solution beginning prior to induction may prevent cardiovascular collapse. The only prior trial examining fluid bolus administration during intubation found no effect on cardiovascular collapse or clinical outcomes overall, but a hypothesis-generating subgroup analysis suggested potential benefit to fluid bolus administration among patients receiving positive pressure ventilation between induction and laryngoscopy. Therefore, we propose a randomized trial comparing fluid bolus administration versus none with regard to cardiovascular collapse among critically adults undergoing intubation with positive pressure ventilation between induction and laryngoscopy.

Primary Aim:

- To compare the effect of administration of a 500 mL fluid bolus versus none on cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy

Primary Hypothesis:

- Administration of a 500 mL fluid bolus will reduce the incidence of cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy

Inclusion Criteria:

1. Patient is undergoing endotracheal intubation in a participating unit
2. Planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Patient is at least 18 years of age
4. Administration of sedation is planned
5. Positive pressure ventilation between induction and laryngoscopy is planned

Exclusion Criteria:

1. Prisoners
2. Pregnant patients
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels administration of a fluid bolus is indicated or contraindicated for the safe performance of the procedure

Consent: Given that (1) administration of a fluid bolus during endotracheal intubation occurs commonly in current practice, (2) there are currently no established risks or benefits with fluid bolus administration versus none in this setting, and (3) treating clinicians will explicitly exclude patients for whom they feel either fluid bolus administration or no fluid bolus administration is required for safe care, we feel this trial poses minimal risk beyond the risks encountered during endotracheal intubation of critically ill adults during routine clinical care. Over 90% of patients undergoing endotracheal intubation in the study locations cannot provide informed consent for the procedure itself, therefore it is impractical to obtain informed consent for research prior to the procedure. Given the minimal risk and impracticality of informed consent, a waiver of informed consent will be requested.

Randomization: Patients will be randomized 1:1 to fluid bolus administration or none.

Study Interventions:

- **Fluid Bolus Group** – (1) 500 mL of an intravenous crystalloid solution of the operator's choosing will be (2) initiated after randomization and prior to induction from (3) above the level of the intravenous or intraosseus access, and (4) allowed to infuse by gravity and bag pressure.

- **No Fluid Bolus Group** – No intravenous fluid administration will be initiated between randomization and induction. The study will not affect intravenous fluid infusions initiated prior to randomization.

Primary Endpoint:

- Cardiovascular collapse, defined as one or more of the following:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation

Secondary Endpoint:

- 28-day in-hospital mortality

Background

Endotracheal intubation is common in the care of critically ill patients (1-3). Complications of intubation in the emergency department (ED) or intensive care unit (ICU) are frequent and are associated with an increased risk of death (1, 2, 4, 5). Preventing complications during urgent and emergent endotracheal intubation is a key focus of clinical care and airway management research (4, 6, 7).

Cardiovascular collapse is defined as severe hypotension, new or increased vasopressor receipt, cardiac arrest, or death. Some airway management experts have proposed that administration of a fluid bolus prior to induction might prevent cardiovascular collapse. A single prior randomized trial (NCT03026777), conducted by our research group in the same centers as the currently proposed trial, found no overall difference in the incidence of cardiovascular collapse with fluid bolus administration compared to none. However, for the subgroup of patients assigned to receive manual ventilation with a bag-valve-mask device between induction and laryngoscopy, administration of a fluid bolus appeared to decrease the incidence of cardiovascular collapse. This hypothesis-generating subgroup analysis requires confirmation in a prospective trial in order to understand whether administration of a fluid bolus prior to induction decreases the incidence of cardiovascular collapse among critically ill adults undergoing endotracheal intubation with positive pressure ventilation between induction and laryngoscopy.

Complications of Endotracheal Intubation of the Critically Ill

Emergent endotracheal intubation of critically ill patients is associated with an increased risk of complications compared to the intubation of patients in the operating room (8). Approximately 30% of emergent endotracheal intubations outside the operating room are associated with complications, including: hypotension, hypoxia, failed intubation, esophageal intubation, airway trauma, aspiration, cardiac arrest, and death (4, 8, 9).

Post-intubation hypotension occurs in 20-40% of intubations among critically ill adults (4, 10). Cardiovascular collapse occurs in almost 20% of intubations in the ICU. Both post-intubation hypotension and cardiovascular collapse are associated increased mortality (10, 11). Post-intubation hypotension and cardiovascular collapse are thought to be due to three potential mechanisms, all of which may respond increased cardiac preload via pre-induction intravenous fluid bolus administration: 1. sedation-induced hypotension, 2. pre-induction hemodynamic instability and increased venous capacitance due to decreased circulating catecholamines, and 3. decreased venous return secondary to positive pressure applied to the thoracic cavity.

Potential Mechanisms of Post-intubation Hypotension in the Critically Ill

A number of mechanisms of post-intubation hypotension may be ameliorated by provision of a fluid bolus:

Sedation-induced hypotension. In an effort to facilitate rapid placement of an endotracheal tube in the trachea, sedating and neuromuscular blocking medications are often chosen by the operator to relax the muscles of the upper airway (12, 13). Propofol and benzodiazepines, commonly selected sedatives to facilitate endotracheal intubation, are commonly associated with post-intubation hypotension. The mechanism by which

propofol induces hypotension is thought to be related the medication's ability to venodilate and decrease preload. In a study of adults undergoing intubation, propofol caused a decrease in systolic blood pressure and increase in venous compliance measured by forearm occlusive plethysmography compared to control patients (14). Additionally, propofol may have a depressive effect on the myocardium and reduce cardiac index beyond an isolated decrease in preload (15). Decreased preload due to venodilation, and a possible decrease in myocardial contractility, are contributors to propofol-associated post-intubation hypotension observed in multiple studies of endotracheal intubation (15-18). The use of midazolam for procedural sedation also results in post-intubation hypotension in critically ill adults (19, 20). Even newer sedative agents used in rapid sequence intubation, such as etomidate and ketamine, can result in venodilation and post-intubation hypotension. Increasing cardiac preload via the administration of an intravenous crystalloid fluid bolus prior to the administration of sedation may reduce the incidence of post-intubation hypotension associated with these medications.

Pre-induction Hemodynamic Instability. Critically ill adults often experience clinical deterioration requiring endotracheal intubation (21-23). In a recent randomized trial of endotracheal intubation for critically ill adults conducted by our group, prior to the start of the procedure patients had severe physiologic derangements resulting in a median APACHE II score of 22. Around 25% of patients were in shock (21, 22). An increase in the APACHE II score by 1 point is associated with a 2% increased risk of post-intubation hypotension (24). Even in the absence of pre-existing shock, in a study of critically ill adults undergoing endotracheal intubation, a pre-procedure shock index (heart rate divided by systolic blood pressure) of ≥ 0.8 was strongly predictive of the development of peri-intubation hypotension (11). Additionally, increasing pre-procedure shock index is also associated with cardiovascular collapse resulting in cardiac arrest (25). These shock and "pre-shock" states seen in critically ill adults are often, in part, a result of decreased cardiac preload due to hypovolemia, and may be amenable to treatment with the administration of an intravenous fluid bolus (26-29).

Patients with shock and "pre-shock" may be dependent on circulating catecholamines to sustain blood pressure. With decreased levels of catecholamines after induction, increased venous capacitance may decrease preload, cardiac output, and mean arterial blood pressure. Again, increasing preload by the pre-induction administration of an intravenous fluid bolus may improve the physiologic derangements commonly seen in critically ill adults and prevent peri-intubation hypotension and cardiovascular collapse.

The New Application of Positive Pressure to the Thoracic Cavity. Venous return to the right atrium is dependent on the pressure gradient between the positive pressure of the extra-thoracic anatomic sites and the negative pressure of the thoracic cavity. The application of positive pressure to the thoracic cavity by non-invasive ventilation, manual ventilation with a bag-valve-mask device, or invasive mechanical ventilation reduces venous return to the right atrium and can cause peri-intubation hypotension or cardiovascular collapse in patients with decreased cardiac preload. In one observational study of critically ill adults with traumatic injuries and presumed hypovolemia, intubation and positive pressure ventilation was independently associated with the new development of hypotension and increased mortality (30). Intravenous administration of a fluid bolus prior to the application of positive pressure may increase extra-thoracic venous pressure, increase cardiac preload, and prevent peri-intubation hypotension and cardiovascular collapse in critically ill adults.

Conversely, fluid bolus could contribute to post-intubation hypotension by certain mechanisms:

Systemic microvascular dysfunction. The provision of a fluid bolus may contribute to cardiovascular collapse by diluting endogenous catecholamines (31) with resultant reduction in vasomotor tone. Fluid bolus mediated increase in right atrial pressure provoke releast of atrial natriuretic peptide, which can cause shedding of the endothelial glycocalyx with resultant increase in capillary leakage (32).

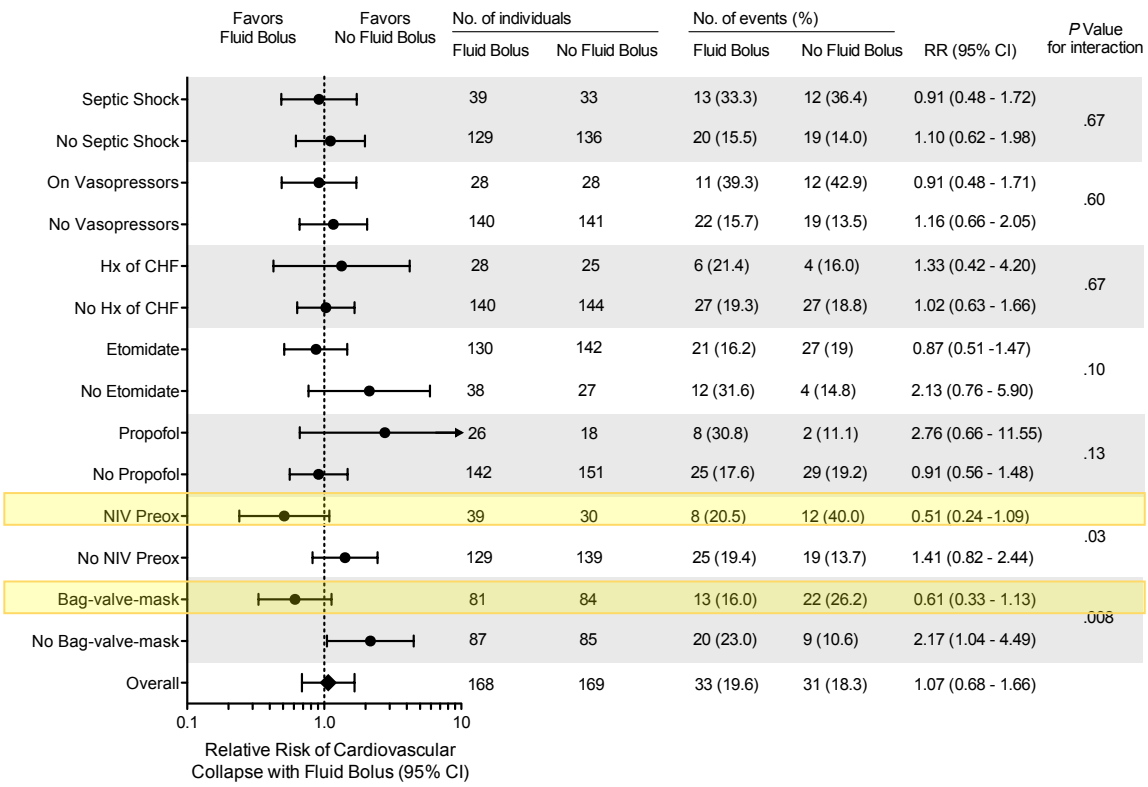
Right ventricular failure. Subjects undergoing endotracheal intubation may experience significant hypoxemia and lung derecruitment, both of which are associated with acutely increased pulmonary vascular resistance and right ventricular dysfunction (33,34). This effect may be exacerbated in subjects not undergoing positive pressure ventilation such as bag-valve mask ventilation during the laryngoscopic period. A fluid bolus during this time of increased pulmonary vascular resistance may cause transient pressure overload of the right ventricle and paradoxical decrease in cardiac output (35). Poor outcomes in hypoxemic patients receiving fluid boluses have been previously described (36).

Existing Evidence on the Use of Fluid Loading to Prevent Post-Intubation Hypotension

Only one prior trial has examined the effect of fluid bolus administration on outcomes of endotracheal intubation among critically ill adults. The PrePARE (Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation) Trial was a pragmatic, multicenter, unblinded, randomized trial conducted between February 6, 2017 and January 9, 2018 (NCT03026777). The PrePARE trial compared administration of a fluid bolus started prior to the administration of procedural medications versus no fluid bolus during endotracheal intubation of critically ill adults. At seven study sites, co-enrollment could occur in a separate randomized trial of bag-valve-mask ventilation (BVM) versus none during endotracheal intubation (NCT03026322).

The PrePARE trial was stopped for futility by the Data and Safety Monitoring Board (DSMB) at a planned interim analysis at the mid-point of the trial. The primary outcome of cardiovascular collapse occurred in 33 of 168 patients (19.6%) in the fluid bolus group compared with 31 of 169 patients (18.3%) in the no fluid bolus group (P = .76). The incidence of each component of the composite outcome did not differ significantly between groups. Study group assignment did not affect oxygen saturation, clinical signs of volume overload, receipt of diuretics, vasopressor receipt, ventilator-free days, vasopressor-free days, or in-hospital mortality.

In the PrePARE trial, however, receipt of positive pressure ventilation appeared to modify the effect of fluid bolus administration on cardiovascular collapse. Patients receiving non-invasive mechanical ventilation or manual ventilation with a bag-valve-mask device appeared to have a lower rate of cardiovascular collapse in the fluid bolus group (**figure below**).



Given the scarcity of evidence on the utility of a pre-intubation fluid bolus administration during endotracheal intubation of critically ill adults, there is significant variability in provider practice, and observational data show that in current usual practice, around 50% of critically ill adults are administered an intravenous fluid bolus during endotracheal intubation (4, 37).

Rationale, Aims, and Hypotheses

To determine the effect of intravenous fluid bolus administration on procedural and clinical outcomes of endotracheal intubation among critically ill patients receiving positive pressure ventilation between induction and laryngoscopy, a randomized trial is needed.

Study Aims:

- **Primary:**
  - To compare the effect of fluid bolus administration versus none on cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy.

- **Secondary:**

- To compare the effect of fluid bolus administration versus none on in-hospital mortality among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy.

Study Hypotheses:

- **Primary:**
  - Among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy, administration of a fluid bolus will reduce the incidence of cardiovascular collapse.

- **Secondary:**
  - Among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy, administration of a fluid bolus will reduce the incidence of 28-day in-hospital mortality.

Study Description

In order to address the aims outlined above, we propose a pragmatic, multi-center, un-blinded, parallel group, randomized trial evaluating the effect of fluid bolus administration on cardiovascular collapse during endotracheal intubation of critically ill adults. Patients admitted to the study sites who are determined by treating clinicians to require intubation and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to fluid bolus administration versus none. All other decisions regarding airway management will remain at the discretion of the treating clinicians. Data will be collected at the time of intubation and prospectively from the medical record in order to determine the effect of the assigned intervention on short- and long-term outcomes. All data are collected non-invasively and are already a part of clinical data obtained in usual care at the bedside or in the medical record. No additional data will be collected that is not observed at the bedside or obtained from the medical record.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Patient is undergoing endotracheal intubation in a participating unit
2. Planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Patient is at least 18 years of age
4. Administration of sedation is planned (with or without neuromuscular blockade)
5. Positive pressure ventilation between induction and laryngoscopy is planned (e.g., non-invasive ventilation or manual ventilation with a bag-valve-mask device)

Exclusion Criteria:

1. Prisoners
2. Pregnant patients
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels administration of a fluid bolus is indicated or contraindicated for the safe performance of the procedure

Patients who do not meet inclusion criteria will be considered 'ineligible'. Patients who meet inclusion criteria, but also meet exclusion criteria 1-3 will be considered 'excluded'. Patients who meet inclusion criteria, but also meet exclusion criteria 4 will be considered 'eligible but not enrolled'. Patients who meet inclusion criteria without meeting exclusion criteria will be enrolled.

Enrollment and Randomization

Study Sites:

Intensive care units (ICUs) and emergency departments (EDs) at Lahey Medical Center, Lincoln Medical Center, Louisiana State University – University Medical Center of New Orleans, Ochsner Health System, University of Alabama at Birmingham, University of Washington, and Vanderbilt University Medical Center.

Study Population

The study population will be critically ill adults for whom the clinical team has decided to perform endotracheal intubation during which sedation and positive pressure ventilation between induction and laryngoscopy are planned. Patients who meet inclusion criteria without meeting exclusion criteria will be included regardless of gender, race, weight or body mass index, initial blood pressure, anticipated grade of view, and other clinical factors.

Enrollment

All patients will be enrolled at the time the clinical team decides that intubation is required and the patient meets inclusion but no exclusion criteria.

Consent

Pre-induction fluid bolus administration and no pre-induction fluid bolus administration are both commonly used approaches during endotracheal of critically ill adults in current practice (4, 38, 39). In prior observational studies of critically ill adults undergoing endotracheal intubation, clinicians have opted to administer a fluid bolus prior to induction in approximately 50% of patients, with significant variability by provider and practice environment (4, 37). Currently, there are no evidence-based guidelines to support the choice between administering a fluid bolus and not administering a fluid bolus prior to endotracheal intubation of critically ill adults in whom positive pressure ventilation is planned. The only randomized trial of this intervention (NCT03026322) in a similar population showed neither harm nor benefit overall, though the effect of fluid bolus administration in the subgroup of patients who receive positive pressure ventilation between induction and laryngoscopy remains unknown.

Because both approaches to peri-intubation fluid management being studied are (1) commonly used as a part of routine care, (2) are interventions to which the patient would likely be exposed even if not participating in the study, and (3) are acceptable options from the perspective of the clinical provider (otherwise patient is excluded), we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Endotracheal intubation of acutely ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the study settings.

Because the study poses minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent.

Randomization:

Computerized randomization using permuted blocks of two, four, or six will be conducted in order to generate a series of study assignments deliberately exceeding the planned enrollment number. Study assignments will be stratified by study site, placed in opaque randomization envelopes, and will be available to operators in the study settings. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study.

Study Procedures

Study Interventions

The study will affect only the initiation of fluid bolus administration for the prevention of cardiovascular collapse between randomization and two minutes after completion of endotracheal intubation. The study will NOT affect fluid administration initiated prior to randomization, fluid administration initiated after two minutes after completion of intubation, or fluid bolus administration for the treatment of cardiovascular collapse. This study will not protocolize any other aspect of endotracheal intubation, such as choice of induction agent and neuromuscular blocker, patient position, choice of laryngoscope – all of which will be determined by the treating clinicians.

Fluid Bolus Group

For patients randomized to fluid bolus administration, the bedside nurse will obtain 500 mL of a crystalloid solution of the operator's choosing, connect this volume to intravenous infusion tubing, and attach the tubing to any intravenous catheter or intraosseous device. The crystalloid solution will then be placed above the level of the intravenous or intraosseous device and allowed to infuse by gravity or pressure bag. At any time after the initiation of fluid bolus administration, the operator can choose to begin the procedure by administering sedation. Fluid loading will continue until all 500 mL are infused. Fluid infusing prior to the decision to perform endotracheal intubation will not be altered by the current study.

No Fluid Bolus Group

For patients randomized to no fluid bolus administration, no additional intravenous crystalloid administration will be initiated between randomization and two minutes after completion of endotracheal intubation. Fluid infusing prior to the decision to perform endotracheal intubation will not be affected by the study. Treating clinicians may initiate a fluid bolus at any time for the treatment of cardiovascular collapse (not considered a protocol violation). Treating clinicians may also initiate a fluid bolus at any time if felt to be mandatory for the safe treatment of the patient (if between randomization and two minutes after intubation and in the absence of cardiovascular collapse this will be recorded as a protocol violation).

Data Collection

All data are collected non-invasively as a part of current usual care. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record.

Baseline: Age, gender, height, weight, race, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, mean arterial pressure and vasopressor use prior to intubation, noninvasive ventilator use, indication for intubation, reintubation, and preoxygenation technique will be collected from the medical record.

Peri-procedural: Date and time of sedative administration, saturation at time of sedative administration, sedative, neuromuscular blocker, device used for pre-oxygenation prior to medication administration, ventilation between induction and laryngoscopy, laryngoscope type and size, total number of attempts, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications (esophageal intubation, aspiration, airway trauma). Lowest arterial oxygen saturation, lowest systolic blood pressure, vasopressor administration, time to intubation, and other key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure.

0-24 hours: Shock or cardiac arrest, oxygen saturation, fraction of inspired oxygen, positive end expiratory pressure, and systolic and mean arterial pressures up to 24 hours after intubation will be collected from the medical record.

In-Hospital Outcomes: Date of extubation (ventilator-free days), date of ICU discharge (ICU-free days), and date of death will be collected from the medical record.

Outcome Measures

Primary Endpoint:

- Cardiovascular collapse, defined as one or more of the following:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation

Secondary Endpoint:

- 28-day in-hospital mortality

Justification of the end-point selection:
Cardiovascular collapse was the primary outcome of the PrePARE I trial, which provide the hypothesis-generating preliminary data on which the PREPARE II trial is designed. Additionally, cardiovascular collapse is a commonly used composite endpoint in airway management research, which is closely associated with longer-term clinical outcomes. In-hospital mortality at 28 days is a traditional patient-centered outcome for critical care clinical trials.

Exploratory (Hypothesis-generating) Endpoints:

Exploratory Efficacy Endpoints

- Each individual component of the composite primary endpoint:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation

- Lowest systolic blood pressure between induction and 2 minutes after intubation
- Change in systolic blood pressure from induction to lowest systolic blood pressure
- Vasopressor-free days to 28 days
- Ventilator-free days to 28 days
- ICU-free days to 28 days

Exploratory Safety Endpoints:

- Lowest arterial oxygen saturation between induction and 2 minutes after intubation
- Incidence of hypoxemia (oxygen saturation < 90%) between induction and 2 minutes after intubation
- Incidence of severe hypoxemia (oxygen saturation < 80%) between induction and 2 minutes after intubation
- Lowest oxygen saturation in the 24 hours after intubation
- Highest fraction of inspired oxygen in the 24 hours after intubation
- Highest positive end expiratory pressure in the 24 hours after intubation
- Lowest systolic blood pressure in the 24 hours after intubation
- Highest vasopressor requirement in the 24 hours after intubation (in norepinephrine equivalents)

Exploratory Process Measures:

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

Risks and Benefits

Among patients for whom the treating team has decided endotracheal intubation is required, there are currently no established risks or benefits to intubation with or without fluid bolus administration. A prior trial of fluid bolus administration in the same study settings did not suggest overall differences between the fluid bolus and no fluid bolus groups in pulmonary edema, oxygen saturation, positive end expiratory pressure, fraction of inspired oxygen, duration of mechanical ventilation, receipt diuretics, or any other procedural or clinical measure.

In addition, the exclusion criteria explicitly exclude patients for whom the treating provider feels a pre-induction fluid bolus administration is needed or is contraindicated. At this time, there is no reason to believe that participation in this study would expose patients to greater medical risks or benefits than those experienced by critically ill patients requiring endotracheal intubation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective airway management for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

Safety Monitoring and Adverse Events

Safety Monitoring

This study will take place in the environment of an intensive care unit at the time of a procedure required for routine clinical care. Thus, at the time of the study intervention, the patient will have in the room a physician trained in the care of critically ill adults, a nurse trained in critical care, and usually a respiratory therapist in addition to continuous invasive or non-invasive monitoring. Additionally, study personnel will be readily available to answer questions at any time during the study course. Even after randomization, if any healthcare provider participating in the intubation procedure believes that the study interventions cannot be performed for the safe performance of the procedure, the study intervention is halted and the patient is intubated in the manner which the clinical team judges to be safest.

A Data and Safety Monitoring Board (DSMB) will oversee the trial. Interim analyses for safety and efficacy will be conducted as described in the Statistical Analysis section of the protocol.

Adverse Events

For this trial, an adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation where a participant is administered an intervention that does not necessarily have to have a causal relationship with the intervention. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

For this trial, a serious adverse event (SAE) is defined as an (1) unexpected and untoward medical occurrence (2) determined by the study investigators or treating clinicians to be either probably or possibly related to the study (3) meeting any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death were it more severe). Life-threatening cardiovascular complications, as defined as the primary endpoint of this trial, will be prospectively and systematically collected as the outcome. As such, these events will not be reported as SAEs. Similarly, life-threatening severe hypoxia will also be systematically collected as a secondary endpoint and will therefore not be reported as an SAE.
c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity

f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events. SAEs will be recorded in a case report form in the study record and reported to the IRB within 7 business days.

Endotracheal intubation of critically ill adults during routine care is independently associated with adverse outcomes including but not limited to: death, cardiac arrest, cardiovascular collapse, hypotension, hypoxemia, esophageal intubation, and failed intubation. These events will be identified as study outcomes and systematically collected in both groups rather than relying on sporadic reporting as adverse events. These outcomes will not be individually reported as adverse events unless they qualify as an SAE. These outcomes will be available for review by the DSMB at the interim analysis and as requested.

Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

Statistical Considerations

Sample Size Determination:

In a prior randomized trial comparing fluid bolus administration to no fluid bolus administration prior to induction 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 in that trial assigned to receive manual ventilation with a bag-valve-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, we will plan to enroll 750 patients.

Statistical Analysis:

Prior to the conclusion of enrollment, we will make publically available a complete, final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

Primary Analysis:

Unadjusted test of treatment effect. 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 a chi-square comparison.

Secondary Analysis:

Unadjusted test of treatment effect. The 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. Between group differences will be tested using a chi-square comparison. All comparisons apart from the primary and secondary analyses will be considered exploratory analyses.

Exploratory Analyses:

Analysis of Exploratory Outcomes. We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the fluid bolus group to patients randomized to the no fluid bolus group with regard to exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test.

Per-Protocol Analysis of Primary Outcome. In addition to the intention-to-treat analysis, we will conduct a per-protocol analysis comparing the primary outcome between patients in which the entire 500 mL of fluid was infused to patients who received no fluid.

Heterogeneity of Treatment Effect (Subgroup Analyses). We will examine whether pre-specified baseline covariates modify the effect of treatment group on the primary outcome using formal tests of statistical interaction.

Interim Analysis:

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, after enrollment of 375 patients. The stopping boundary for efficacy will be met if the P value for the difference in the incidence of the primary outcome (cardiovascular collapse) or secondary outcome (28-day in-hospital mortality)

between groups using a chi-square test is 0.001 or less. Assuming a 25.0% incidence of cardiovascular collapse in the no fluid bolus group, these criteria would allow 80% statistical power to detect a difference for a 12% absolute risk reduction (53% relative risk reduction). Using this conservative Haybittle–Peto boundary ($P \leq 0.001$) will allow the final analysis to be performed using an unchanged level of significance.

The DSMB will also formally evaluate the safety of the trial at the interim analysis. The DSMB will review the lowest oxygen saturation, highest fraction of inspired oxygen, and highest positive end expiratory pressure in the 24 hours after intubation in each group. If the *P* value for the difference between study groups in any of these three physiologic variables is 0.001 and is concordant in direction with the point-estimate for mortality, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

Finally, at the interim analysis, the DSMB will monitor 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.

Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

Follow-up and Record Retention

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

References

1. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114:42–48.
2. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;108:792–799.
3. Leibowitz AB. Tracheal intubation in the intensive care unit: extremely hazardous even in the best of hands. *Crit Care Med* 2006;34:2497–2498.
4. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, Verzilli D, Jonquet O, Eledjam J-J, Lefrant J-Y. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36:248–255.
5. Griesdale DEG, Bosma TL, Kurth T, Isac G, Chittock DR. Complications of endotracheal intubation in the critically ill. *Intensive Care Med* 2008;34:1835–1842.
6. van Zundert A, Pieters B, Doerges V, Gatt S. Videolaryngoscopy allows a better view of the pharynx and larynx than classic laryngoscopy. *Br J Anaesth* 2012;109:1014–1015.
7. Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltramini A, Gamand P, Albizzati S, Perdrizet D, Lebail G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant J-Y, Bollaert P-E, Megarbane B, Ricard J-D, Anguel N, Vicaut E, Adnet F, KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009;374:293–300.
8. Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *Br J Anaesth* 2011;106:632–642.
9. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth* 2004;16:508–516.
10. Green RS, Turgeon AF, McIntyre LA, Fox-Robichaud AE, Fergusson DA, Doucette S, Butler MB, Erdogan M, Canadian Critical Care Trials Group (CCCTG). Postintubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30:1055–1060.
11. Heffner AC, Swords DS, Nussbaum ML, Kline JA, Jones AE. Predictors of the complication of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27:587–593.
12. Walz JM, Zayaruzny M, Heard SO. Airway management in critical illness. *Chest* 2007;131:608–620.
13. Natt BS, Malo J, Hypes CD, Sakles JC, Mosier JM. Strategies to improve first attempt success at intubation in critically ill patients. In: Asai T, editor. *Br J Anaesth* 2016;aew061.doi:10.1093/bja/aew061.
14. Muzi M, Berens RA, Kampine JP, Ebert TJ. Venodilation contributes to propofol-mediated hypotension in humans. *Anesth Analg* 1992;74:877–883.
15. Möller Petrun A, Kamenik M. Bispectral index-guided induction of general

anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. *Br J Anaesth* 2013;110:388–396.
16. Shah SB, Chowdhury I, Bhargava AK, Sabbharwal B. Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels. *J Anaesthesiol Clin Pharmacol* 2015;31:180–185.
17. Kaushal RP, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. *Ann Card Anaesth* 2015;18:172–178.
18. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, Bodian CA. Predictors of hypotension after induction of general anesthesia. *Anesth Analg* 2005;101:622–8– table of contents.
19. Choi YF, Wong TW, Lau CC. Midazolam is more likely to cause hypotension than etomidate in emergency department rapid sequence intubation. *Emerg Med J* 2004;21:700–702.
20. Davis DP, Kimbro TA, Vilke GM. The use of midazolam for prehospital rapid-sequence intubation may be associated with a dose-related increase in hypotension. *Prehosp Emerg Care* 2001;5:163–168.
21. Janz DR, Semler MW, Lentz RJ, Matthews DT, Assad TR, Norman BC, Keriwala RD, Ferrell BA, Noto MJ, Shaver CM, Richmond BW, Zinggeler Berg J, Rice TW, Facilitating EndotracheaL intubation by Laryngoscopy technique and apneic Oxygenation Within the ICU Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Video Laryngoscopy for Endotracheal Intubation of Critically Ill Adults. *Crit Care Med* 2016;doi:10.1097/CCM.0000000000001841.
22. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE, Rice TW, FELLOW Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med* 2016;193:273–280.
23. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016;44:120–129.
24. Perbet S, De Jong A, Delmas J, Futier E, Pereira B, Jaber S, Constantin J-M. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. *Crit Care* 2015;19:257.
25. Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. *Resuscitation* 2013;84:1500–1504.
26. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683–1693.
27. Semler MW, Rice TW. Sepsis Resuscitation: Fluid Choice and Dose. *Clin Chest Med* 2016;37:241–250.
28. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, SPLIT Investigators, ANZICS CTG. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical

Trial. *JAMA* 2015;314:1701–1710.
29. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013. pp. 580–637.
30. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. *J Trauma* 2005;59:1140–5– discussion 1145–7.
337. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal J-M, Guitton C, Allaouchiche B, Paugam-Burtz C, Constantin J-M, Lefrant J-Y, Leone M, Papazian L, Asehnoune K, Maziers N, Azoulay E, Pradel G, Jung B, Jaber S, AzuRéa Network for the Frida-Réa Study Group. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187:832–839.
38. Boyd JH, Forbes J, Nakada T-A, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39:259–265.
39. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.

(2) Final Study Protocol

Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II)

Title	Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation
Acronym	PREPARE II
Version	Version 1.2
Date	December 20, 2019
Protocol Chair	Derek W. Russell, MD Assistant Professor of Medicine Pulmonary and Critical Care Medicine University of Alabama at Birmingham
Protocol Co-Chair	David R. Janz, MD, MSc Assistant Professor of Medicine Section of Pulmonary/Critical Care & Allergy/Immunology Louisiana State University
Coordinating Center	Vanderbilt University Medical Center DCC Chair: Jonathan D. Casey, MD CCC Chair: Todd W. Rice, MD, MSc
Network	Pragmatic Critical Care Research Group (PCCRG) Steering Committee Chair: Matthew W. Semler, MD, MSc
Sponsor	Arthur and Lisa Wheeler Critical Care Research Grant

Table of Contents

PREPARE II Investigators

Baylor Scott & White Medical Center-Temple – Shekhar Ghamande; Heath White

Lahey Medical Center - James Dargin, Joanne Wozniak**,** Susan Stempek

Louisiana State University - David R. Janz, Derek J. Vonderhar

Ochsner Health System: Derek J. Vonderhaar, Jairo I. Santanilla, Kevin M. Dischert

Oregon Health & Science University – Akram Khan

University of Alabama at Birmingham –Derek W. Russell, Swati Gulati, Sarah Robison, William S. Stigler

University of Mississippi Medical Center – Joseph M. Brewer

University of Washington - Aaron Joffe;

Vanderbilt University Medical Center - Jonathan D. Casey**,** Matthew W. Semler**,** Michael G. Lester**,** Todd W. Rice**,** Wesley H. Self

Wake Forest Baptist Medical Center – Kevin W. Gibbs

Trial Summary

Title: Preventing cardiovascular collapse with Administration of fluid Resuscitation during Induction and Intubation (PREPARE II)

Study Sites: Intensive care units (ICUs) at Baylor Scott & White Medical Center – Temple, Lahey Medical Center, Louisiana State University, Ochsner Health System, Oregon Health & Science University, University of Alabama at Birmingham, University of Mississippi Medical Center, University of Washington, Wake Forest Baptist Medical Center, Hennepin County Medical Center, and Vanderbilt University Medical Center.

Background: Severe complications are common during endotracheal intubation of critically ill patients. Nearly one in five patients undergoing intubation in the intensive care unit experiences cardiovascular collapse, defined as severe hypotension, vasopressor administration, cardiac arrest or death. Cardiovascular collapse during intubation is associated with increased resource utilization and decreased survival. Administration of 500 mL of intravenous crystalloid solution beginning prior to induction may prevent cardiovascular collapse. The only prior trial examining fluid bolus administration during intubation found no effect on cardiovascular collapse or clinical outcomes overall, but a hypothesis-generating subgroup analysis suggested potential benefit to fluid bolus administration among patients receiving positive pressure ventilation between induction and laryngoscopy. Therefore, we propose a randomized trial comparing fluid bolus administration versus none with regard to cardiovascular collapse among critically adults undergoing intubation with positive pressure ventilation between induction and laryngoscopy.

Primary Aim:

- To compare the effect of administration of a 500 mL fluid bolus versus none on cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy

Primary Hypothesis:

- Administration of a 500 mL fluid bolus will reduce the incidence of cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy

Inclusion Criteria:

1. Patient is undergoing endotracheal intubation in a participating unit
2. Planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Patient is at least 18 years of age
4. Administration of sedation is planned (with or without neuromuscular blockade)
5. Positive pressure ventilation between induction and laryngoscopy is planned (e.g., non-invasive ventilation or bag-mask ventilation)

Exclusion Criteria:

1. Prisoners
2. Pregnant patients
3. Urgency of intubation precludes safe performance of study procedures

4. Operator feels administration of a fluid bolus is indicated or contraindicated for the safe performance of the procedure

Consent: Given that (1) administration of a fluid bolus during endotracheal intubation occurs commonly in current practice, (2) there are currently no established risks or benefits with fluid bolus administration versus none in this setting, and (3) treating clinicians will explicitly exclude patients for whom they feel either fluid bolus administration or no fluid bolus administration is required for safe care, we feel this trial poses no more than minimal risk beyond the risks encountered during endotracheal intubation of critically ill adults during routine clinical care. Over 90% of patients undergoing endotracheal intubation in the study locations cannot provide informed consent for the procedure itself, therefore it is impractical to obtain informed consent for research prior to the procedure. Given the minimal risk and impracticality of informed consent, a waiver of informed consent will be requested.

Randomization: Patients will be randomized 1:1 to fluid bolus administration or none.

Study Interventions:

- **Fluid Bolus Group** – (1) 500 mL of an intravenous crystalloid solution of the operator's choosing will be (2) initiated after randomization and prior to induction from (3) above the level of the intravenous or intraosseus access, and (4) allowed to infuse by gravity and bag pressure.

- **No Fluid Bolus Group** – No intravenous fluid administration will be initiated between randomization and induction. The study will not affect intravenous fluid infusions initiated prior to randomization.

Primary Endpoint:

- Cardiovascular collapse, defined as one or more of the following:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation

Secondary Endpoint:

- 28-day in-hospital mortality

Background

Endotracheal intubation is common in the care of critically ill patients (1-3). Complications of intubation in the emergency department (ED) or intensive care unit (ICU) are frequent and are associated with an increased risk of death (1, 2, 4, 5). Preventing complications during urgent and emergent endotracheal intubation is a key focus of clinical care and airway management research (4, 6, 7).

Cardiovascular collapse is defined as severe hypotension, new or increased vasopressor receipt, cardiac arrest, or death. Some airway management experts have proposed that administration of a fluid bolus prior to induction might prevent cardiovascular collapse. A single prior randomized trial (NCT03026777), conducted by our research group in the same centers as the currently proposed trial, found no overall difference in the incidence of cardiovascular collapse with fluid bolus administration compared to none. However, for the subgroup of patients assigned to bag-mask ventilation between induction and laryngoscopy, administration of a fluid bolus appeared to decrease the incidence of cardiovascular collapse. This hypothesis-generating subgroup analysis requires confirmation in a prospective trial in order to understand whether administration of a fluid bolus prior to induction decreases the incidence of cardiovascular collapse among critically ill adults undergoing endotracheal intubation with positive pressure ventilation between induction and laryngoscopy.

Complications of Endotracheal Intubation of the Critically Ill

Emergent endotracheal intubation of critically ill patients is associated with an increased risk of complications compared to the intubation of patients in the operating room (8). Approximately 30% of emergent endotracheal intubations outside the operating room are associated with complications, including: hypotension, hypoxia, failed intubation, esophageal intubation, airway trauma, aspiration, cardiac arrest, and death (4, 8, 9).

Post-intubation hypotension occurs in 20-40% of intubations among critically ill adults (4, 10). Cardiovascular collapse occurs in almost 20% of intubations in the ICU. Both post-intubation hypotension and cardiovascular collapse are associated increased mortality (10, 11). Post-intubation hypotension and cardiovascular collapse are thought to be due to three potential mechanisms, all of which may respond increased cardiac preload via pre-induction intravenous fluid bolus administration: 1. sedation-induced hypotension, 2. pre-induction hemodynamic instability and increased venous capacitance due to decreased circulating catecholamines, and 3. decreased venous return secondary to positive pressure applied to the thoracic cavity.

Potential Mechanisms of Post-intubation Hypotension in the Critically Ill

A number of mechanisms of post-intubation hypotension may be ameliorated by provision of a fluid bolus:

Sedation-induced hypotension. In an effort to facilitate rapid placement of an endotracheal tube in the trachea, sedating and neuromuscular blocking medications are often chosen by the operator to relax the muscles of the upper airway (12, 13). Propofol and benzodiazepines, commonly selected sedatives to facilitate endotracheal intubation, are commonly associated with post-intubation hypotension. The mechanism by which propofol induces hypotension is thought to be related the medication's ability to

venodilate and decrease preload. In a study of adults undergoing intubation, propofol caused a decrease in systolic blood pressure and increase in venous compliance measured by forearm occlusive plethysmography compared to control patients (14). Additionally, propofol may have a depressive effect on the myocardium and reduce cardiac index beyond an isolated decrease in preload (15). Decreased preload due to venodilation, and a possible decrease in myocardial contractility, are contributors to propofol-associated post-intubation hypotension observed in multiple studies of endotracheal intubation (15-18). The use of midazolam for procedural sedation also results in post-intubation hypotension in critically ill adults (19, 20). Even newer sedative agents used in rapid sequence intubation, such as etomidate and ketamine, can result in venodilation and post-intubation hypotension. Increasing cardiac preload via the administration of an intravenous crystalloid fluid bolus prior to the administration of sedation may reduce the incidence of post-intubation hypotension associated with these medications.

Pre-induction Hemodynamic Instability. Critically ill adults often experience clinical deterioration requiring endotracheal intubation (21-23). In a recent randomized trial of endotracheal intubation for critically ill adults conducted by our group, prior to the start of the procedure patients had severe physiologic derangements resulting in a median APACHE II score of 22. Around 25% of patients were in shock (21, 22). An increase in the APACHE II score by 1 point is associated with a 2% increased risk of post-intubation hypotension (24). Even in the absence of pre-existing shock, in a study of critically ill adults undergoing endotracheal intubation, a pre-procedure shock index (heart rate divided by systolic blood pressure) of ≥ 0.8 was strongly predictive of the development of peri-intubation hypotension (11). Additionally, increasing pre-procedure shock index is also associated with cardiovascular collapse resulting in cardiac arrest (25). These shock and “pre-shock” states seen in critically ill adults are often, in part, a result of decreased cardiac preload due to hypovolemia, and may be amenable to treatment with the administration of an intravenous fluid bolus (26-29).

Patients with shock and “pre-shock” may be dependent on circulating catecholamines to sustain blood pressure. With decreased levels of catecholamines after induction, increased venous capacitance may decrease preload, cardiac output, and mean arterial blood pressure. Again, increasing preload by the pre-induction administration of an intravenous fluid bolus may improve the physiologic derangements commonly seen in critically ill adults and prevent peri-intubation hypotension and cardiovascular collapse.

The New Application of Positive Pressure to the Thoracic Cavity. Venous return to the right atrium is dependent on the pressure gradient between the positive pressure of the extra-thoracic anatomic sites and the negative pressure of the thoracic cavity. The application of positive pressure to the thoracic cavity by non-invasive ventilation, bag-mask ventilation, or invasive mechanical ventilation reduces venous return to the right atrium and can cause peri-intubation hypotension or cardiovascular collapse in patients with decreased cardiac preload. In one observational study of critically ill adults with traumatic injuries and presumed hypovolemia, intubation and positive pressure ventilation was independently associated with the new development of hypotension and increased mortality (30). Intravenous administration of a fluid bolus prior to the application of positive pressure may increase extra-thoracic venous pressure, increase cardiac preload, and prevent peri-intubation hypotension and cardiovascular collapse in critically ill adults.

Conversely, fluid bolus could contribute to post-intubation hypotension by certain mechanisms:

Systemic microvascular dysfunction. The provision of a fluid bolus may contribute to cardiovascular collapse by diluting endogenous catecholamines (31) with resultant reduction in vasomotor tone. Fluid bolus mediated increase in right atrial pressure provoke release of atrial natriuretic peptide, which can cause shedding of the endothelial glycocalyx with resultant increase in capillary leakage (32).

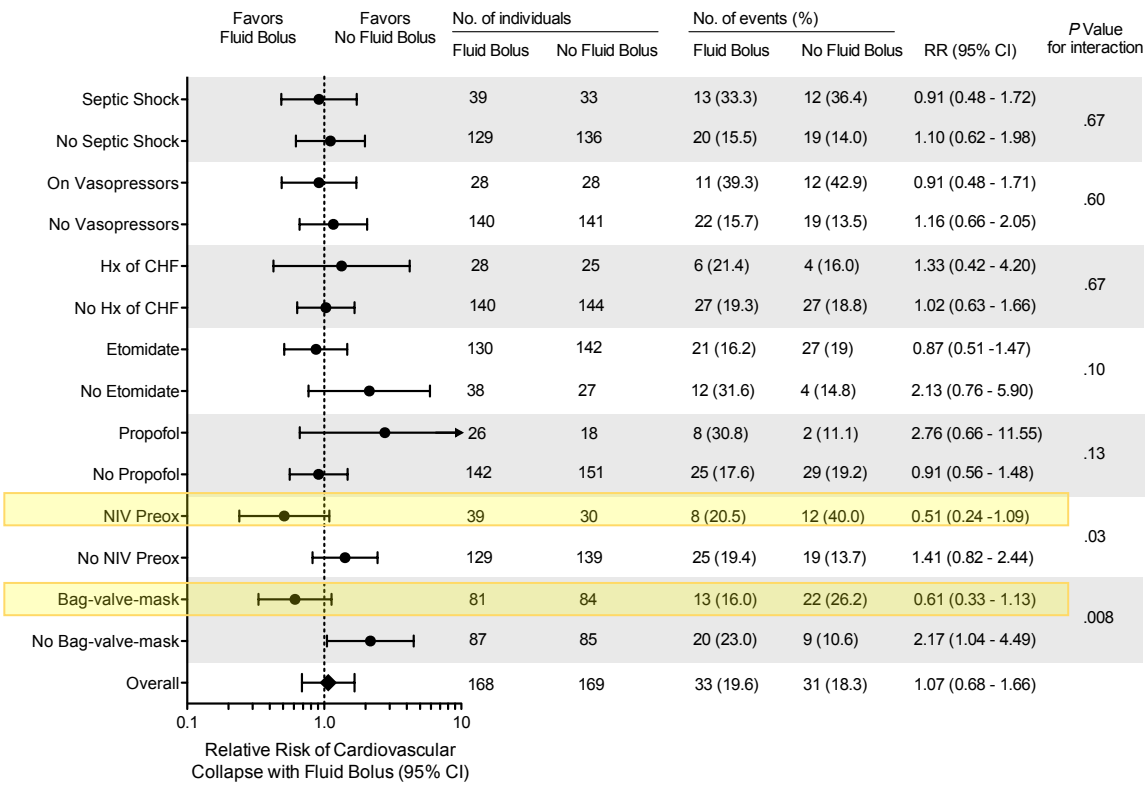
Right ventricular failure. Subjects undergoing endotracheal intubation may experience significant hypoxemia and lung derecruitment, both of which are associated with acutely increased pulmonary vascular resistance and right ventricular dysfunction (33,34). This effect may be exacerbated in patients who do not receive positive pressure, from non-invasive ventilation or bag-mask ventilation between induction and laryngoscopy. A fluid bolus during this period of increased pulmonary vascular resistance may cause transient pressure overload of the right ventricle and paradoxical decrease in cardiac output (35). Poor outcomes in hypoxemic patients receiving fluid boluses have been previously described (36).

Existing Evidence on the Use of Fluid Loading to Prevent Post-Intubation Hypotension

Only one prior trial has examined the effect of fluid bolus administration on outcomes of endotracheal intubation among critically ill adults. The PrePARE (Preventing cardiovascular collaPse with Administration of fluid Resuscitation before Endotracheal intubation) Trial was a pragmatic, multicenter, unblinded, randomized trial conducted between February 6, 2017 and January 9, 2018 (NCT03026777). The PrePARE trial compared administration of a fluid bolus started prior to the administration of procedural medications versus no fluid bolus during endotracheal intubation of critically ill adults. At seven study sites, co-enrollment could occur in a separate randomized trial of bag-valve-mask ventilation (BVM) versus none during endotracheal intubation (NCT03026322).

The PrePARE trial was stopped for futility by the Data and Safety Monitoring Board (DSMB) at a planned interim analysis at the mid-point of the trial. The primary outcome of cardiovascular collapse occurred in 33 of 168 patients (19.6%) in the fluid bolus group compared with 31 of 169 patients (18.3%) in the no fluid bolus group (P = .76). The incidence of each component of the composite outcome did not differ significantly between groups. Study group assignment did not affect oxygen saturation, clinical signs of volume overload, receipt of diuretics, vasopressor receipt, ventilator-free days, vasopressor-free days, or in-hospital mortality.

However, the receipt of positive pressure ventilation appeared to modify the effect of fluid bolus administration on cardiovascular collapse. Patients who received positive pressure from non-invasive mechanical ventilation or bag-mask ventilation appeared to have a lower rate cardiovascular collapse in the fluid bolus group, compared to the no fluid bolus group (**figure below**).



Given the scarcity of evidence on the utility of a pre-intubation fluid bolus administration during endotracheal intubation of critically ill adults, there is significant variability in provider practice, and observational data show that in current usual practice, around 50% of critically ill adults are administered an intravenous fluid bolus during endotracheal intubation (4, 37).

Rationale, Aims, and Hypotheses

To determine the effect of intravenous fluid bolus administration on procedural and clinical outcomes of endotracheal intubation among critically ill patients receiving positive pressure ventilation between induction and laryngoscopy, a randomized trial is needed.

Study Aims:

- **Primary:**
  - To compare the effect of fluid bolus administration versus none on cardiovascular collapse among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy.

- **Secondary:**

- To compare the effect of fluid bolus administration versus none on in-hospital mortality among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy.

Study Hypotheses:

- **Primary:**
  - Among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy, administration of a fluid bolus will reduce the incidence of cardiovascular collapse.

- **Secondary:**
  - Among critically ill adults undergoing endotracheal intubation with planned positive pressure ventilation between induction and laryngoscopy, administration of a fluid bolus will reduce the incidence of 28-day in-hospital mortality.

Study Description

In order to address the aims outlined above, we propose a pragmatic, multi-center, un-blinded, parallel group, randomized trial evaluating the effect of fluid bolus administration on cardiovascular collapse during endotracheal intubation of critically ill adults receiving positive pressure ventilation between induction and laryngoscopy. Patients admitted to the study sites who are determined by treating clinicians to require intubation and fulfill inclusion criteria without meeting exclusion criteria will be enrolled and randomly assigned to fluid bolus administration versus none. All other decisions regarding airway management will remain at the discretion of the treating clinicians. Data will be collected at the time of intubation and prospectively from the medical record in order to determine the effect of the assigned intervention on short- and long-term outcomes. All data are collected non-invasively and are already a part of clinical data obtained in usual care at the bedside or in the medical record. No additional data will be collected that is not observed at the bedside or obtained from the medical record.

Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Patient is undergoing endotracheal intubation in a participating unit
2. Planned operator is a provider expected to routinely perform endotracheal intubation in the participating unit
3. Patient is at least 18 years of age
4. Administration of sedation is planned (with or without neuromuscular blockade)
5. Positive pressure ventilation between induction and laryngoscopy is planned (e.g., non-invasive ventilation or bag-mask ventilation)

Exclusion Criteria:

1. Prisoners
2. Pregnant patients
3. Urgency of intubation precludes safe performance of study procedures
4. Operator feels administration of a fluid bolus is indicated or contraindicated for the safe performance of the procedure

Patients who do not meet inclusion criteria will be considered 'ineligible'. Patients who meet inclusion criteria, but also meet exclusion criteria 1-3 will be considered 'excluded'. Patients who meet inclusion criteria, and meet only exclusion criteria 4 will be considered 'eligible but not enrolled'. Patients who meet inclusion criteria without meeting exclusion criteria will be enrolled.

Enrollment and Randomization

Study Sites:

Intensive care units (ICUs) at Baylor Scott & White Medical Center – Temple, Lahey Medical Center, Louisiana State University – University Medical Center of New Orleans, Ochsner Health System, Oregon Health & Science University, University of Alabama at Birmingham, , University of Mississippi Medical Center, University of Washington, Wake Forest Baptist Medical Center, Hennepin County Medical Center, and Vanderbilt University Medical Center.

Study Population

The study population will be critically ill adults for whom the clinical team has decided to perform endotracheal intubation during which sedation and positive pressure ventilation between induction and laryngoscopy are planned. Patients who meet inclusion criteria without meeting exclusion criteria will be included regardless of gender, race, weight or body mass index, initial blood pressure, anticipated grade of view, and other clinical factors.

Enrollment

All patients will be enrolled at the time the clinical team decides that intubation is required and the patient meets inclusion but no exclusion criteria.

Consent

Pre-induction fluid bolus administration and no pre-induction fluid bolus administration are both commonly used approaches during endotracheal intubation of critically ill adults in current practice (4, 38, 39). In prior observational studies of critically ill adults undergoing endotracheal intubation, clinicians have opted to administer a fluid bolus prior to induction in approximately 50% of patients, with significant variability by provider and practice environment (4, 37). Currently, there are no evidence-based guidelines to support the choice between administering a fluid bolus and not administering a fluid bolus prior to endotracheal intubation of critically ill adults in whom positive pressure ventilation is planned. The only randomized trial of this intervention (NCT03026322) in a similar population showed neither harm nor benefit overall, though the effect of fluid bolus administration in the subgroup of patients who receive positive pressure ventilation between induction and laryngoscopy remains unknown.

Because both approaches to peri-intubation fluid management being studied are (1) commonly used as a part of routine care, (2) are interventions to which the patient would likely be exposed even if not participating in the study, and (3) are acceptable options from the perspective of the clinical provider (otherwise patient is excluded), we feel the study meets criteria for minimal risk.

Additionally, obtaining informed consent in the study would be impracticable. Endotracheal intubation of acutely ill patients is frequently a time-sensitive procedure. Despite the availability of a formal informed consent document for the procedure itself, time allows discussion of risks and benefits in less than 10% of airway management events in the study settings.

Because the study poses minimal risk, would not adversely affect the welfare or privacy rights of the participant, and consent would be impracticable, we will request a waiver of informed consent. Information regarding the study will be made available to patients and families by one of three mechanisms: (1) a patient and family notification sheet provided to each patient and family following enrollment informing the patient of his or her enrollment and describing the study, (2) a patient and family information sheet posted in at least three publicly-visible locations within the study unit containing general information about the study and contact information for the research team for additional questions or concerns, (3) a patient and family information sheet provided to each patient and family on admission as part of an “admission packet” containing general study information and contact information for the research team for additional questions or concerns. Which mechanism of providing information to patients and families will be used at each study site will be determined by site investigators in coordination with the local context assessment of the site IRB.

Randomization:

Computerized randomization using permuted blocks of two, four, or six will be conducted in order to generate a series of study assignments deliberately exceeding the planned enrollment number. Study assignments will be stratified by study site, placed in opaque randomization envelopes, and will be available to operators in the study settings. Study group assignment will remain concealed to study personnel and operators until after the decision has been made to enroll the patient in the study.

Study Procedures

Study Interventions

The study will affect only the initiation of fluid bolus administration for the prevention of cardiovascular collapse between randomization and two minutes after completion of endotracheal intubation. The study will NOT affect fluid administration initiated prior to randomization, fluid administration initiated after two minutes after completion of intubation, or fluid bolus administration for the treatment of cardiovascular collapse. This study will not protocolize any other aspect of endotracheal intubation, such as choice of induction agent and neuromuscular blocker, patient position, choice of laryngoscope – all of which will be determined by the treating clinicians.

Fluid Bolus Group

For patients randomized to fluid bolus administration, the bedside nurse will obtain 500 mL of a crystalloid solution of the operator's choosing, connect this volume to intravenous infusion tubing, and attach the tubing to any intravenous catheter or intraosseous device. The crystalloid solution will then be placed above the level of the intravenous or intraosseous device and allowed to infuse by gravity or pressure bag. At any time after the initiation of fluid bolus administration, the operator can choose to begin the procedure by administering sedation. Fluid loading will continue until all 500 mL are infused. Fluid infusing prior to the decision to perform endotracheal intubation will not be altered by the current study.

No Fluid Bolus Group

For patients randomized to no fluid bolus administration, no additional intravenous crystalloid administration will be initiated between randomization and two minutes after completion of endotracheal intubation. Fluid infusing prior to the decision to perform endotracheal intubation will not be affected by the study. Treating clinicians may initiate a fluid bolus at any time for the treatment of cardiovascular collapse (not considered a protocol violation). Treating clinicians may also initiate a fluid bolus at any time if felt to be mandatory for the safe treatment of the patient (if between randomization and two minutes after intubation and in the absence of cardiovascular collapse this will be recorded as a protocol violation).

Data Collection

All data are collected non-invasively as a part of current usual care. No additional data will be obtained beyond that which is obtained by bedside observation and from the electronic medical record.

Baseline: Age, gender, height, weight, race, ethnicity, APACHE II score, active medical problems at the time of intubation, active comorbidities complicating intubation, vasopressor use in the hour prior to enrollment, most recent pre-procedural GCS, noninvasive ventilator and high flow nasal cannula use in the hour prior to starting pre-oxygenation, indication for intubation, whether or not the intubation is a reintubation

(intubation within 72 hours of prior extubation), presence of sepsis or septic shock at the time of enrollment, highest FiO2 in the hours preceding enrollment.

Peri-procedural: Intravenous fluid being administered at time of enrollment, administration of new fluid bolus after enrollment, volume of fluid administered between enrollment and induction, volume of fluid administered between enrollment and two minutes after intubation, oxygen saturation at time of sedative administration, blood pressure at time of sedative administration, type and dose of sedative and neuromuscular blocker, vasopressor administration prior to or with induction, device used for pre-oxygenation prior to medication administration, ventilation between induction and laryngoscopy, laryngoscope type and size, total number of attempts, airway grade, airway difficulty, rescue device use, need for additional operators, mechanical complications (esophageal intubation, aspiration, airway trauma). Lowest arterial oxygen saturation from induction to two minutes after intubation, lowest systolic blood pressure from induction to two minutes after intubation, vasopressor administration between induction and two minutes after intubation, administration of new fluid bolus between induction and two minutes after intubation, duration of intubation. Key peri-procedural outcomes will be collected by a trained, independent observer not affiliated with the performance of the procedure.

0-24 hours: Cardiac arrest within 1 hour of intubation, death within 1 hour of intubation, oxygen saturation, fraction of inspired oxygen, positive end expiratory pressure, and systolic and mean arterial pressures at 24 hours.

In-Hospital Outcomes: 28 day in-hospital mortality, days from enrollment to death, ventilator-free days, and ICU-free days

Outcome Measures

Primary Endpoint:

- Cardiovascular collapse, defined as one or more of the following:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation

Secondary Endpoint:

- 28-day in-hospital mortality

Justification of the end-point selection:
Cardiovascular collapse was the primary outcome of the PrePARE I trial, which provide the hypothesis-generating preliminary data on which the PREPARE II trial is designed. Additionally, cardiovascular collapse is a commonly used composite endpoint in airway management research, which is closely associated with longer-term clinical outcomes. In-hospital mortality at 28 days is a traditional patient-centered outcome for critical care clinical trials.

Exploratory (Hypothesis-generating) Endpoints:

Exploratory Efficacy Endpoints

- Each individual component of the composite primary endpoint:
  - New systolic blood pressure < 65 mmHg between induction and 2 minutes after intubation
  - New or increased vasopressor between induction and 2 minutes after intubation
  - Cardiac arrest within 1 hour of intubation
  - Death within 1 hour of intubation
- Lowest systolic blood pressure between induction and 2 minutes after intubation
- Change in systolic blood pressure from induction to lowest systolic blood pressure
- Ventilator-free days to 28 days
- ICU-free days to 28 days

Exploratory Safety Endpoints:

- Lowest arterial oxygen saturation between induction and 2 minutes after intubation
- Incidence of hypoxemia (oxygen saturation < 90%) between induction and 2 minutes after intubation
- Incidence of severe hypoxemia (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
- Systolic blood pressure at 24 hours after intubation

Exploratory Process Measures:

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

Risks and Benefits

Among patients for whom the treating team has decided endotracheal intubation is required, there are currently no established risks or benefits to intubation with or without fluid bolus administration. A prior trial of fluid bolus administration in the same study settings did not suggest differences between the fluid bolus and no fluid bolus groups in oxygen saturation, positive end-expiratory pressure, fraction of inspired oxygen, duration of mechanical ventilation, receipt diuretics, or any other procedural or clinical measure.

In addition, the exclusion criteria explicitly exclude patients for whom the treating provider feels a pre-induction fluid bolus administration is needed or is contraindicated. At this time, there is no reason to believe that participation in this study would expose

patients to greater medical risks or benefits than those experienced by critically ill patients requiring endotracheal intubation as a part of routine care. The greater benefit of the study would be to society in the form of improved understanding of safe and effective airway management for critically ill patients.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure online database (REDCap) only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

Safety Monitoring and Adverse Events

Safety Monitoring

This study will take place in the environment of an intensive care unit at the time of a procedure required for routine clinical care. Thus, at the time of the study intervention, the patient will have in the room a physician trained in the care of critically ill adults, a nurse trained in critical care, and usually a respiratory therapist in addition to continuous invasive or non-invasive monitoring. Additionally, study personnel will be readily available to answer questions at any time during the study course. Even after randomization, if any healthcare provider participating in the intubation procedure believes that the study interventions cannot be performed for the safe performance of the procedure, the study intervention is halted and the patient is intubated in the manner which the clinical team judges to be safest.

A Data and Safety Monitoring Board (DSMB) will oversee the trial. Interim analyses for safety and efficacy will be conducted as described in the Statistical Analysis section of the protocol.

Adverse Events

For this trial, an adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation where a participant is administered an intervention that does not necessarily have to have a causal relationship with the intervention. An adverse event therefore can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an intervention, whether or not the incident is considered related to the intervention.

For this trial, a serious adverse event (SAE) is defined as an (1) unexpected and untoward medical occurrence (2) determined by the study investigators or treating clinicians to be either probably or possibly related to the study (3) meeting any of the following criteria:

a. Results in death
b. Is life-threatening (defined as an event in which the participant was at risk of death at the time of the event and NOT an event that hypothetically might have caused death were it more severe). Life-threatening cardiovascular complications, as defined as the primary endpoint of this trial, will be prospectively and systematically collected as the outcome. As such, these events will not be reported as SAEs. Similarly, life-threatening severe hypoxia

will also be systematically collected as a secondary endpoint and will therefore not be reported as an SAE.

c. Requires inpatient hospitalization
d. Prolongs an existing hospitalization
e. Results in persistent or significant disability or incapacity
f. Results in a congenital anomaly or birth defect
g. Important medical event that requires an intervention to prevent any of a-f above.

The Principal Investigator will be responsible for overseeing the safety of this trial on a daily basis. He will be available at any time for questions from the bedside nurses, who will also be monitoring the patients continuously for adverse events and serious adverse events. SAEs will be recorded in a case report form in the study record and reported to the IRB within 7 business days.

Endotracheal intubation of critically ill adults during routine care is independently associated with adverse outcomes including but not limited to: death, cardiac arrest, cardiovascular collapse, hypotension, hypoxemia, esophageal intubation, and failed intubation. These events will be identified as study outcomes and systematically collected in both groups rather than relying on sporadic reporting as adverse events. These outcomes will not be individually reported as adverse events unless they qualify as an SAE. These outcomes will be available for review by the DSMB at the interim analysis and as requested.

Study Withdrawal/Discontinuation

Patients can be withdrawn from study participation in the following circumstances:

- The investigator decides that the patient should be withdrawn for safety considerations.
- There is a significant protocol violation in the judgment of the PI.

The reason and date of every withdrawal will be recorded in the patient study records. Follow-up will be performed for all patients who discontinue due to an adverse event or any other safety parameter. Follow-up will also be performed for all patients who end participation in the protocol for another reason, but who also have an adverse event or other safety parameter that could have led to discontinuation. Follow-up will be conducted until the condition has resolved, until diagnosis of the adverse event or safety parameter is deemed chronic and stable, or as long as clinically appropriate. This follow-up will be documented in the patient study record as well.

Statistical Considerations

Initial Sample Size Determination:

In a prior randomized trial comparing fluid bolus administration to no fluid bolus administration prior to induction 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 in that trial assigned to receive bag-mask ventilation 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, we will plan to enroll 750 patients.

Sample Size Re-Estimation

The initial study protocol specified that, after completion of the interim analysis and the recommendation to continue enrollment, "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 on 11/12/19 with the recommendation to continue enrollment, 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:

Prior to the conclusion of enrollment, we will make publically available a complete, final statistical analysis plan. Analyses conducted in accordance with the statistical analysis plan will be identified as *a priori*. Any additional analyses requested by the investigators or reviewers will be identified as *post hoc*.

Primary Analysis:

Unadjusted test of treatment effect. 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 a chi-square comparison.

Secondary Analysis:

Unadjusted test of treatment effect. The 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. Between group differences will be tested using a chi-square comparison. All comparisons apart from the primary and secondary analyses will be considered exploratory analyses.

Exploratory Analyses:

Analysis of Exploratory Outcomes. We will conduct unadjusted, intention-to-treat analyses comparing patients randomized to the fluid bolus group to patients randomized

to the no fluid bolus group with regard to exploratory outcomes. Continuous outcomes will be compared with the Mann-Whitney U test and categorical variables with the chi-square test.

Heterogeneity of Treatment Effect (Subgroup Analyses). We will examine whether pre-specified baseline covariates modify the effect of treatment group on the primary outcome using formal tests of statistical interaction.

Interim Analysis:

The DSMB will conduct a single interim analysis for efficacy at the anticipated halfway point of the trial, after enrollment of 375 patients. The stopping boundary for efficacy will be met if the P value for the difference in the incidence of the primary outcome (cardiovascular collapse) or secondary outcome (28-day in-hospital mortality) between groups using a chi-square test is 0.001 or less. Using this conservative Haybittle–Peto boundary ($P \leq 0.001$ cardiovascular collapse and in-hospital mortality) will allow the final analysis to be performed using an unchanged level of significance.

The DSMB will also formally evaluate the safety of the trial at the interim analysis. The DSMB will review the lowest oxygen saturation, highest fraction of inspired oxygen, and highest positive end expiratory pressure between 6 and 24 hours after intubation in each group. If the *P* value for the difference between study groups in any of these three physiologic variables is 0.001 or less and is concordant in direction with the point-estimate for mortality, it is recommended that the study be stopped early for safety. Additionally, the DSMB will reserve the right to stop the trial at any point, request additional data or interim analyses, or request modifications of the study protocol as required to protect patient safety.

Finally, after the interim analysis, 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.

Privacy and Confidentiality

At no time during the course of this study, its analysis, or its publication will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. All patients will be assigned a unique study ID number for tracking. Data collected from the medical record will be entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event will be stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data will be maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified version of the database will be generated.

Follow-up and Record Retention

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

References

1. Martin LD, Mhyre JM, Shanks AM, Tremper KK, Kheterpal S. 3,423 emergency tracheal intubations at a university hospital: airway outcomes and complications. *Anesthesiology* 2011;114:42–48.
2. Simpson GD, Ross MJ, McKeown DW, Ray DC. Tracheal intubation in the critically ill: a multi-centre national study of practice and complications. *Br J Anaesth* 2012;108:792–799.
3. Leibowitz AB. Tracheal intubation in the intensive care unit: extremely hazardous even in the best of hands. *Crit Care Med* 2006;34:2497–2498.
4. Jaber S, Jung B, Corne P, Sebbane M, Muller L, Chanques G, Verzilli D, Jonquet O, Eledjam J-J, Lefrant J-Y. An intervention to decrease complications related to endotracheal intubation in the intensive care unit: a prospective, multiple-center study. *Intensive Care Med* 2010;36:248–255.
5. Griesdale DEG, Bosma TL, Kurth T, Isac G, Chittock DR. Complications of endotracheal intubation in the critically ill. *Intensive Care Med* 2008;34:1835–1842.
6. van Zundert A, Pieters B, Doerges V, Gatt S. Videolaryngoscopy allows a better view of the pharynx and larynx than classic laryngoscopy. *Br J Anaesth* 2012;109:1014–1015.
7. Jabre P, Combes X, Lapostolle F, Dhaouadi M, Ricard-Hibon A, Vivien B, Bertrand L, Beltramini A, Gamand P, Albizzati S, Perdrizet D, Lebail G, Chollet-Xemard C, Maxime V, Brun-Buisson C, Lefrant J-Y, Bollaert P-E, Megarbane B, Ricard J-D, Anguel N, Vicaut E, Adnet F, KETASED Collaborative Study Group. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial. *Lancet* 2009;374:293–300.
8. Cook TM, Woodall N, Harper J, Benger J, Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 2: intensive care and emergency departments. *Br J Anaesth* 2011;106:632–642.
9. Mort TC. The incidence and risk factors for cardiac arrest during emergency tracheal intubation: a justification for incorporating the ASA Guidelines in the remote location. *J Clin Anesth* 2004;16:508–516.
10. Green RS, Turgeon AF, McIntyre LA, Fox-Robichaud AE, Fergusson DA, Doucette S, Butler MB, Erdogan M, Canadian Critical Care Trials Group (CCCTG). Postintubation hypotension in intensive care unit patients: A multicenter cohort study. *J Crit Care* 2015;30:1055–1060.
11. Heffner AC, Swords DS, Nussbaum ML, Kline JA, Jones AE. Predictors of the complication of postintubation hypotension during emergency airway management. *J Crit Care* 2012;27:587–593.
12. Walz JM, Zayaruzny M, Heard SO. Airway management in critical illness. *Chest* 2007;131:608–620.
13. Natt BS, Malo J, Hypes CD, Sakles JC, Mosier JM. Strategies to improve first attempt success at intubation in critically ill patients. In: Asai T, editor. *Br J Anaesth* 2016;aew061.doi:10.1093/bja/aew061.
14. Muzi M, Berens RA, Kampine JP, Ebert TJ. Venodilation contributes to propofol-mediated hypotension in humans. *Anesth Analg* 1992;74:877–883.

15. Möller Petrun A, Kamenik M. Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. *Br J Anaesth* 2013;110:388–396.
16. Shah SB, Chowdhury I, Bhargava AK, Sabbharwal B. Comparison of hemodynamic effects of intravenous etomidate versus propofol during induction and intubation using entropy guided hypnosis levels. *J Anaesthesiol Clin Pharmacol* 2015;31:180–185.
17. Kaushal RP, Vatal A, Pathak R. Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass. *Ann Card Anaesth* 2015;18:172–178.
18. Reich DL, Hossain S, Krol M, Baez B, Patel P, Bernstein A, Bodian CA. Predictors of hypotension after induction of general anesthesia. *Anesth Analg* 2005;101:622–8– table of contents.
19. Choi YF, Wong TW, Lau CC. Midazolam is more likely to cause hypotension than etomidate in emergency department rapid sequence intubation. *Emerg Med J* 2004;21:700–702.
20. Davis DP, Kimbro TA, Vilke GM. The use of midazolam for prehospital rapid-sequence intubation may be associated with a dose-related increase in hypotension. *Prehosp Emerg Care* 2001;5:163–168.
21. Janz DR, Semler MW, Lentz RJ, Matthews DT, Assad TR, Norman BC, Keriwala RD, Ferrell BA, Noto MJ, Shaver CM, Richmond BW, Zinggeler Berg J, Rice TW, Facilitating EndotracheaL intubation by Laryngoscopy technique and apneic Oxygenation Within the ICU Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Video Laryngoscopy for Endotracheal Intubation of Critically Ill Adults. *Crit Care Med* 2016;doi:10.1097/CCM.0000000000001841.
22. Semler MW, Janz DR, Lentz RJ, Matthews DT, Norman BC, Assad TR, Keriwala RD, Ferrell BA, Noto MJ, McKown AC, Kocurek EG, Warren MA, Huerta LE, Rice TW, FELLOW Investigators and the Pragmatic Critical Care Research Group. Randomized Trial of Apneic Oxygenation during Endotracheal Intubation of the Critically Ill. *Am J Respir Crit Care Med* 2016;193:273–280.
23. Kangelaris KN, Ware LB, Wang CY, Janz DR, Zhuo H, Matthay MA, Calfee CS. Timing of Intubation and Clinical Outcomes in Adults With Acute Respiratory Distress Syndrome. *Crit Care Med* 2016;44:120–129.
24. Perbet S, De Jong A, Delmas J, Futier E, Pereira B, Jaber S, Constantin J-M. Incidence of and risk factors for severe cardiovascular collapse after endotracheal intubation in the ICU: a multicenter observational study. *Crit Care* 2015;19:257.
25. Heffner AC, Swords DS, Neale MN, Jones AE. Incidence and factors associated with cardiac arrest complicating emergency airway management. *Resuscitation* 2013;84:1500–1504.
26. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, Filbin MR, Shapiro NI, Angus DC. A randomized trial of protocol-based care for early septic shock. *N Engl J Med* 2014;370:1683–1693.
27. Semler MW, Rice TW. Sepsis Resuscitation: Fluid Choice and Dose. *Clin Chest Med* 2016;37:241–250.
28. Young P, Bailey M, Beasley R, Henderson S, Mackle D, McArthur C, McGuinness S, Mehrtens J, Myburgh J, Psirides A, Reddy S, Bellomo R, SPLIT Investigators, ANZICS CTG. Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney

Injury Among Patients in the Intensive Care Unit: The SPLIT Randomized Clinical Trial. *JAMA* 2015;314:1701–1710.
29. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM, Sevransky JE, Sprung CL, Douglas IS, Jaeschke R, Osborn TM, Nunnally ME, Townsend SR, Reinhart K, Kleinpell RM, Angus DC, Deutschman CS, Machado FR, Rubenfeld GD, Webb SA, Beale RJ, Vincent J-L, Moreno R, Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013. pp. 580–637.
30. Shafi S, Gentilello L. Pre-hospital endotracheal intubation and positive pressure ventilation is associated with hypotension and decreased survival in hypovolemic trauma patients: an analysis of the National Trauma Data Bank. *J Trauma* 2005;59:1140–5– discussion 1145–7.
31. Balasaraswathi K, Glisson SN, El-Etr AA, Azad C. Effect of priming volume on serum catecholamines during cardiopulmonary bypass. Can Anaesth Soc J 1980; 27(2): 135-9.
32. Bruegger D, Jacob M, Rehm M, et al. Atrial natriuretic peptide induces shedding of endothelial glycocalyx in coronary vascular bed of guinea pig hearts. Am J Physiol Heart Circ Physiol 2005; 289(5): H1993-9.
33. Duggan M, McCaul CL, McNamara PJ, Engelberts D, Ackerley C, Kavanagh BP. Atelectasis causes vascular leak and lethal right ventricular failure in uninjured rat lungs. Am J Respir Crit Care Med 2003; 167(12): 1633-40.
34. Duggan M, McNamara PJ, Engelberts D, et al. Oxygen attenuates atelectasis-induced injury in the in vivo rat lung. Anesthesiology 2005; 103(3): 522-31.
35. Muller-Strahl G, Hemker J, Zimmer HG. Comparison between left and right heart function in the isolated biventricular working rat heart. Exp Clin Cardiol 2002; 7(1): 7-19.
36. Andrews B, Muchemwa L, Kelly P, Lakhi S, Heimburger DC, Bernard GR. Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. Crit Care Med 2014; 42(11): 2315-24.
37. De Jong A, Molinari N, Terzi N, Mongardon N, Arnal J-M, Guitton C, Allaouchiche B, Paugam-Burtz C, Constantin J-M, Lefrant J-Y, Leone M, Papazian L, Asehnoune K, Maziers N, Azoulay E, Pradel G, Jung B, Jaber S, AzuRéa Network for the Frida-Réa Study Group. Early identification of patients at risk for difficult intubation in the intensive care unit: development and validation of the MACOCHA score in a multicenter cohort study. *Am J Respir Crit Care Med* 2013;187:832–839.
38. Boyd JH, Forbes J, Nakada T-A, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011;39:259–265.
39. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, Connors AF, Hite RD, Harabin AL. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564–2575.

(3) Summary of Changes to Trial Protocol

Protocol 1.0, dated: 7/4/2018

Protocol 1.1 (revision date: 3/13/19)

- Based on feedback from local site IRBs and site investigators who expressed concern that, in their local context, providing a detailed patient and family notification sheet to the patient and family immediately after enrollment had the potential to cause undue stress to patients at a time point when any potential risks and benefits of the study had already been experienced, the protocol was modified to allow study sites and site IRBs to choose which of three mechanism of providing information to patients and families was most suited to local context.

Protocol 1.2 (revision date: 12/20/19)

- Following completion of the interim analysis, the sample size was increased from 750 to 1,065 patients at the recommendation of the DMSB in order to maintain the pre-planned 80% statistical power to detect the pre-planned relative risk reduction of 35% in the primary outcome, based on a lower than expected event rate.

(4) **Original Statistical Analysis Plan**

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.

Sources of Funding: Jonathan D. Casey was supported in part by the NHLBI (2T32HL087738-12 and K12HL133117). Matthew W. Semler was supported in part by the NHLBI (K23HL143053). Derek W. Russell was supported in part by the UAB Walter Frommeyer, Jr. Fellowship in Investigative Medicine and by the Department of Veteran's Affairs (VISN 7 Research Development Award). Data collection utilized the Research Electronic Data Capture (REDCap) tool developed and maintained with Vanderbilt Institute for Clinical and Translational Research grant support (UL1 TR002234 from NCATS/NIH). The funding institutions had no role in (1) conception,

design, or conduct of the study, (2) collection, management, analysis, interpretation, or presentation of the data, or (3) preparation, review, or approval of the manuscript.

Competing Interest Statement: The authors report no conflicts of interest with the contents of this manuscript.

Key words for indexing: Endotracheal intubation, fluid loading, post-intubation hypotension, cardiovascular collapse

Manuscript Word Count (body only): 4099 words
Abstract Word Count: 295/300

Supplemental digital content is available for this article.

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 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. 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

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. **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

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	1,11-13
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	1-4,
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, 10-12

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	6-8, 25
	6b	Explanation for choice of comparators	6-8
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	10,11
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)	11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12,13, Figure 2
	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	22-24
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 2, 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	18,19
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	10,11

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	11,12
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	11,12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14-16, Fig. S2
	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, 24
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 19,20
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	20,21
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	21-25
	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)	24

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Supplement 12-18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	19,20, Supplement 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	Supplement 14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Supplement 16,17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	4,10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Supplement 19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	25,26
	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 19,20
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 19,20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	4
	31b	Authorship eligibility guidelines and any intended use of professional writers	1,2, 26
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	4,5
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. Randomization Assignment Forms

A.

NO Fluid Bolus

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

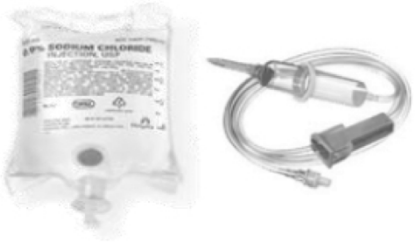
OK to continue any IV fluids already running or ordered

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.

3. 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 enrollment. 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 day 28 or after a hospital discharge does not affect VFDs).

4. Definition of ICU-Free Days (ICUFDs)

ICU-FDs are defined as the number of days alive and not admitted to an intensive care unit service, from the patient’s final discharge from the intensive care unit to 28 days after enrollment. If a patient is not discharged from the intensive care unit 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 intensive care unit 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 intensive care unit service after day 28 or after a hospital discharge does not affect ICU-FDs).

5. Definition of 28-day in-hospital mortality

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

6. Definition of "days from enrollment to in-hospital death"

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

7. 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.

8. 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.

9. 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 enrollment, 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 enrollment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate >2mmol/L in the absence of hypovolemia) at the time of enrollment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrollment, and whether or not 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 enrollment to death, ventilator-free days, and ICU-free days – all censored at hospital discharge. See **Supplementary file** for definitions of these terms.

10. Site Characteristics:
Table S1

	VUMC MICU	LSU 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 enrollment informing the patient of his or her enrollment and describing the study. “Information Sheet” is a patient and family information sheet containing general information about the study and contact information for the research team displayed in at least three publicly-visible locations within the study unit. “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.

(5) **Description of Final Statistical Analysis Plan**

On May 26, 2020 after completing peer review, the final version of the Statistical Analysis Plan was submitted. On September 18, 2020, this was published online in the *British Medical Journal Open*. Due to copyright concerns and journal prohibition of previously published material in new submissions, a facsimile of this Statistical Analysis Plan is not included in this Supplementary Appendix. This document, along with the full revision and review history can be found in the following reference:

Russell DW, Casey JD, Gibbs KW, Dargin JM, Vonderhaar DJ, Joffe AM, Ghamande S, Khan A, Dutta S, Landsperger JS, Robison SW, Bentov I, Wozniak JM, Stempek S, White HD, Krol OF, Prekker ME, Driver BE, Brewer JM, Wang L, Lindsell CJ, Self WH, Rice TW, Semler MW, Janz D, Investigators PI. Protocol and statistical analysis plan for the PREventing cardiovascular collaPse with Administration of fluid REsuscitation during Induction and Intubation (PREPARE II) randomised clinical trial. BMJ Open 2020; 10: e036671. PMCID: PMC7511643

(6)	**Statistical Analysis Plan Revision Sequence**
December 26, 2019	Original Statistical Analysis Plan completed
January 7, 2020	Original Statistical Analysis Plan submitted for publication
May 26, 2020	Revision of Statistical Analysis Plan submitted for publication*
September 18, 2020	Statistical Analysis Plan published online*
May 24, 2021	Enrollment completed

*The revised Statistical Analysis Plan included no substantive changes from the original; the final version differs from the original only by including more detailed language around how clinical equipoise is determined for this trial into the discussion section, a change made based on feedback during the peer review process.