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

Russell DW, *et al. BMJ Open* 2020; 10:e036671. doi: 10.1136/bmjopen-2019-036671

Table of Contents

1. SPIRIT 2013 Checklist

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1,10-12
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	1-5,
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	2
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,2
	5b	Name and contact information for the trial sponsor	2
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	2

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	1,2, 9,10, 24,
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	7,8, 13
	6b	Explanation for choice of comparators	7,8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9,10
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centers and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12,
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12,13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12-14

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	12-14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13-15
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15-17
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	10-13

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11,12, Fig. S1
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	11-13

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12-22, Supplement 15-17
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12-14, Supplement 14
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Supplement 14
Statistical methods	20a	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18, 22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-23
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomized analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18, 22
Methods: Monitoring			

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16, 17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16,17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	16, 17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16,17

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	24
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	25, Supplement 13, 14
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	23,24
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Supplement 14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2

Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Supplement 14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	5,9, 25
	31b	Authorship eligibility guidelines and any intended use of professional writers	1,2,
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25, Supplement 14
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorized surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

2. Site Characteristics:

Table S1

	VUMC MICU	LSU UMCNO MICU	Ochsner MICU	UW Harborview MICU	UW Harborview NICU	UW Harborview TICU	Lahey MICU
Number of Beds	35	20	33	17	30	24	20
Patient Notification Strategy	Information Sheet	Notification Sheet	Information Sheet	Information Sheet	Information Sheet	Information Sheet	Admission Information Sheet
IRB Process	Central*	Central	Central	Central	Central	Central	Local

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

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

3. Randomization Assignment Forms

A.

NO Fluid Bolus

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

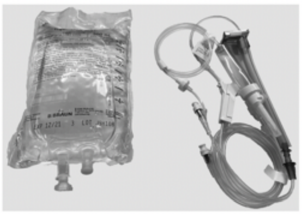
OK to continue any IV fluids already running or ordered

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

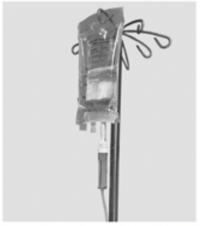
B.

Fluid Bolus

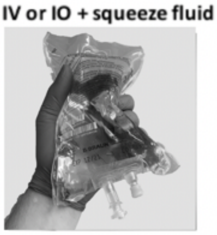
1 **Obtain 500 ml of crystalloid & gravity IV tubing**



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



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



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

Complete 500 mL infusion

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

4. Data Collection:

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

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

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

Baseline: Age, gender, height, weight, race, ethnicity, Acute Physiology and Chronic Health Evaluation (APACHE) II score[2], active medical problems at the time of intubation, active and chronic comorbidities complicating intubation, indication for intubation, most recent pre-procedural Glasgow Coma Score[3], non-invasive ventilator and high flow nasal cannula use in the hour prior to starting pre-oxygenation, vasopressor use in the hour preceding enrolment, presence of sepsis (defined as life-threatening organ dysfunction caused by a dysregulated host response to infection) or septic shock (defined as presence of sepsis plus vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate >2mmol/L in the absence of hypovolemia) at the time of enrolment, the highest fraction of inspired oxygen delivered (FiO_2) in the hour preceding enrolment, and whether or not the intubation was a reintubation (defined as patient who had been extubated from invasive mechanical ventilation within the prior 72 hours).

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

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

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

5. Definition of 28-day in-hospital mortality

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

6. Definition of Ventilator Free Days

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

7. Definition of ICU-Free Days (ICUFDs)

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

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

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

9. Plan for communication of protocol changes

Any changes to the trial protocol (e.g., changes to eligibility criteria, outcomes, analyses) will be reflected in a new version of the full trial protocol, tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes made with each protocol revision will be included at the end of each protocol. The updated protocol will be submitted to the relevant IRBs for tracking and approval

prior to implementation of each protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be provided in the supplementary material for publication.

10. Patient Privacy and Data Storage

At no time during the course of this study, its analysis, or its publication, will patient identities be revealed in any manner. The minimum necessary data containing patient or provider identities or other private healthcare information (PHI) is collected. All subjects are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. The PHI required to accurately collect clinical and outcomes data is available only to investigators at the site at which the subject is enrolled. All data available to the coordinating center and investigators at other sites are completely de-identified and contain no PHI. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until. The de-identified dataset housed in REDCap will be accessed by the coordinating center for analyzing and reporting the results of this trial. All data will be maintained in the secure online database REDCap until the time of study publication. After publication, all PHI at local centers will be expunged and only the de-identified version of the database will be retained. Potential future use of de-identified data generated in the course of this study by the coordinating center and other participating sites will be governed by mutual data use agreements.

11. References:

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