ONLINE SUPPLEMENT TO:

Protocolized Post-extubation Respiratory Support to Prevent Reintubation: Protocol and Statistical Analysis Plan for a Randomized Trial

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Contents

Supplemental Methods

1. Definitions

Study Intervention

Post-extubation respiratory support: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started immediately following extubation to prevent subsequent respiratory failure

Rescue therapy: respiratory support with non-invasive ventilation (NIV) or high-flow nasal cannula (HFNC), started minutes, hours, or days after extubation as treatment for respiratory failure

Hours to discontinuation of post-extubation respiratory support: number of hours from extubation to the permanent discontinuation of post-extubation respiratory support. Use of NIV or HFNC as rescue therapy will not be included.

Duration of respiratory support within the first 24 hours: number of hours spent receiving either NIV or HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

Duration of HFNC within the first 24 hours: number of hours spent receiving HFNC as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

Duration of NIV within the first 24 hours: number of hours spent receiving NIV as post-extubation respiratory support or as rescue therapy within the first 24 hours following extubation.

Outcomes:

Ventilator Free Days (VFD): Ventilator-free days are defined as the number of days alive and breathing without assistance from the patient's final receipt of assisted breathing to 28 days after enrollment. If a patient dies before day 28, VFD is 0. If a patient is receiving assisted ventilation at day 28, VFD is 0. If the patient is discharged while receiving assisted ventilation, VFD is 0. If a patient survives to discharge and is never reintubated after enrollment, VFD is 28. Otherwise, VFD is calculated as 28 minus the study day on which the patient ultimately achieved unassisted breathing. All data will be censored at the time of first hospital discharge or 28 days.

In-hospital mortality: In-hospital mortality will be defined as death from any cause prior to hospital discharge.

2. 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, 3, 8
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4, 9
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	2
	5a	Names, affiliations, and roles of protocol contributors	1

Roles and responsibilities	5b	Name and contact information for the trial sponsor	1, 2, 9
	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	9
	5d	Composition, roles, and responsibilities of the coordinating center, 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

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	2
	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	9
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	11-15
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11-15
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
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	18, 19

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
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	19-20
Recruitment	15	Strategies for achieving adequate participant enrollment to reach target sample size	19-20

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	10, 11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10, 11
Implementation	16c	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	10, 11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	5

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	5

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	16-19
	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	16,17
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	2
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	21-22
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	22-26
	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)	26, 27

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	20, 21
	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	N/A

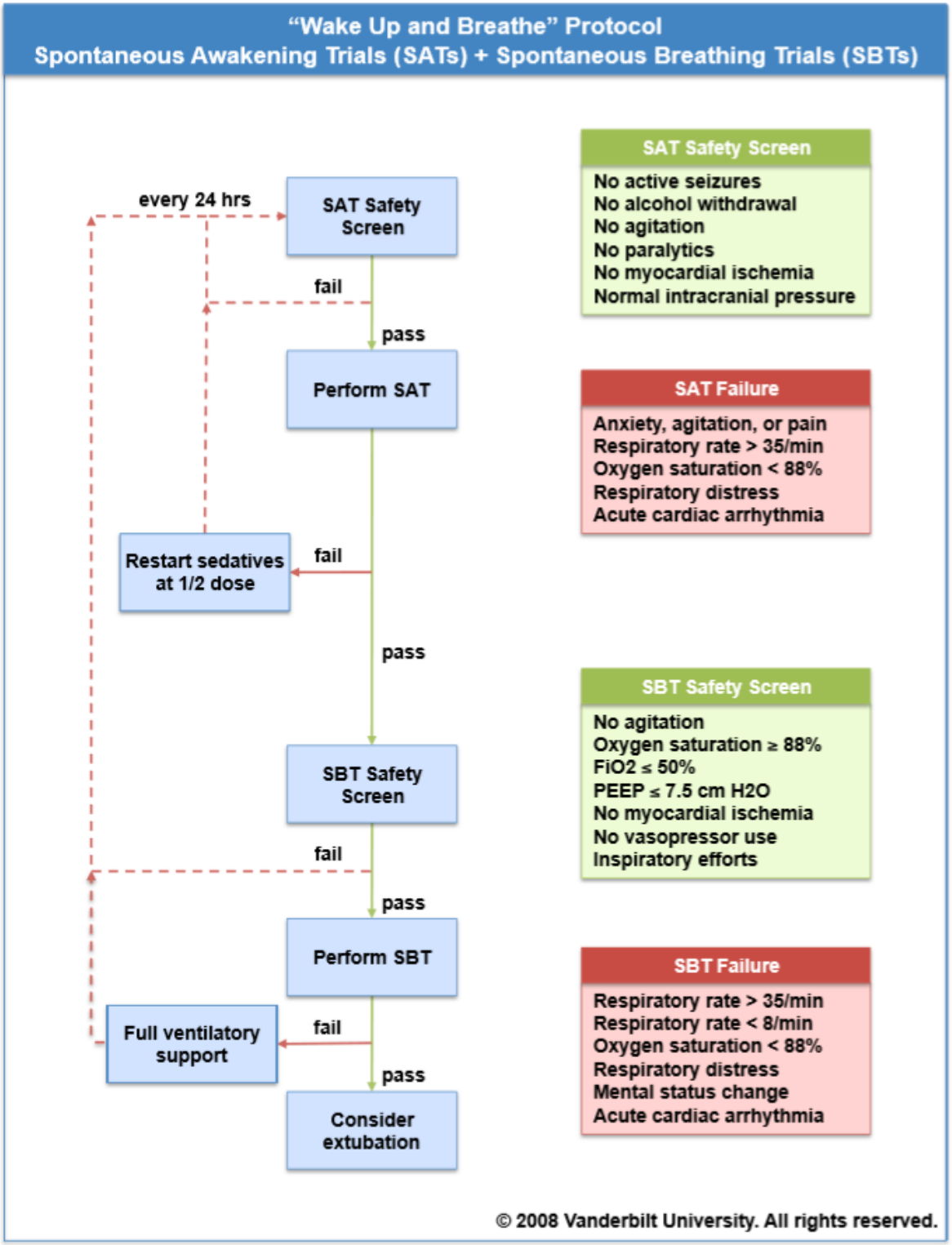
Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	9, 28
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)	S19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	27, 28
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	27, 28
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	S20

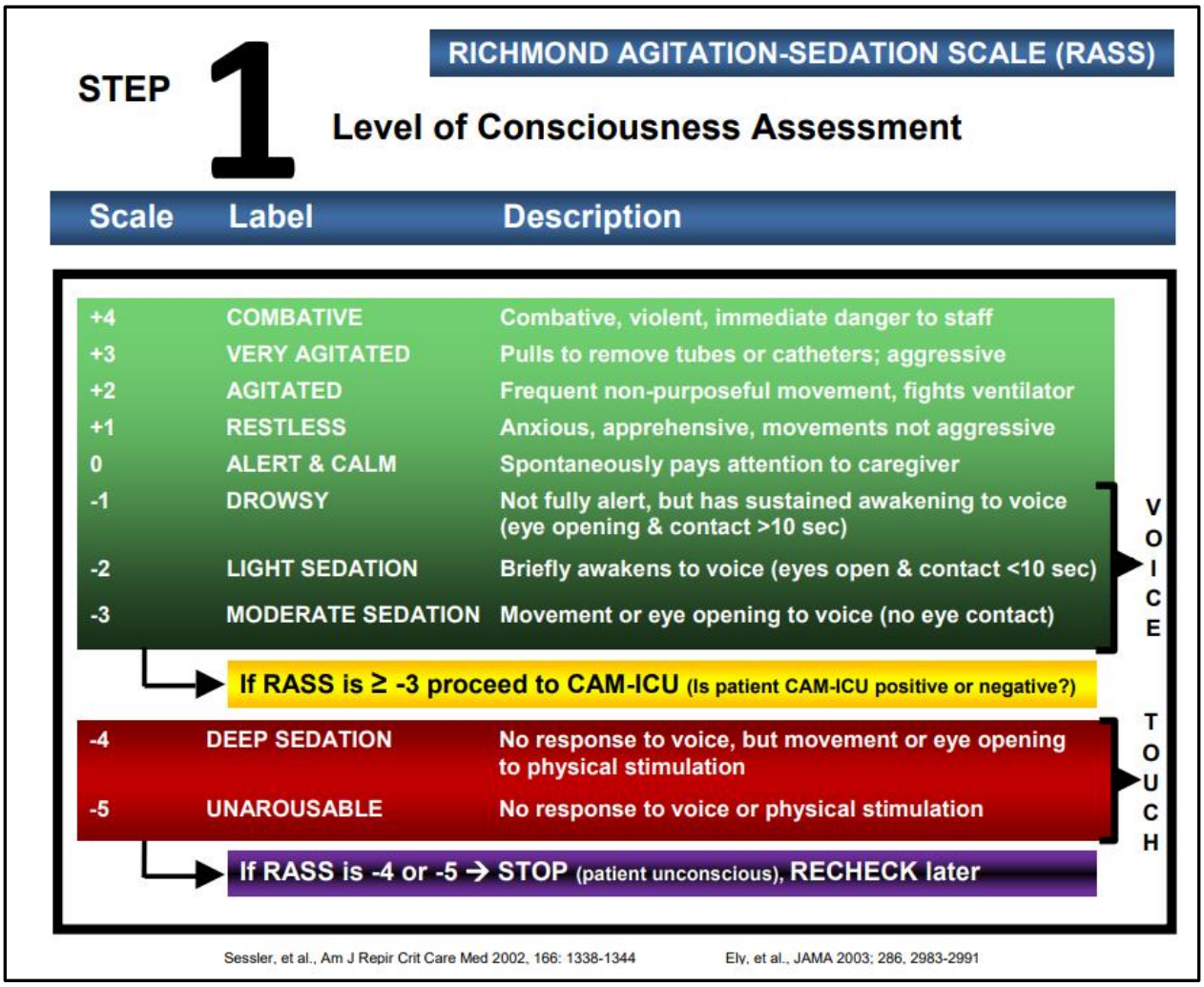
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	2
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	2, 9
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	29
	31b	Authorship eligibility guidelines and any intended use of professional writers	1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
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.

3. Protocol for Daily Spontaneous Awakening Trial (SAT) Safety Screen, SAT Performance, Spontaneous Breathing Trial (SBT) Safety Screen, and SBT Performance



4. Protocol for Assessment of Agitation (RASS score)



5. Protocol for Choice of Analgesia and Sedation in Mechanically Ventilated Patients

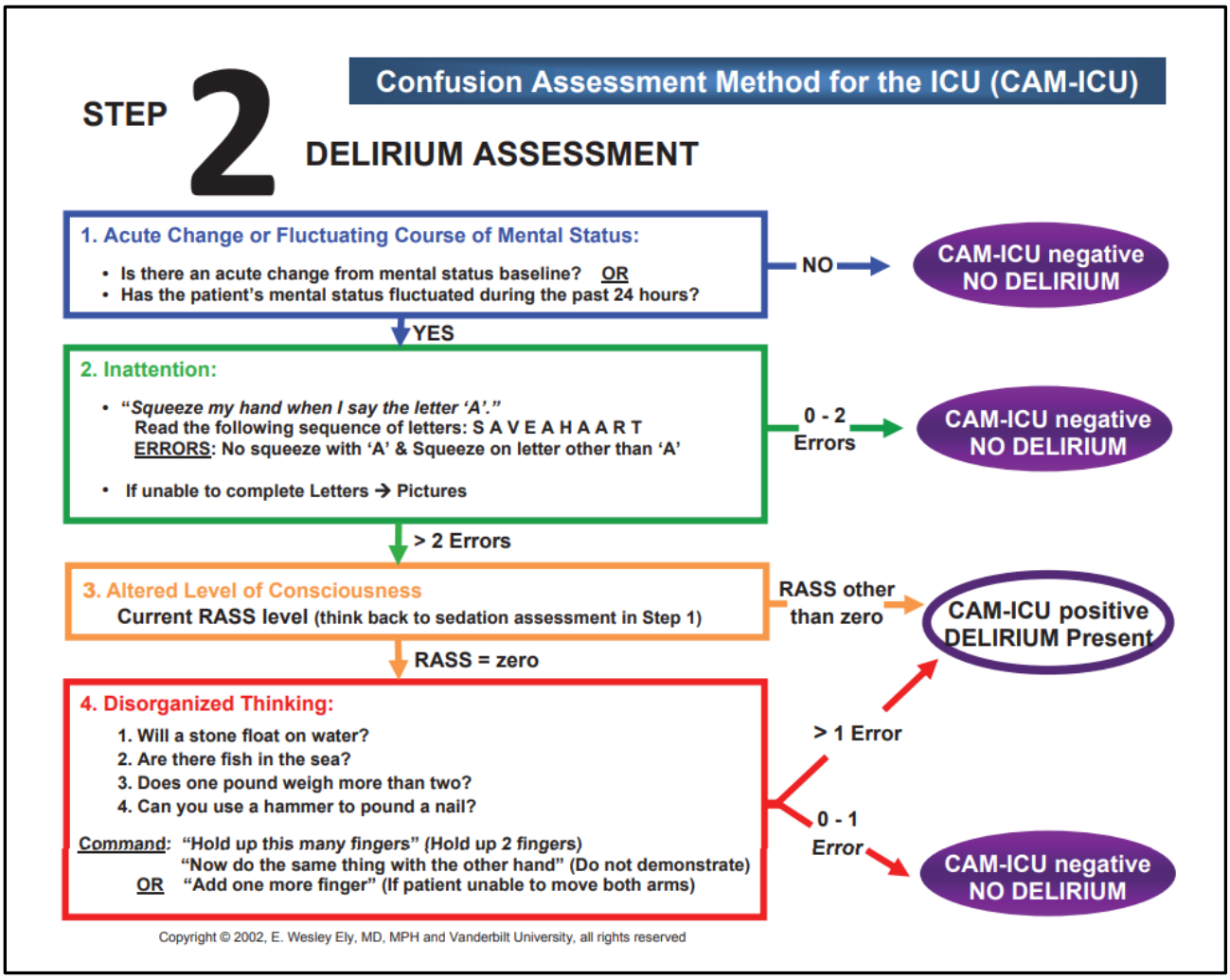
- Analgesia
    a. Intermittent Dosing
        i. Fentanyl 50 mcg IV push every 15 minutes to goal CPOT ≤3, then 50mcg IV push every 2 hours as needed to maintain a CPOT ≤ 3
        ii. Hydromorphone 0.2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 0.2 mg IV push every 4 hours as needed to maintain CPOT ≤ 3
        iii. Morphine 2 mg IV push every 15 minutes to goal CPOT ≤ 3, then 2 mg IV push as needed to maintain CPOT ≤ 3
    b. Continuous Infusions
        i. None
        ii. Fentanyl infusion 50mcg/hr, titrate by 25 mcg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 400mcg/hr. NHO when CPOT target not met with maximum rate.
        iii. Morphine infusion 2mg/hr, titrate by 0.5mg/hr every 15 minutes to goal CPOT score ≤ 3. Max infusion rate 20 mg/hr. NHO when CPOT target not met with maximum rate.
- Sedation
    a. None (if RASS at goal with analgesia-based regimen)
    b. Propofol Infusion 5mcg/kg/min, titrate by 5mcg/kg/min every 15 minutes to goal RASS. Max rate of 50mcg/kg/min. NHO when RASS target not met with maximum rate.
    c. Dexmedetomidine Infusion 0.2mcg/kg/hr, titrate by 0.1 mcg/kg/hr every 15 minutes to goal RASS. Max rate 1.5 mcg/kg/hr. NHO when RASS target not met with maximum rate.

    For propofol intolerance consider one of the following:

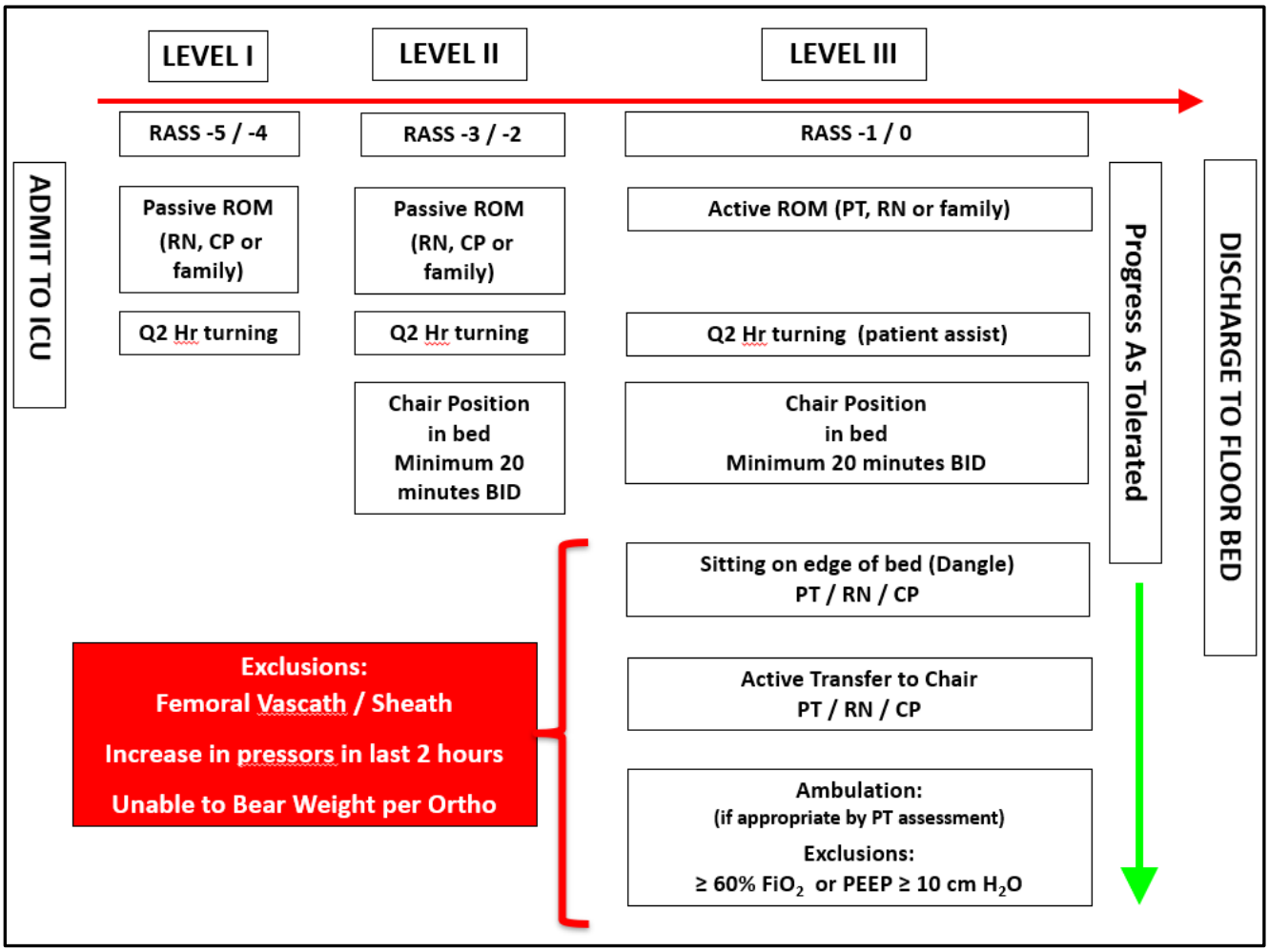
    d. Midazolam 1mg IV push every 2 hours as needed to meet goal RASS.
    e. Midazolam Infusion 0.5mg/hr, titrate by 0.5mg/hr every 15 minutes to achieve goal RASS. Max infusion rate 10mg/hr. NHO when RASS target not met with maximum rate.

(Propofol intolerance refers to propofol infusion syndrome, hemodynamic instability precluding propofol use, elevated creatinine phosphokinase (CPK) >5000 International units/L, triglycerides>500mg/dl, or propofol use >96 hours)

6. Protocol for Delirium Assessment (CAM-ICU)



7. Protocol for Early Mobility



8. Development of the Model for the Primary Analysis

In preparation for PROPER, we collected data on the provision of post-extubation respiratory support and the incidence of reintubation from 420 patients who met inclusion/exclusion criteria for PROPER in a 12-month period (6/1/2015 to 5/31/2016) prior to the trial. Using generalized linear mixed-effects modeling treating the two geographic regions of the unit as clusters and the four 3-month blocks as periods, we calculated the intra-cluster correlation coefficient to be <0.001, the intra-period correlation coefficient to be <0.001, and the intra-cluster intra-period correlation coefficient to be <0.001.

9. Plan for communication of protocol changes

Any changes to the trial protocol (eg, changes to eligibility criteria, outcomes, analyses) will require a new version of the full trial protocol which will be tracked with the date of the update and the version number of the trial protocol. A list summarizing the changes that are made with each protocol revision will be included at the end of each protocol. The updated protocol will be sent to the Vanderbilt IRB for tracking and approval prior to implementation of the protocol change. At the time of publication, the original trial protocol and the final trial protocol, including the summary of changes made with each protocol change, will be included in the supplementary material for publication.

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 is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

11. 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 is collected. All patients are assigned a unique study ID number for tracking. Data collected from the medical record is entered into the secure online database REDCap. Hard copies of the data collection sheet completed at the time of the airway management event are stored in a locked room until after the completion of enrollment and data cleaning. Once data are verified and the database is locked, all hard copies of data collection forms will be destroyed. All data is maintained in the secure online database REDCap until the time of study publication. At the time of publication, a de-identified database will be generated.

12. Data Sharing Plan

Upon reasonable request, a completely de-identified data set may be provided by the authors. Request to share data from the PROPER trial should be sent to the principal investigator, Jonathan Casey, MD at Jonathan.D.Casey@vumc.org. The data set will be provided to researchers whose proposed use of the data has been approved by the steering committee and an Institutional Review Board.

SUPPLEMENTAL FIGURES

Figure S1. PROPER Consort Diagram Template

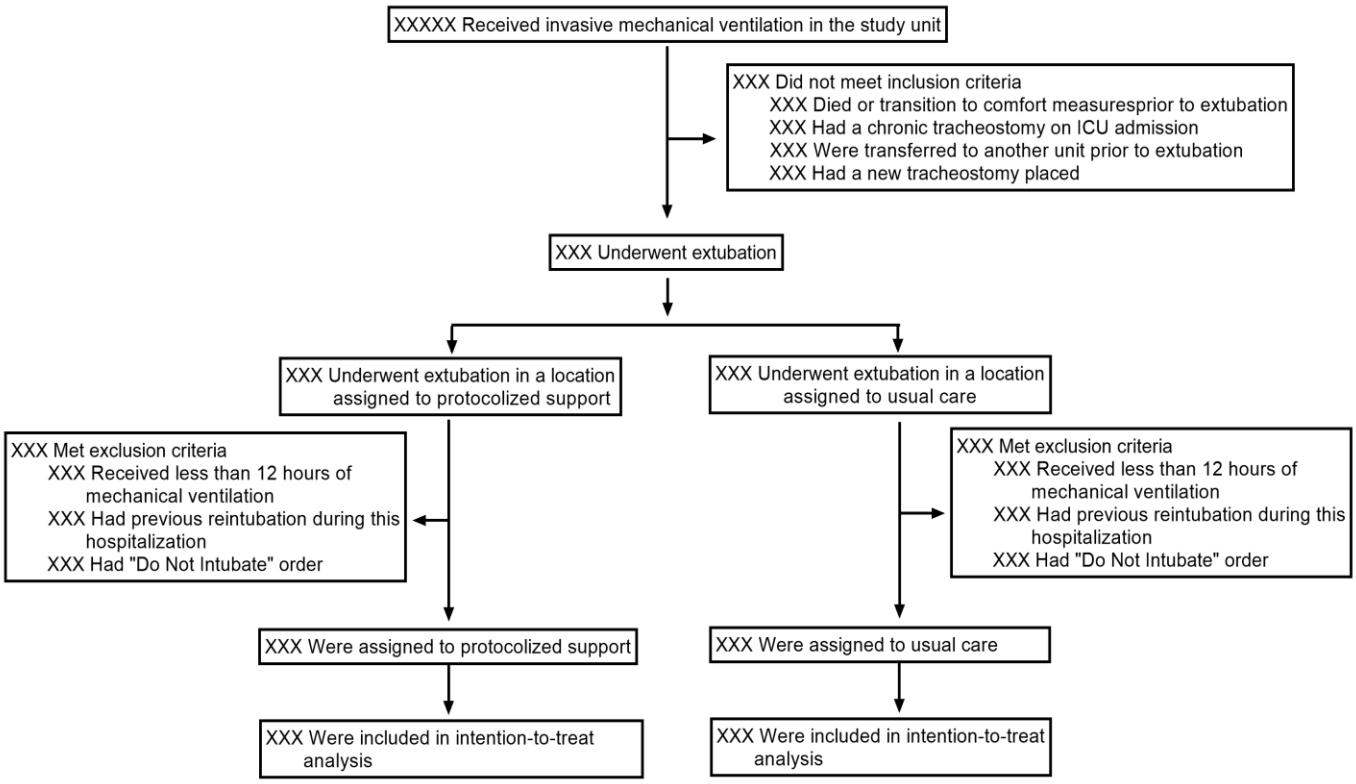


Figure S2. Protocol for Initiation, Titration, and Weaning of Non-Invasive Ventilation

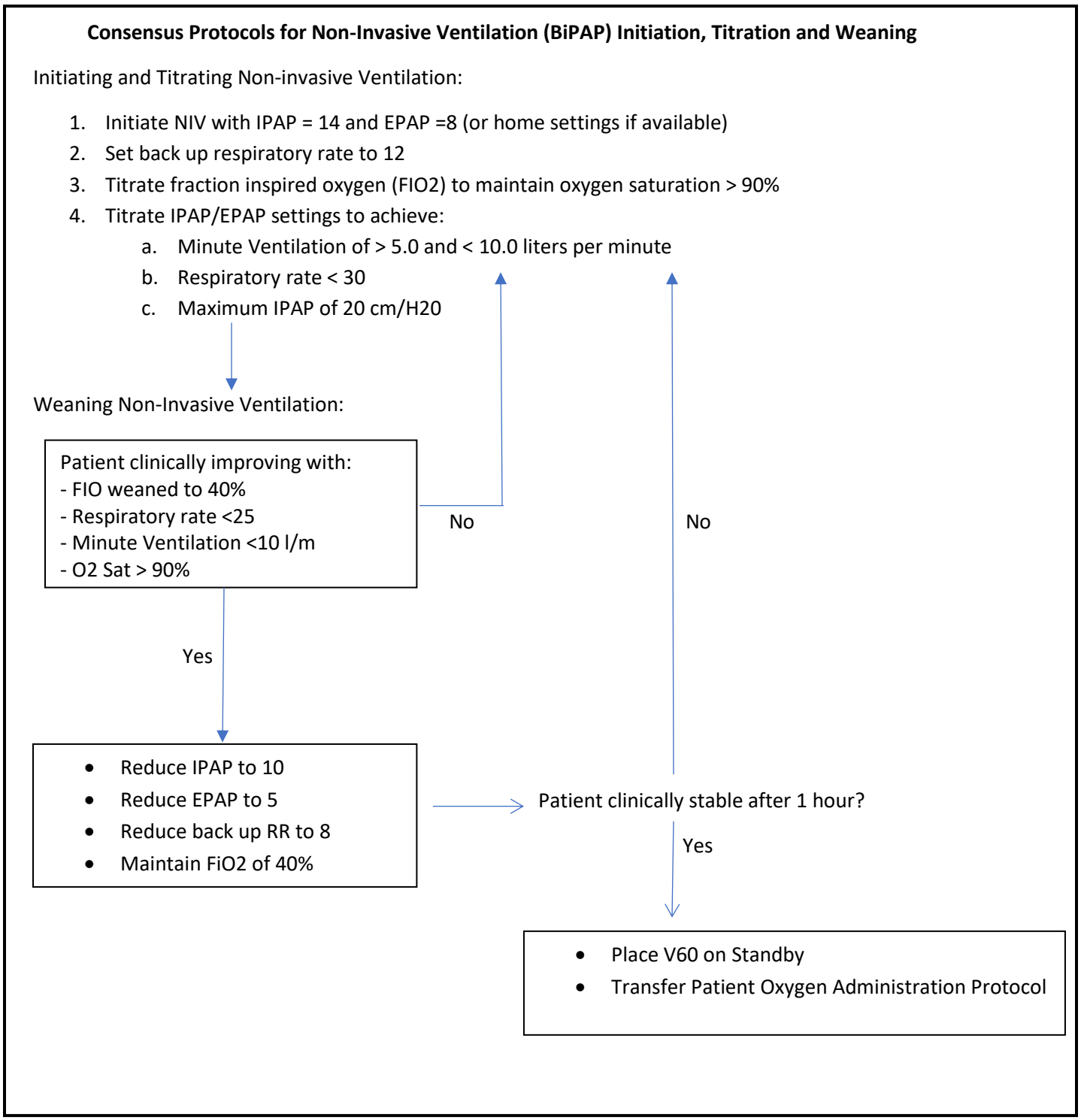


Figure S3. Protocol for Initiation, Titration, and Weaning of High Flow Nasal Cannula