Statistical analysis plan for the Identification and Treatment of Hypoxemic Respiratory Failure (HRF) and ARDS with Protection, Paralysis, and Proning: a type-1 hybrid stepped-wedge cluster randomized effectiveness-implementation study

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ABSTRACT:

Background: The Identification and Treatment of Hypoxemic Respiratory Failure (HRF) and ARDS with Protection, Paralysis, and Proning (TheraPPP) study is a type-1 hybrid stepped-wedge cluster randomized effectiveness-implementation study involving 17 adult Intensive Care Units (ICUs). This study will evaluate the effectiveness and implementation of an evidence-based, stakeholder-informed, multidisciplinary care pathway called *Venting Wisely* that standardizes the diagnosis and delivery of life-saving therapies for critically ill patients with Hypoxemic Respiratory Failure (HRF) and acute respiratory distress syndrome (ARDS).

Objective: To describe a pre-specified statistical analysis plan (SAP) for the TheraPPP study prior to completion of recruitment, electronic data retrieval, and before any analysis has been conducted.

Methods and analysis: The Statistical Analysis Plan (SAP) was designed by the principal investigators and senior biostatistician and reviewed in detail by the *Venting Wisely* Scientific Steering Group before being approved. This statistical analysis plan is reported in accordance with Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. A study specific CONSORT diagram and baseline characteristics table were developed. We estimate a total of 18816 mechanically ventilated patients will be included in this study with 11424 patients pre-implementation and 7392 patients post implementation. Given that ARDS patients are an important subgroup within this study, we estimate that this will generate a sample size of 2688 sustained ARDS patients within our TheraPPP study cohort. The primary clinical outcome is 28-day ventilator free days (VFDs). For the primary analysis, we will compare the mean 28-day VFDs pre-implementation and post-implementation using a mixed effects linear regression model to account for clustering of patients within site. Secondary clinical outcomes will be similarly compared pre-implementation and post-implementation using mixed effects linear or logistic regression models, as appropriate. All models will be adjusted for age, sex, severity of illness (sequential organ failure assessment score on admission) and severity of hypoxemia on admission based on PF ratio, as well as type and size of ICU. Pre-specified subgroups will include patient sex, age, HRF, ARDS, Covid-19 and cardiac surgical status, body mass index (BMI), height, illness acuity, and ICU volume.

Ethics and Trial Registration: The study has received ethics approval from the University of Calgary (20-0646) and the University of Alberta (pro00112232). The trial was registered with ClinicalTrials.gov (NCT04744298) prior to the enrollment of any patients on Feb 8, 2021.

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Protocol version:	2.5 (February 14, 2023)
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Protocol and SAP revision history

Protocol		**SAP**	
Version & Date	Summary of Change	Version	Action
1.0 04/27/2020	First version	N/A	SAP not finalized
2.0 12/09/2020	Access to data in new Clinical Information System	N/A	SAP not finalized
2.1 02/23/2022	Updated with the completion of the SAP by the Scientific Steering Group: • Follow-up period increased from 2 to 4 months	1.0	SAP finalized Feb 22, 2022
2.2 06/13/2022	Incentive added for Focus Group participants	1.0	SAP reviewed, **no change**
2.3 09/02/2022	Increased total number of Focus Groups	1.0	SAP reviewed, **no change**
2.4 10/28/2022	Incentive added for survey participation	1.0	SAP reviewed, **no change**
2.5 02/14/2023	Editorial updates, added summary of amendments table	1.0	SAP reviewed, **no change**

1 Table of Contents

2 Abbreviations

ABG	Arterial Blood Gas
ARDS	Acute Respiratory Distress Syndrome
CXR	Chest x-ray
CFS	Composite Fidelity Score
CI	Confidence Interval
FiO_2	Fraction of Inspired Oxygen
HRF	Hypoxemic Respiratory Failure
ICU	Intensive Care Unit
ICC	Intraclass Correlation Coefficient
IQR	Interquartile range
LOS	Length of Stay
PaO2	Partial pressure of oxygen
PF ratio	PaO2/FiO2
PEEP	Positive End Expiratory Pressure
PBW	Predicted Body Weight
SD	Standard Deviation
SpO2	Peripheral oxygen saturation
TFA	Theoretical Framework of Acceptability
VFDs	Ventilator Free Days
TV	Tidal volume
VV-ECMO	Veno-venous Extracorporeal Membrane Oxygenation

3 Administrative Information

This document has been written based on information contained in the study protocol version 2.5, dated February 14, 2023 in accordance with Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.(1) Study methods will be conducted and reported in accordance with standards for reporting stepped wedge cluster randomised trials (CONSORT, SW-CRT extension),(2) and standards for reporting implementation studies(StaRI)(3) and their replication (TIDieR).(4) Qualitative work will be reported using Standards of Reporting of Quality Research guidelines (SRQR) and Consolidated criteria for Reporting Qualitative research (COREQ).(5, 6) The protocol is also reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance and checklist 2013.(7)

The study has received ethics approval from the University of Calgary (20-0646) and the University of Alberta (pro00112232). The study protocol is registered on clinicaltrials.gov NCT04744298.

4 Introduction

4.1 Background and rationale

Hypoxemic respiratory failure (HRF) and acute respiratory distress syndrome (ARDS) are common conditions among patients admitted to the intensive care unit (ICU). Treatment of the patients is complex. Evidence-based therapies that improve survival exist; however, implementation is inconsistent and variable. The Institute of Medicine has recommended standardized care processes to improve the reliability and safety of care.(8) We developed the *Venting Wisely* pathway to reduce practice variation and improve adherence to evidence-informed therapy. A study is needed to evaluate effectiveness, cost effectiveness, and implementation of the pathway.

4.2 Study objectives and hypothesis

The overall objective of this study is to improve the quality of care for patients with HRF by implementing a rigorously developed, evidence-based, stakeholder-informed, multidisciplinary standardized care pathway called *Venting Wisely* that standardizes the diagnosis and delivery of life-saving therapies for critically ill patients with HRF.

The specific objectives are to evaluate:

(1) **Clinical Effectiveness** of the pathway using a pragmatic registry-based cluster randomized stepped-wedge implementation study involving 17 adult ICUs.

(2) **Implementation** of the pathway by conducting a process evaluation which will assess the **fidelity** of the delivered interventions and clinician perceptions about the **acceptability** of the pathway.

(3) A **cost-effectiveness** analysis of the pathway.

We *hypothesize* that the pathway will increase adherence to life-saving therapies, improve patient outcomes, and save costs within the health care system.

5 Study Methods

5.1 Study design

The study is designed as an effectiveness-implementation hybrid study design (type 1).(9) This study design evaluates both clinical e*ffectiveness* and *implementation* of the pathway, but is primarily powered to the primary clinical effectiveness outcome. Implementation will occur via a pragmatic registry-based stepped wedge cluster randomized implementation study.(9)

5.2 Setting

The study will be conducted at 17 adult ICUs in Alberta, Canada. These 17 ICUs comprise a mix of tertiary, community, and rural ICUs. One ICU (Calgary) served as the setting for a pilot study (completed September 2020). The remaining 16 ICUs will participate in the full study.

5.3 Randomization

The unit of randomization will be a cluster. Two ICUs will comprise each cluster. Each ICU will be randomly assigned to one of the 8 clusters to initiate the intervention at different times according to the stepped wedge allocation schedule (See Figure 1). Sites will be randomized using computer generated random number sequence by a blinded investigator. Details of the randomization method are held securely in the statistics master file. Two sites will be selected at any time. ICU sites will be deferred from a randomization step if critical unreadiness events are identified which would include Covid-19 related capacity strain, transition to a new electronic health record, or undergoing Provincial ICU accreditation. Sites will be randomized and notified four to eight weeks prior to the initiation schedule to prevent contamination.

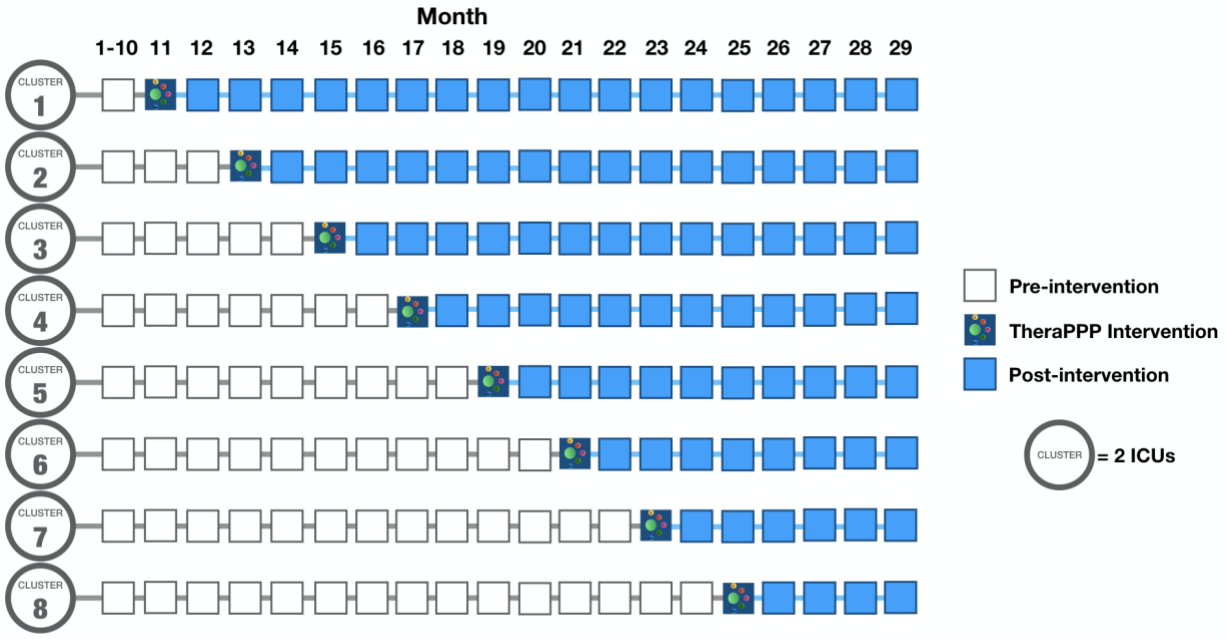

Figure 1. TheraPPP Study: stepped wedge cluster randomization

5.4 Study Duration

There will be a 10-month (June 2020 - March 2021) baseline data collection period at the beginning of the study common to all sites. Baseline data will continue to be collected until the intervention is implemented in an ICU. The intervention will be implemented into one cluster (two ICUs) every two months. The first month of each step will be a transition period from usual care, during which data will not be analyzed. Once implemented, the cluster will continue to receive the intervention for the remainder of the study. There will be a four month follow up period after implementation of the final cluster. The total study duration will be 29 months (June 2020-October 2022).

5.5 Sample Size

This study will assess both the effectiveness and implementation of a standardized management pathway for HRF and ARDS. The study is a type 1 hybrid effectiveness-implementation design and therefore is primarily powered for the effectiveness outcome.(9) We also provide sample size

calculations for the implementation outcomes to estimate the effect sizes and precision of estimates that can be detected.

5.5.1 Clinical Effectiveness Sample Size

The design of the cluster randomized stepped wedge TheraPPP trial incorporated several considerations. The study balances detection of a meaningful clinical difference in the primary outcome of 28-day ventilator free days (VFDs), with a pragmatic and efficient implementation of the pathway. A step duration that was too long would potentially result in contamination or secular changes in practice. A step duration that was too short would not allow adequate time for implementation of the pathway within each cluster. The number of ICUs per cluster also balanced the study team's ability to implement the pathway in a given step. Too many ICUs per cluster would not be feasible for the implementation team, but alternatively, too few would result in a study duration that was too long and also susceptible to contamination or secular changes in practice.

Based on the considerations above, the final study design included a ten-month baseline data collection period, eight clusters with two ICUs per cluster, and implementation of the pathway in one cluster every two months followed by a four month post implementation period following the last cluster. Based on historical ICU admission rates in Alberta from 2018-2019 (unpublished eCritical registry data), we estimate a total of 18816 mechanically ventilated patients will be included in this study with 11424 patients pre-implementation and 7392 patients post implementation. Based on this, a baseline mean VFDs of 21 (standard deviation (SD) 10, intraclass correlation coefficient (ICC) = 0.15), a 90% power and a two-sided α=0.05 we estimate an ability to detect a difference of 0.9 VFDs (see Table 1).

Given that ARDS is an important subgroup of patients within this cohort that would receive most steps of the pathway, we also wanted to ensure that we would recruit enough patients from this subgroup of interest over the study duration. To estimate the ARDS population within this cohort, we applied a population-based incidence of ARDS that was derived within Calgary using standardized screening for ARDS.(10) Using this historical population-based incidence, we anticipate an average of 12 sustained ARDS patients (see Appendix Table 1 for definition) per 2-month period per site (based on our observed sustained ARDS incidence of 0.42 per bed per month in Calgary).(10) Based on the stepped wedge design, we estimate that this will generate a sample size of 2688 sustained ARDS patients within our TheraPPP study cohort. This number of patients will provide the ability to detect a minimum difference of 2.4 days (11 to 13.4) in the mean 28-day VFDs (with a 90% power and a two-sided α=0.05, ICC = 0.01) within this subgroup. The minimal clinically important difference of 2.4 days is similar to other ARDS trials.(11-13) The ICC was estimated to be 0.011 (95% confidence interval (CI) 0.00-0.20) based on our previous epidemiological description of patients with sustained ARDS which was based on four sites in Alberta.(10) The VFD effect difference in ARDS patients that this study is powered to is conservative, and targets the lower limit of the pooled effect difference observed in our previously published systematic review on the use of standardized management pathways for HRF and ARDS (standardized mean difference increase of 3.48 (2.43-4.54) days).(14)

To improve the reliability of these estimations we conducted several sensitivity analyses. In order to ensure these assumptions were applicable to the cohort of 16 ICUs, particularly the ICCs that we are using to estimate our detectable difference, we conducted an alternative estimation based on provincial eCritical registry data from 2018-2019. Given that all mechanically ventilated patients are

eligible for the pathway but not all patients may receive all elements, we also estimated the sample size based on recent data from 2018-2019 using a more liberal approach to eligible patients that would be estimated based upon patients with sustained HRF (see Appendix Table 1 and Table 1*)*. The detectable difference was similar to our previous estimates. We also examined the proportion of patients with ARDS, as well as the detectable difference in VFDs using two registry-based definitions of ARDS (ARDS definition 1 and definition 2, see Appendix Table 1 & 4*)*. ARDS is not formally or routinely documented in day-to-day electronic health records and therefore a registry based method was used. The diagnosis of ARDS by this method may be less precise; however, was used to provide an ICC for all 16 ICUs. Using these alternative assumptions, the minimum detectable difference would be similar (see Table 1). The power calculation was performed using the Stata function "steppedwedge".(15, 16)

Table 1. Ventilator Free Days Detectable Differences (Primary Clinical Effectiveness Outcome)

Cohort	Population	Baseline mean VFDs	SD	Total # of measurements	ICC	Power (%)	Detectable Difference in mean VFDs
All MV patients	Primary	21	10	18816	0.15	90	0.9
Sustained HRF patients	Subgroup	15	11	4928	0.02	90	2.1
ARDS definition 1 patients	Subgroup	15	11	4032	0.02	90	2.3
ARDS definition 2 patients	Subgroup	15	10	1792	0.02	90	3.0
Sustained ARDS (Calgary)	Subgroup	11	10	2688	0.01	90	2.4

ARDS=acute respiratory distress syndrome. ICC=intraclass correlation coefficient. HRF=hypoxemic respiratory failure. MV=mechanically ventilated. SD=standard deviation. VFDs=ventilator free days. Calculations for all MV patients, sustained HRF patients, ARDS definition 1 patients, and ARDS definition 2 patients are based on eCritical registry data from November 2018 to November 2019. Calculations for the ARDS Calgary cohort is based on standardized screening for ARDS in four ICUs in Calgary. See Appendix 1 Table 1 for details on criteria for sustained HRF, ARDS definition 1 and 2, and sustained ARDS.

5.5.2 Implementation Sample Size

Implementation will be assessed by the fidelity to the intervention and by the acceptability of the pathway to the healthcare team.

Fidelity

Given this is a type 1 hybrid study, we also estimated the detectable difference in our primary implementation outcome (Composite Fidelity Score [CFS%]). Based on our primary implementation outcome of CFS%, and using a baseline CFS of 20%, a standard deviation of 32%, 18816 patients, ICC of 0.31, (with a 90% power and a two-sided α=0.05), we estimate the study could detect a difference of 2.6% in mechanically ventilated patients (See table 2). We conducted similar sensitivity analyses for the sample size using recent data from 2018-2019 from the eCritical registry using a more liberal approach to eligible patients that would include based upon patients with sustained HRF and registry-based definitions of ARDS (Table 2). Estimates for sustained HRF or using registry-based ARDS definitions were similar (Table 2). Based on the sample of 2688 sustained ARDS patients (calculated for the primary clinical outcome) and a baseline mean CFS% of 56% (SD of 29%), this study would have power to detect a minimum difference of 7.1% (56% to 63.1%) in the mean CFS score (with 90% power and a two-sided α=0.05, ICC=0.02). This difference was believed to represent a clinically important difference, as a similar improvement was observed in our pilot intervention. Despite the pilot study not being powered for clinical outcomes, this degree of

improvement was associated a reduction in driving pressure, mechanical power, and ICU length of stay (LOS). The power calculation was performed using the Stata function "steppedwedge".(15, 16)

Table 2. Composite Fidelity Score Detectable Differences (Primary Implementation Outcome)

Cohort	Population	Baseline mean CFS (%)	SD (%)	Total # of measurements	ICC	Power (%)	Detectable Difference in mean CFS (%)
All MV patients	Primary	20	32	18816	0.31	90	2.6
Sustained HRF patients	Subgroup	35	29	4928	0.32	90	4.6
ARDS definition 1 patients	Subgroup	36	30	4032	0.33	90	5.2
ARDS definition 2 patients	Subgroup	38	30	1792	0.38	90	7.4
Sustained ARDS (Calgary)	Subgroup	56	29	2688	0.02	90	7.1

ARDS=acute respiratory distress syndrome. CFS=composite fidelity score. ICC=intraclass correlation coefficient. HRF=hypoxemic respiratory failure. MV=mechanically ventilated. SD=standard deviation. See Appendix 1 for criteria on sustained HRF, and ARDS definition 1 and 2. Calculations for all MV patients, sustained HRF patients, ARDS definition 1 patients, and ARDS definition 2 patients are based on eCritical registry data from November 2018 to November 2019. Calculations for the ARDS Calgary cohort is based on standardized screening for ARDS in four ICUs in Calgary. See Appendix 1 Table 1 for details on criteria for sustained HRF, ARDS definition 1 and 2, and sustained ARDS.

Acceptability (Surveys)

We estimate up to a total of 1000 survey responses from clinicians. Based on our pilot study and previous work (5) we anticipate a conservative response rate of 50% (625 surveys completed of 1250 distributed) which will provide 95% binomial confidence intervals of ±3.9%.

5.6 Framework

This study is designed as a superiority hypothesis testing framework.

5.7 Interim analysis

Interim analyses are not planned and will not be performed.

5.8 Timing of final analysis

The primary analysis will be prepared once all patients have reached 90-days of follow-up (with time=0 being the initiation of mechanical ventilation). Final electronic data will be available within six months of the 90-day follow-up period (see Figure 2). Completion of final analysis is targeted for October 2023). This statistical analysis plan version 1 (February 22, 2022) was added to clinicaltrials.gov and posted publicly on a preprint server (medrxiv.org) prior to the retrieval of electronic data and before any analyses had been conducted.

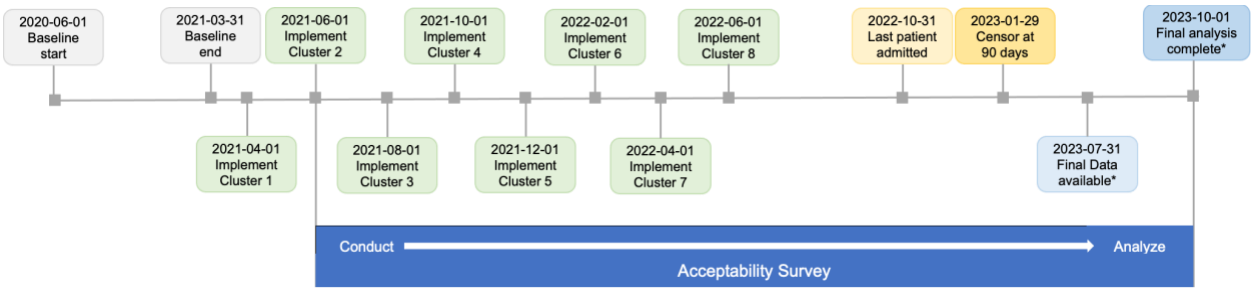

Figure 2. Study Timeline

*=Estimated date

5.9 Timing of outcome assessments

Timing of outcome assessments for primary outcomes are listed below and all outcomes (primary, secondary, and exploratory) are detailed in section 8.1 and Appendix Table 3.

5.9.1 Clinical effectiveness

For the primary outcome of 28-days VFDs, which is a composite outcome of survival and days spent not ventilated over the first 28 days, *timing* is measured as follows:

- The first day of ventilation is day 0
- The end date is the date of first ventilation + 28 days (censored at hospital discharge)

VFDs are calculated as previously described (17, 18):

- 0 if the patient dies within 28 days of mechanical ventilation
- 0 if the patient is still being ventilated after 28-days following initiation of mechanical ventilation whether they are extubated and survive or die after this timepoint
- 28 – x (if the patient successfully liberated from ventilation x days after initiation, within the 28-day timeframe)
- If a patient is invasively mechanically ventilated via endotracheal tube or tracheostomy for any period of time in a 24-hour period (0000-2359) this is considered a ventilated day
- In the case of repeat intubation episodes, liberation will be counted from the day of final successful extubation

5.9.2 Implementation

<u>Fidelity</u>

The primary outcome of adherence is the CFS. The individual metrics of the CFS are measured per admission (height) and daily. See *Implementation Outcomes – Fidelity Indicators* section in Appendix Table 3 for details.

<u>Acceptability (survey)</u>

To evaluate acceptability outcomes, invitations to participate in the *acceptability survey* will be sent to clinicians (nurses, physicians, and Respiratory Therapists) two to six months post implementation in each cluster.

6 Statistical Principles

6.1 Confidence intervals and P values

The threshold for the entire analysis of primary and secondary outcomes will be two-sided using a 5% significance level (α=0.05). Measures of association will be reported using difference in means or odds ratios with 95% CI as appropriate. There is only one primary clinical effectiveness outcome, therefore no adjustment for multiplicity is required. For secondary outcomes we will the report the false discovery rate to account for multiplicity of testing.

6.2 Adherence and protocol deviations

6.2.1 Adherence

Fidelity of the intervention will be tracked using five evidence-based process of care indicators that reflect the five key steps of the pathway which are routinely charted in the electronic health record:

1) Proportion of patients ventilated with a height measured (step 1)
2) Proportion of eligible patient days who receive a tidal volume ≤8mL/kg predicted body weight (step2/3)
3) Proportion eligible patient days who have a plateau pressure measured (step 3)
4) Proportion of eligible patient days who receive neuromuscular blockade (step 4)
5) Proportion of eligible patient days who receive prone ventilation (step 5)

The CFS awards points for the five indicators above that are met and provides an overarching indicator of adherence. See 8.1.2 and the *Implementation Outcomes – Fidelity Indicators* section in Appendix Table 3 for additional details of adherence indicators.

Adherence will be presented pre and post implementation of the intervention (Mean, Median, interquartile range (IQR), p-value). Time trends in the CFS will also be presented for all mechanically ventilated patients, patients with HRF, and patients with ARDS (definition 2, see Appendix Table 1 for definition). Fidelity process of care indicators will also be used to improve pathway adherence through monthly audit and feedback reports.

6.2.2 Protocol deviations

The following protocol deviations will be summarized:

1) An ICU site withdraws from implementation of the pathway.
2) An ICU is not able to initiate implementation on their scheduled start date.
3) An ICU is not able to chart the requisite data required for audit and feedback, implementation outcomes and clinical outcomes (e.g., due to pandemic surge crisis charting).

6.3 Analysis populations

We will analyse the data using an intention to treat analysis. In the event of a patient moving from an intervention site to a non-intervention site, see section 7.4 for details.

7 Trial Population

7.1 Screening Data

All patients admitted to the adult ICU will be screened daily for eligibility for the pathway.

7.2 Eligibility

All mechanically ventilated patients admitted to the ICU will be included in the study and receive the pathway intervention. There are no exclusion criteria for entry into in the pathway; however, not all steps will be applicable to all mechanically ventilated patients. Patients cared for in non-traditional ICU settings due to expanded Covid-19 surge capacity (e.g. Coronary Care Unit, post-operative care units) will be included.

7.3 Recruitment

Number of ICUs, number of eligible patients, and exclusions will be detailed in the CONSORT flow diagram. See Figure 3.

7.4 Withdrawal / Follow-up

At the site level – a site will be withdrawn from the study if they decline or refuse to implement the pathway. All sites agreed to participate.

At the patient level, in the case of a patient transfer from a site where implementation is active to a non-active site or vice-versa, a patient will be deemed to be assigned to that original site for the purposes of assessing all outcomes if they have spent 48 hours or longer mechanically ventilated at that original site. This is based on a previous study that demonstrated that a lung protective ventilation strategy was most influential within the first 48 hours of initiation of invasive mechanical ventilation following ARDS diagnosis.(19) A sensitivity analysis will be conducted using alternative thresholds of 24 hours, 72 hours, and 1 week to test the robustness of this finding (see Section 8.2.1).

We will present any loss to follow-up but we expect this to be minimal due to electronic data collection.

7.5 Baseline patient characteristics

Categorical data will be summarized by frequencies and percentages. Continuous data will be summarized as medians and IQR. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted. Appendix Table 2 lists the baseline patient characteristics and how they will be reported.

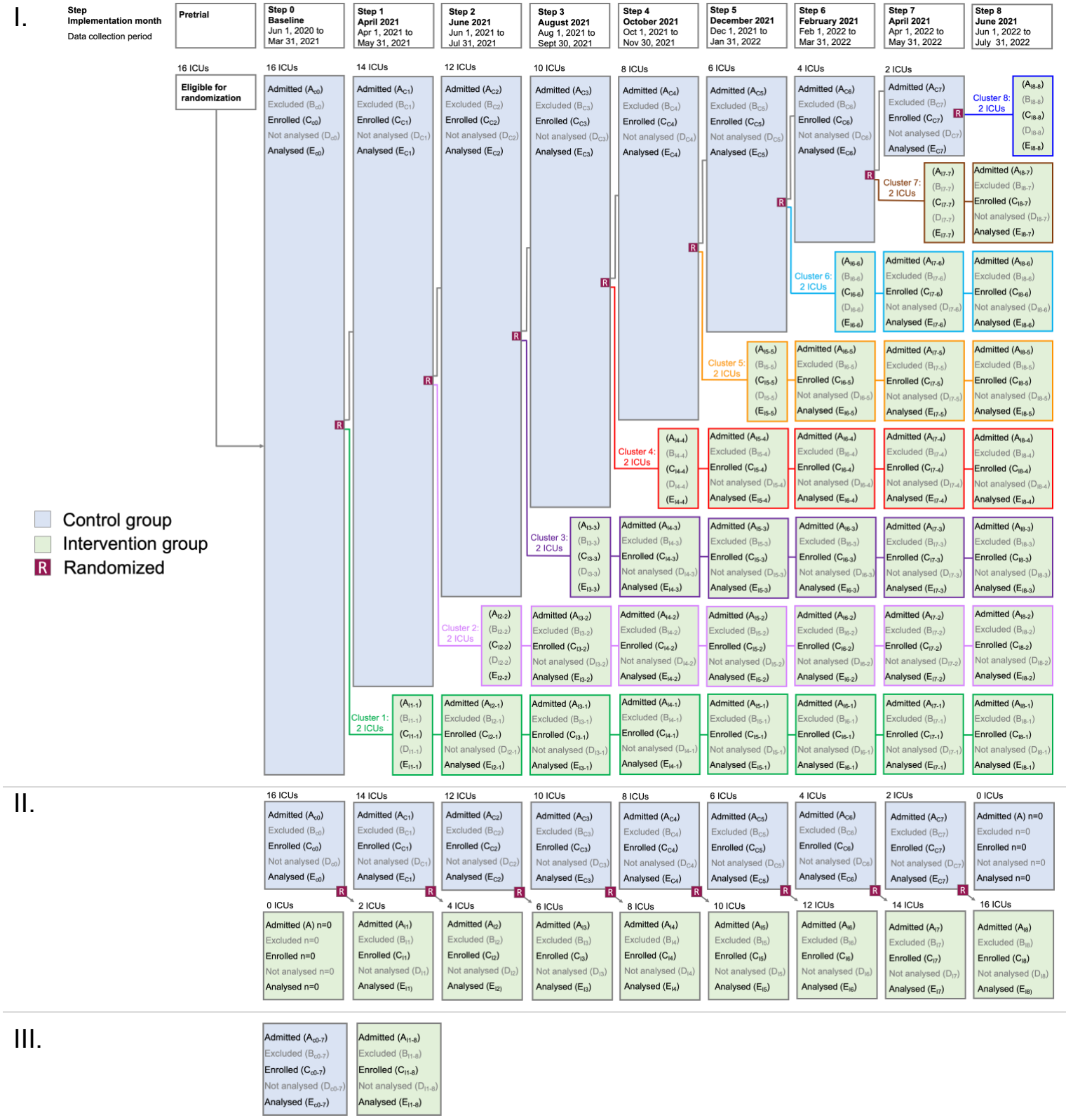

Figure 3. CONSORT Diagram

I=patients by step. II=patients by cluster. III=patients at trial level. Admitted (A) = The number of patients admitted. Excluded (B) = The number of patients who were excluded e.g. NOT mechanically ventilated. Enrolled (C) = the number of patients who were enrolled. (C=A - B). Not analysed (D) = the number of patients who were NOT analysed e.g. no chart available. Analysed (E) = the number of patients who were analyzed (E=C - D). $_c$=Control $_i$=Intervention. In each box the symbols represent the analysis status (A, B, C, D, E), whether it is control ($_c$) or intervention ($_i$) group, step of the stepped wedge (0 to 8), and in section I, for the intervention groups, which cluster (1-8). For example, $A_{15\text{-}2}$ is the number of patients admitted (A) in the intervention group ($_i$) in the step 5 ($_5$) of the study period for cluster 2 sites ($_{-2}$).

8 Analysis

8.1 Outcome measures

8.1.1 Primary clinical effectiveness outcome

The primary clinical outcome is **28-day ventilator free days (VFDs)** (in-hospital) a composite outcome of survival and days spent not ventilated over the first 28 days. 28-day VFDs are measured per admission, censored at hospital discharge and reported as mean (SD) and median (IQR).

8.1.2 Primary implementation outcome

The primary implementation outcome is a **composite fidelity score (CFS)** that awards points for up to 5 key fidelity indicators that are met and is reported as a percentage. The individual indicators are measured per admission (height) or daily. Trends in mean CFS by time since implementation will be presented for all mechanically ventilated patients, patients with HRF, and patients with ARDS (definition 2, see Appendix Table 1 for definition).

8.1.3 Secondary clinical effectiveness outcomes

(1) *28-day hospital, ICU, and hospital survival* are measured per admission and reported as frequency with proportion of patients. 28-day hospital survival is measured at 28-days and censored at hospital discharge. Hospital survival is censored at 90 days. The first day of ventilation is day 0. 28-day hospital survival is the component of VFDs that reflects survival.

(2) Ventilator duration is the number of ventilated days. If a patient is invasively mechanically ventilated via endotracheal tube or tracheostomy for any period of time in a 24-hour period (0000-2359) this is considered a ventilated day. A ventilated day is the component of VFDs that reflects duration of ventilation.

(3) *Driving Pressure.* Driving pressure is calculated on patients ventilated with PF ratio (partial pressures of oxygen (PaO2) / fraction of inspired oxygen (FiO2)) ≤ 300 on a controlled mode as plateau pressure – positive end expiratory pressure (PEEP). It is reported throughout the ICU stay as median (IQR).

(4) *Mechanical power.* Mechanical power is calculated on patients ventilated with PF ratio ≤ 300 on a controlled mode using the formula *Power = 0.098*respiratory rate•(tidal volume/1000)*(Peak Pressure – (0.5 • Driving Pressure)).*(20) It is reported throughout the ICU stay as median (IQR).

(5) *Length of Stay (LOS).* ICU and hospital LOS are measured per admission and reported as median (IQR). Hospital LOS is censored at 90 days.

(6) *Utilization of veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO).* Utilization of VV-ECMO is measured per admission and reported as frequency with proportion of patients.

8.1.4 Secondary implementation outcomes

<u>Fidelity</u>

Secondary fidelity outcomes are process of care indicators that reflect the five key steps of the pathway:

(1) Proportion of patients ventilated with a *height ever documented (*step 1) are measured per admission and reported as frequency (proportion). Additional secondary height outcomes are detailed in Appendix Table 3.

(2) The proportion of eligible patient days (PF ratio≤ 300) who receive a *tidal volume ≤ 8ml/kg* predicted body weight on controlled mode ventilation (step2/3) is measured daily and reported as a frequency (proportion). If height is not documented, a tidal volume indicator is determined based on using an average height of:

- 162cm for females [Predicted Body Weight 54.2kg, tidal volume <=434ml]
- 176cm for males [Predicted Body Weight 71.5kg, tidal volume <=572ml]
- Predicted body weight will be calculated as previously described.(21)

If inhaled or set tidal volume is not available, exhaled tidal volume is used.

(3) The proportion of eligible patient days (PF ratio ≤ 300) who have a *plateau pressure measured* on controlled mode ventilation (step 3) is measured daily and reported as a frequency (proportion).

(4) The proportion of eligible patient days (PF ratio ≤ 150) *receiving neuromuscular blockade* on controlled mode ventilation (step 4) is measured daily and reported as a frequency (proportion).

(5) The proportion of eligible patient days (PF ratio ≤ 150 and FiO2 ≥ 0.60) *receiving prone ventilation* on controlled mode ventilation (step 5) is measured daily and reported as a frequency (proportion).

Please see Appendix Table 3 for full details on the criteria for eligible patient days and definitions for each process of care indicator.

Acceptability

The acceptability outcomes assess clinician perceptions about the pathway and are based on the seven component constructs of the Theoretical Framework of Acceptability (TFA) listed below.(22) These are measured on a five-point Likert scale, a median of four or above indicates agreement.

(1) Composite acceptability score is the proportion of the seven TFA constructs (see below 2 to 8) on the acceptability survey graded with a median score of four or above on a five-point Likert scale, indicating agreement.

(2) Intervention coherence (the extent to which the clinician understands the intervention).

(3) Opportunity costs (benefits or costs to the clinician for using the pathway).

(4) Perceived effectiveness of the pathway (the extent to which the intervention is perceived by clinicians as likely to achieve its purpose).

(5) Self-efficacy (a clinician's confidence that they can use the pathway).

(6) Affective attitude (how a clinician feels about the intervention).

(7) Burden (a clinician's perceived amount of effort required to participate in the intervention).

(8) Ethicality (the extent to which the intervention aligns with a clinician's value system).

See Appendix Table 3 for additional details of outcomes.

8.2 Analysis Methods

8.2.1 Clinical effectiveness

Clinical outcomes will be analyzed at the patient-level. For the primary analysis, we will compare the mean 28-day VFDs pre-implementation and post-implementation using a mixed effects linear regression model to account for clustering of patients within site. Secondary clinical outcomes will be similarly compared pre-implementation and post-implementation using mixed effects linear or logistic regression models, as appropriate. All models will be adjusted for age, sex, severity of illness (sequential organ failure assessment score on admission) and severity of hypoxemia on admission based on PF ratio, as well as type and size of ICU. We will include time (days) in the models to account for secular trends over time, since failure to include such time effects can bias estimates of effect sizes. Data from the 1-month implementation transition phase within each step will not be included in the analysis of primary and secondary outcomes. If the distribution of a continuous outcome is skewed, a log-transformation of the outcome will be considered if applicable. A two-sided p-value < 0.05 will indicate statistical significance.

Sensitivity analysis. As a sensitivity analyses, we will analyze VFDs using a time-to-event analysis censored at 28 days using Fine and Gray competing risk regression since we have two mutually exclusive potential endpoints (successful extubation or death). If the proportional hazards assumption is not satisfied, the subdistribution hazard ratio obtained from the Fine and Gray model can be interpreted as the average subdistribution hazard ratio.(18) Schoenfeld-type residuals will be used to assess the proportional subdistribution hazard assumption.(23, 24) Differences in secondary outcomes pre and post-implementation will be analyzed using mixed effects linear and logistic regression models accounting for clustering of patients within site, as appropriate. For VFDs, we will also conduct a sensitivity analysis in which we exclude patients cared for in non-traditional ICU settings due to potential differences with patient cared for in traditional ICU settings (electronic data extraction). In the case of transfer delays out of the ICU due to bed availability, a sensitivity analysis will be conducted on ICU LOS. The sensitivity analysis will be conducted on ICU LOS by excluding ICU avoidable days and instead use the date ready for transfer.

8.2.1.1 Subgroup analysis

The following subgroup analyses will be conducted for both the primary effectiveness outcome (28d VFDs) and also the primary implementation outcome (CFS). We will test for heterogeneity of treatment effect across these subgroups and report the corresponding p-value for interaction with a p-value less than 0.05 being deemed significant. To account for multiple testing for the subgroup analyses, we will report the false discovery rate.

- High vs low ICU volume (split at the median, over study period)
  - *Low volume ICUs most likely to improve VFDs given lower baseline CFS*
- HRF (HRF vs non-HRF)
  - *HRF patients most likely to improve VFDs as eligible to get more elements of pathway*
- ARDS definition 2 (see Appendix 1, Table 1 & 4) (ARDS vs non-ARDS)
  - *ARDS patients most likely to improve VFDs as eligible to get more elements of pathway*
- Females vs males
  - *Females most likely to improve VFDs given lower baseline CFS*
- Covid positive vs Covid negative
  - *COVID patients most likely to improve VFDs as eligible to get more elements of pathway*
- Cardiac Surgery vs non-cardiac surgery patients
  - *Non cardiac surgery patients most likely to improve VFDs as eligible to get more elements of pathway*

- Average height of patients (3 categories: quartile 1, quartile 2 and 3, quartile 4)
    - *Lower quartile height patients to most likely to improve VFDs given lower baseline lung protective strategies*
- Severity of HRF within the first 24 hours of mechanical ventilation (severe vs moderate vs mild)
    - *Severe HRF patients most likely to improve VFDs as eligible to get more elements of pathway*
- Age >60 vs 60 and under (median age)
    - *Age > 60 patients most likely to improve VFDs as mortality at presentation is higher*
- Weight by Body Mass Index classifications (<18.5, 18.5 to <25, 25 to <30, >30)
    - *Higher BMI patients to most likely to improve VFDs given lower baseline lung protective strategies*
- Severity of illness high vs low SOFA score (SOFA score <12 vs 12 or more)
    - *SOFA > 12 patients most likely to improve VFDs as mortality at presentation is higher*

8.2.2 Implementation

Fidelity

Quantitative assessment of fidelity will be tracked using process of care indicators that reflect the five key steps of the pathway. Differences in fidelity outcomes pre-implementation and post-implementation will be analyzed similarly to the effectiveness clinical outcomes using mixed effects regression models.

Acceptability (surveys)

Survey data will be presented as aggregated frequencies with proportions. Data will be stratified by clinician profession, years of experience, and type of institution. Differences will be compared using Fisher's exact test or Chi-squared test for categorical variables, or the Wilcoxon rank-sum test or Kruskal Wallis test for Likert scale data, as appropriate.

8.3 Missing Data

Outcome data is expected to be available for all ventilated ICU patients admitted to the study ICUs during the study period as all clinical effectiveness and patient characteristics data is available electronically and will be extracted retrospectively following study completion. If patient data is not available electronically, data will be extracted from paper charts where available. If a PF ratio is unavailable, for example due to an arterial blood gas not being obtained or a patient does not having an arterial line, a non-invasive approach using pulse oximetry and the peripheral oxygen saturation (SpO2:FiO2) ratio will be used as previously described.(25-27)

8.4 Additional Analysis

Additional statistical analysis is not currently required.

8.5 Harms

Safety reporting is not being done as the intervention is not experimental it is standard of care. Harms are assessed in outcomes of VFDs and survival.

8.6 Statistical software

R will be used to carry out analysis.

8.7 References

References for statistical methods are listed below. Data management is detailed in the Data Access, Transfer, Encryption, and Storage sections of the protocol. The *Trial Master File* and *Statistical Master*

File are separate files and stored on a secure password-protected AHS computer held by the study biostatistician with restricted access.

9 Additional Information

9.1 Health Economics

Details of the health economics analysis will be outlined in a separate Health Economics Analysis Plan. In this study we consider LOS both a clinical effectiveness and economic outcome.

9.2 Scientific Steering Group

The Protocol and Statistical Analysis plan have been reviewed by the TheraPPP Scientific Steering Group (see Appendix Table 5).

10 **Signatures of approval**

This SAP version 1.0 February 22, 2022 has been reviewed in detail by the Venting Wisely Scientific Steering Group and approved for dissemination and release. At the time of this dissemination no retrieval of electronic data or analyses has been conducted.

Dr. Ken Kuljit Parhar		March 7, 2023
Principal Investigator name	Principal Investigator signature	Date
Dr Andrea Soo		March 9, 2023
Senior Biostatistician name	Senior Biostatistician signature	Date

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Statistical analysis plan for the Identification and Treatment of Hypoxemic Respiratory Failure (HRF) and ARDS with Protection, Paralysis, and Proning: a type-1 hybrid stepped-wedge cluster randomized effectiveness-implementation study

Appendix

Table 1. Criteria for definitions of Hypoxemic Respiratory Failure and ARDS

Definition	PF ratio	Timing of ABG	CXR	Dx
HRF	≤300	At least 1 PF ratio 0000-0800	N/A	N/A
Sustained HRF	≤300	At least 1 PF ratio on any ABG 6-36 hours after initial HRF diagnosis (2 ABGs)	N/A	N/A
Sustained ARDS	≤300	Any ABG done 6-36 hours after initial HRF diagnosis (2 ABGs)	Bilateral infiltrates	All **excluding** CHF & cardiogenic shock
eCritical ARDS **definition 1** (**exclusion** method)	≤300	Any ABG done 6-36 hours after initial HRF diagnosis (2 ABGs)	*	**Excludes** all primary diagnoses (e.g., cardiac conditions) not consistent with ARDS in eCritical†
eCritical ARDS **definition 2** (**inclusion** method)	≤300	Any ABG done 6-36 hours after initial HRF diagnosis (2 ABGs)	**	**Includes** only conditions that could be indirect and direct causes of ARDS†

ABG=arterial blood gas. ARDS=acute respiratory distress syndrome. CHF=congestive heart failure. CXR=chest x-ray. Dx=diagnoses. eCritical=data repository of patient-specific critical care clinical information. HRF=hypoxemic respiratory failure. PF ratio=PaO2/FiO2.

*When comparing the performance of the **exclusion** method definition to one that requires the **addition** of bilateral infiltrates on CXR, the specificity was 89.6% (95% CI 87.1%-91.8%) while the sensitivity was 100% (95% CI 98.3%-100%) with a kappa of 0.74 (95% CI 0.70-0.78).
When comparing the performance of this definition to one that requires the **addition of bilateral infiltrates on CXR, the specificity was 82.4% (95% CI 79.2%-85.3%) while the sensitivity was 100% (95% CI 98.7%-100%) with a kappa of 0.80 (95% CI 0.76-0.85).

†See Appendix Table 4 for a complete list of conditions defined as ARDS and non-ARDS by the exclusion and inclusion methods (ARDS definition 1 & 2).

Table 2. List of baseline characteristics of mechanically ventilated patients to be summarized

Patient characteristic	Reported as
Age	median (IQR)
Sex	n (%)
Weight	median (IQR)
Height	median (IQR)
Predicted body weight	median (IQR)
Any comorbidity	n (%)
AIDS	
Acute renal failure	
Congestive heart failure	
Cirrhosis	
Dialysis	
Diabetes	
Hepatic failure	
Immunosuppression	
Leukemia	
Lymphoma	
Metastatic Cancer	
Respiratory insufficiency	
SOFA score on admission	median (IQR)
APACHE II score on admission	median (IQR)
Clinical Frailty Score	median (IQR)
Admission type	n (%)
Elective	
Emergent	
No surgery	
Unknown	
Reason for ICU admission	n (%)
Medical	
Surgical	
Neurological	
Trauma	
Unknown	
First PF ratio closest to 0800	median (IQR)
Median PF ratio within the first 24 hours of being ventilated[±]	median (IQR)
Tidal volume (exhaled) (mL/kg)[±]	median (IQR)
Tidal volume (exhaled) (mL/kg) on controlled mode[±]	median (IQR)
Respiratory rate[±]	median (IQR)
Minute ventilation[±]	median (IQR)
PEEP[±]	median (IQR)
Plateau pressure[±]	median (IQR)
Plateau pressure on controlled mode[±]	median (IQR)
Peak pressure[±]	median (IQR)
Mean airway pressure[±]	median (IQR)
Driving pressure on controlled mode[±]	median (IQR)
Mechanical power on controlled mode[±]	median (IQR)
Hypoxemic respiratory failure (HRF)*	n (%)
ARDS (definition 2)**	n (%)
Vasoactive medications	n (%)
Continuous renal replacement therapy	n (%)
Intermittent hemodialysis	n (%)

[±]Within the first 24 hours of being ventilated. *Based on having at least 1 PF ≤300 on an arterial blook gas (ABG) done between 0000-0800. **HRF sustained (Based on PF ≤ 300 on any ABG done 6-36 hours after initial HRF diagnosis) (2 ABGs) + includes only conditions that could be direct and indirect causes of ARDS. APACHE=Acute Physiology and Chronic Health Evaluation. ARDS=acute respiratory distress syndrome. Driving pressure=Plateau pressure - Positive End Expiratory Pressure. IQR =interquartile range. PEEP=Positive End Expiratory Pressure. PF ratio=PaO_2:FiO_2 ratio. Mechanical power=0.098*resp rate*(tidal volume/1000)*(peak-(0.5*driving)). SOFA=Sequential Organ Failure Assessment. VFD=ventilator free days.

Table 3. Primary and secondary effectiveness, fidelity, and acceptability outcomes

Clinical Effectiveness Outcomes	**Patient or subgroup**	**Timepoints at which the outcomes are measured**	**Primary or Secondary Outcome**	**Reporting of results (unit of measurement)**
28-day ventilator-free days (VFDs) (a composite of survival & days spent not ventilated over the first 28 days)	All pts / subgroups	Per admission 28-days Censored at hospital discharge	Primary	Mean (SD) and Median with interquartile range (IQR)
ICU survival	All pts / select subgroups€	Per admission	Secondary	Frequency with proportion of pts
ICU Length of Stay	All pts / select subgroups€	Per admission	Secondary	Median with IQR
28-day hospital survival	All pts / select subgroups€	Per admission 28-days The first day of MV is day 0 Censored at hospital d/c	Secondary	Frequency with proportion of pts
Ventilator duration	All pts /select subgroups€	Per admission	Secondary	Median with IQR
Hospital survival	All pts /select subgroups€	Per admission Censored 90 days after MV	Secondary	Frequency with proportion of pts
Hospital Length of stay	All pts /select subgroups€	Per admission Censored 90 days after MV	Secondary	Median with IQR
Driving Pressure (Plateau pressure – PEEP)	Pts MV with PF ratio ≤300 on controlled mode€	Throughout the ICU stay	Secondary	Median with IQR
Mechanical Power Calculated using the formula: Power = 0.098*respiratory rate•*(tidal volume/1000)*(Peak Pressure – (0.5 • Driving Pressure)	Pts MV with PF ratio ≤300 on controlled mode€	Throughout the ICU stay	Secondary	Median with IQR
Utilization of veno-venous Extracorporeal Membrane Oxygenation (VV-ECMO)	All pts /select subgroups€	Per admission	Secondary	Frequency with proportion of pts
Implementation outcomes - Fidelity Indicators	**Patient or subgroup**	**Timepoints at which the outcomes are measured**	**Primary or Secondary Outcome**	**Reporting of results (unit of measurement)**
Composite fidelity score (CFS) The CFS awards points for fidelity indicators. It can be interpreted as the average proportion of time pathway elements are appropriately performed, it: - Includes all MV patients - Is based on pts being eligible for up to 4 possible interventions per day and height ever documented during the ICU stay (specific indicators indicated by asterisk* below) - A day is only included if pt is eligible for that day - Height measurement only contributes 1 point to the score if it is ever measured during the ICU stay	All pts / subgroups Pt subgroups for individual fidelity indicators are indicated by asterisk* in rows below	Per admission (height) & daily (tidal volume, plateau pressure, neuromuscular blockade and proning)	Primary	For each pt, the CFS is calculated as the number of times pathway elements were appropriately performed out of the number of times the pt was eligible for pathway elements throughout their ICU stay. The CFS is reported as Median (IQR) % and Mean (SD) %
*Height ever documented	MV pts	Per admission	Secondary	Frequency with proportion of pts
Height documented within 1 hour of admission to ICU	MV pts	Per admission	Secondary	Frequency with proportion of pts
Height documented within 2 hours of admission to ICU	MV pts	Per admission	Secondary	Frequency with proportion of pts
Time in minutes to height measurement from ICU admission (among pts with height ever documented)	MV pts with a height measured	Per admission	Secondary	Median with IQR
*****Tidal volume (TV) ≤ 8ml/kg PBW: Previously noted as *Days of safe ventilation* If height is not documented, TV indicator is determined based on using an average height of: • 162cm for females [PBW 54.2kg, TV <=434ml] • 176cm for males [PBW 71.5kg, TV <=572ml]	MV pts: - ABG done that day between 0000-0800 - PF ratio ≤ 300 on that day - On controlled mode	Daily	Secondary	Median (IQR) and mean (SD) proportion of eligible days Outcome is assessed QD, but then summarized as a proportion for each pt, and then the median or mean is taken

TV set will be used for volume-controlled mode and TV inhaled will be used for pressure-controlled mode. If inhaled or set TV is not available, exhaled TV is used. Indicator is based on the median daily TV being ≤ 8 ml/kg PBW				
*****Plateau pressure measured	*Patients ventilated - ABG done that day - PF ratio ≤ 300 on that day - On controlled mode	Daily	Secondary	"
*****Receive any neuromuscular blockade in the consider group (including as little as a single bolus to an infusion)	*Patients ventilated - ABG done that day - PF ratio ≤ 150 on that day - On controlled mode	Daily	Secondary	"
*****Patient proned for those in the consider group	*Patients ventilated - ABG done that day - PF ratio ≤150 and FiO2 ≥0.60 on that day - On controlled mode - Not receiving ECMO that day	Daily	Secondary	"
Implementation Outcomes – Acceptability (survey)	**Patient or subgroup**	**Timepoints at which the outcomes are measured**	**Primary or Secondary Outcome**	**Reporting of results (unit of measurement)**
C**omposite Acceptability Score:** Summary of pathway acceptability measured using the 7 Theoretical Framework of Acceptability (TFA) component constructs (listed below†)	Survey clinicians and pathway educators / champions	Two to six months after implementation	Secondary	Proportion of TFA components with median score of 4 or 5 on a 5-point Likert scale, indicating agreement
†Affective attitude (How an individual feels about the intervention)	"	"	Secondary	Median (IQR)
†Burden (The perceived amount of effort that is required to participate in the intervention)	"	"	Secondary	"
†Ethicality (The extent to which the intervention has a good fit with an individual's value)	"	"	Secondary	"
†Intervention coherence (The extent to which the participant understands the invention and how it works)	"	"	Secondary	"
†Opportunity costs (The extent to which benefits, profits, or values must be given up to engage in the intervention	"	"	Secondary	"
†Perceived effectiveness (The extent to which the intervention is perceived as likely to achieve its purpose)	"	"	Secondary	"
†Self-efficacy (The participant's confidence that they can perform the behavior(s) required to participate in the intervention)	"	"	Secondary	"

€hypoxemic respiratory failure and ARDS subgroups only. ABG=arterial blood gas. CFS=composite fidelity score. d/c=discharge. ECMO=extra corporeal membrane oxygenation. ICU=intensive care unit. IQR= Interquartile range. MV=mechanical ventilation. PEEP=positive end expiratory unit. PF ratio=PaO2/FiO2. PBW=predicted body weight. QD=daily. SD=standard deviation. Pts=patients. TFA=theoretical framework of acceptability. TV=tidal volume. VFDs=ventilator free days. VV-ECMO= veno-venous Extracorporeal Membrane Oxygenation.

Table 4. Conditions defined as ARDS and non-ARDS by Definition 1 (Exclusion method) and Definition 2 (Inclusion method)

Condition	Definition 1	Definition 2
Abdomen only trauma	ARDS	ARDS
Abdomen only trauma, surgery for	ARDS	ARDS
Abdomen/extremity trauma	ARDS	ARDS
Abdomen/extremity trauma, surgery for	ARDS	ARDS
Abdomen/face trauma	ARDS	ARDS
Abdomen/face trauma, surgery for	ARDS	ARDS
Abdomen/multiple trauma	ARDS	ARDS
Abdomen/multiple trauma, surgery for	ARDS	ARDS
Abdomen/pelvis trauma	ARDS	ARDS
Abdomen/pelvis trauma, surgery for	ARDS	ARDS
Abdomen/spinal trauma	ARDS	ARDS
Abdomen/spinal trauma, surgery for	ARDS	ARDS
Ablation or mapping of cardiac conduction pathway	nonARDS	nonARDS
Abscess, neurologic	ARDS	nonARDS
Abscess/infection-cranial, surgery for	ARDS	nonARDS
Acid-base electrolyte disturbance	ARDS	nonARDS
Addisons disease	ARDS	nonARDS
Adrenal neoplasm (including pheochromocytoma)	ARDS	nonARDS
Adrenalectomy	ARDS	nonARDS
Alcohol withdrawal	ARDS	nonARDS
All Burn Patients	ARDS	ARDS
All Surgical Burn Patients	ARDS	ARDS
Amputation (non-traumatic)	ARDS	nonARDS
Amyotrophic lateral sclerosis	ARDS	nonARDS
Anaphylaxis	ARDS	nonARDS
Anastomosis, vascular	ARDS	nonARDS
Anemia	ARDS	nonARDS
Aneurysm repair, ventricular	ARDS	nonARDS
Aneurysm, abdominal aortic	ARDS	nonARDS
Aneurysm, abdominal aortic; with dissection	ARDS	nonARDS
Aneurysm, abdominal aortic; with rupture	ARDS	nonARDS
Aneurysm, dissecting aortic	ARDS	nonARDS
Aneurysm, thoracic aortic	ARDS	nonARDS
Aneurysm, thoracic aortic; with dissection	ARDS	nonARDS
Aneurysm, thoracic aortic; with rupture	ARDS	nonARDS
Aneurysm/pseudoaneurysm, other	ARDS	nonARDS
Aneurysms, repair of other (except ventricular)	ARDS	nonARDS
Angina, stable (asymp or stable pattern of symptoms w/meds)	nonARDS	nonARDS
Angina, unstable (angina interferes w/quality of life or meds are tolerated poorly)	nonARDS	nonARDS
Aortic and Mitral valve replacement	nonARDS	nonARDS
Aortic valve replacement (isolated)	nonARDS	nonARDS
Apnea-sleep; surgery for (i.e. UPPP -uvulopalatopharyngoplasty)	ARDS	nonARDS
Apnea, sleep	ARDS	nonARDS
Appendectomy	ARDS	nonARDS
ARDS-adult respiratory distress syndrome, non-cardiogenic pulmonary edema	ARDS	ARDS
Arrest, respiratory (without cardiac arrest)	ARDS	nonARDS
Arteriovenous malformation, surgery for	ARDS	nonARDS
Arthritis, septic	ARDS	nonARDS
Asthma	ARDS	nonARDS
Atelectasis	nonARDS	nonARDS
Atrial Septal Defect (ASD) Repair	nonARDS	nonARDS
Biopsy, brain	ARDS	nonARDS
Biopsy, open lung	ARDS	nonARDS
Bladder repair for perforation/rupture	ARDS	nonARDS
Bleeding-lower GI, surgery for	ARDS	nonARDS
Bleeding-other GI, surgery for	ARDS	nonARDS
Bleeding-upper GI, surgery for	ARDS	nonARDS
Bleeding, GI-location unknown	ARDS	nonARDS
Bleeding, GI from esophageal varices/portal hypertension	ARDS	nonARDS
Bleeding, lower GI	ARDS	nonARDS
Bleeding, upper GI	ARDS	nonARDS
Blood transfusion reaction	ARDS	nonARDS
Bone marrow transplant	ARDS	ARDS
Bullectomy	ARDS	nonARDS
Burr hole placement	ARDS	nonARDS
CABG alone, coronary artery bypass grafting	nonARDS	nonARDS
CABG alone, redo	nonARDS	nonARDS
CABG redo with other operation	nonARDS	nonARDS
CABG redo with valve repair/replacement	nonARDS	nonARDS

CABG with aortic valve replacement	nonARDS	nonARDS
CABG with double valve repair/replacement	nonARDS	nonARDS
CABG with mitral valve repair	nonARDS	nonARDS
CABG with mitral valve replacement	nonARDS	nonARDS
CABG with other operation	nonARDS	nonARDS
CABG with pulmonic or tricuspid valve repair or replacement ONLY.	nonARDS	nonARDS
Cancer-colon/rectal, surgery for (including abdominoperineal resections)	ARDS	nonARDS
Cancer-esophageal, surgery for (abdominal approach)	ARDS	nonARDS
Cancer-laryngeal/tracheal, surgery for	ARDS	nonARDS
Cancer-other GI tract, surgery for (i.e. hepatoma, gallbladder etc.)	ARDS	nonARDS
Cancer-small intestinal, surgery for	ARDS	nonARDS
Cancer-stomach, surgery for	ARDS	nonARDS
Cancer oral/sinus, surgery for	ARDS	nonARDS
Cancer, colon/rectal	ARDS	nonARDS
Cancer, esophageal	ARDS	nonARDS
Cancer, laryngeal	ARDS	nonARDS
Cancer, lung	ARDS	nonARDS
Cancer, oral	ARDS	nonARDS
Cancer, other GI	ARDS	nonARDS
Cancer, pancreatic	ARDS	nonARDS
Cancer, stomach	ARDS	nonARDS
Cancer, tracheal	ARDS	nonARDS
CAPD catheter insertion	ARDS	nonARDS
Cardiac arrest (with or without respiratory arrest; for respiratory arrest see Respiratory System)	ARDS	nonARDS
Cardiomyopathy	nonARDS	nonARDS
Cardiovascular medical, other	ARDS	nonARDS
Cardiovascular surgery, other	nonARDS	nonARDS
Cellulitis and localized soft tissue infections	ARDS	nonARDS
Cellulitis and localized soft tissue infections, surgery for	ARDS	ARDS
Cerebrospinal fluid leak, surgery for	ARDS	nonARDS
Cesarean section	ARDS	nonARDS
Chest pain, epigastric	nonARDS	nonARDS
Chest/abdomen trauma	ARDS	ARDS
Chest/abdomen trauma, surgery for	ARDS	ARDS
Chest/extremity trauma	ARDS	ARDS
Chest/extremity trauma, surgery for	ARDS	ARDS
Chest/face trauma	ARDS	ARDS
Chest/face trauma, surgery for	ARDS	ARDS
Chest/multiple trauma	ARDS	ARDS
Chest/multiple trauma, surgery for	ARDS	ARDS
Chest/pelvis trauma	ARDS	ARDS
Chest/pelvis trauma, surgery for	ARDS	ARDS
Chest/spinal trauma	ARDS	ARDS
Chest/spinal trauma, surgery for	ARDS	ARDS
Chest/thorax only trauma	ARDS	ARDS
Chest/thorax only trauma, surgery for	ARDS	ARDS
CHF, congestive heart failure	nonARDS	nonARDS
Cholangitis	ARDS	nonARDS
Cholecystectomy/cholangitis, surgery for (gallbladder removal)	ARDS	nonARDS
Coagulopathy	ARDS	nonARDS
Coma/change in level of consciousness (for hepatic see GI, for diabetic see Endocrine, if related to cardiac arrest , see CV)	ARDS	nonARDS
Complications of prev. peripheral vasc. surgery,surgery for (i.e.ligation of bleeder, debridement, pseudoaneurysms, clots, fistula, etc.)	ARDS	nonARDS
Complications of previous GI surgery; surgery for (anastomotic leak, bleeding, abscess, infection, dehiscence, etc.)	ARDS	nonARDS
Complications of previous open-heart surgery, surgery for (i.e. bleeding, infection, mediastinal rewiring,leaking aortic graft etc.)	nonARDS	nonARDS
Complications of previous open heart surgery (i.e. bleeding, infection etc.)	nonARDS	nonARDS
Complications of previous spinal cord surgery, surgery for	ARDS	nonARDS
Congenital Defect Repair (Other)	ARDS	nonARDS
Connective tissue disease (mixed)	ARDS	nonARDS
Contusion, myocardial	ARDS	nonARDS
Cosmetic surgery (all)	ARDS	nonARDS
Cranioplasty and complications from previous craniotomies	ARDS	nonARDS
CVA, cerebrovascular accident/stroke	ARDS	nonARDS
Cyst, ruptured ovarian	ARDS	nonARDS
Cystectomy (other reasons)	ARDS	nonARDS
Cystectomy for neoplasm	ARDS	nonARDS
Defibrillator, automatic implantable cardiac; insertion of	nonARDS	nonARDS
Devices for spine fracture/dislocation	ARDS	nonARDS
Diabetic hyperglycemic hyperosmolar nonketotic coma (HHNC)	ARDS	nonARDS
Diabetic ketoacidosis	ARDS	nonARDS
Diverticular disease	ARDS	nonARDS

Diverticular disease, surgery for	ARDS	nonARDS
Drug withdrawal	ARDS	nonARDS
Ectopic pregnancy (all)	ARDS	nonARDS
Efffusion, pericardial	nonARDS	nonARDS
Effusions, pleural	nonARDS	nonARDS
Embolectomy (with general anesthesia)	ARDS	nonARDS
Embolus, pulmonary	nonARDS	nonARDS
Emphysema/bronchitis	ARDS	nonARDS
Encephalitis	ARDS	nonARDS
Encephalopathies (excluding hepatic)	ARDS	nonARDS
Encephalopathy, hepatic	ARDS	nonARDS
Endarterectomy (other vessels)	ARDS	nonARDS
Endarterectomy, carotid	ARDS	nonARDS
Endocarditis	ARDS	nonARDS
Esophageal surgery, other	ARDS	nonARDS
Exenteration, pelvic-female	ARDS	nonARDS
Exenteration, pelvic -male	ARDS	nonARDS
Extremity only trauma	ARDS	ARDS
Extremity only trauma, surgery for	ARDS	ARDS
Extremity/face trauma	ARDS	ARDS
Extremity/face trauma, surgery for	ARDS	ARDS
Extremity/multiple trauma	ARDS	ARDS
Extremity/multiple trauma, surgery for	ARDS	ARDS
Face only trauma	ARDS	ARDS
Face only trauma, surgery for	ARDS	ARDS
Face/multiple trauma	ARDS	ARDS
Face/multiple trauma, surgery for	ARDS	ARDS
Facial surgery (if related to trauma, see Trauma)	ARDS	nonARDS
Fistula/abscess, surgery for (not inflammatory bowel disease)	ARDS	nonARDS
Fracture-pathological, non-union, non-traumatic, for fractures due to trauma see Trauma	ARDS	ARDS
Fusion-spinal/Harrington rods	ARDS	nonARDS
Gastrostomy	ARDS	nonARDS
Genitourinary medical, other	ARDS	nonARDS
Genitourinary surgery, other	ARDS	nonARDS
GI Abscess/cyst	ARDS	nonARDS
GI Abscess/cyst-primary, surgery for (for complications of GI surgery see below)	ARDS	nonARDS
GI medical, other	ARDS	nonARDS
GI Obstruction	ARDS	nonARDS
GI obstruction, surgery for (including lysis of adhesions)	ARDS	nonARDS
GI Perforation/rupture	ARDS	nonARDS
GI perforation/rupture, surgery for	ARDS	nonARDS
GI surgery, other	ARDS	nonARDS
GI Vascular insufficiency	ARDS	nonARDS
GI vascular ischemia, surgery for (resection)	ARDS	nonARDS
Graft for dialysis, insertion of	ARDS	nonARDS
Graft, aorto-femoral bypass	ARDS	nonARDS
Graft, aorto-iliac bypass	ARDS	nonARDS
Graft, femoral-femoral bypass	ARDS	nonARDS
Graft, femoral-popliteal bypass	ARDS	nonARDS
Grafting, skin (all)	ARDS	nonARDS
Grafts, all other bypass (except renal)	ARDS	nonARDS
Grafts, all renal bypass	ARDS	nonARDS
Grafts, removal of infected vascular	ARDS	nonARDS
Guillian-Barre syndrome	ARDS	nonARDS
Head (CNS) only trauma	ARDS	ARDS
Head (CNS) only trauma, surgery for	ARDS	ARDS
Head/abdomen trauma	ARDS	ARDS
Head/abdomen trauma, surgery for	ARDS	ARDS
Head/chest trauma	ARDS	ARDS
Head/chest trauma, surgery for	ARDS	ARDS
Head/extremity trauma	ARDS	ARDS
Head/extremity trauma, surgery for	ARDS	ARDS
Head/face trauma	ARDS	ARDS
Head/face trauma, surgery for	ARDS	ARDS
Head/multiple trauma	ARDS	ARDS
Head/multiple trauma, surgery for	ARDS	ARDS
Head/pelvis trauma	ARDS	ARDS
Head/pelvis trauma, surgery for	ARDS	ARDS
Head/spinal trauma	ARDS	ARDS
Head/spinal trauma, surgery for	ARDS	ARDS

Heart-lung transplant	ARDS	nonARDS
Heart transplant	ARDS	nonARDS
Heat exhaustion/stroke	ARDS	nonARDS
Hematologic medical, other	ARDS	nonARDS
Hematologic surgery, other	ARDS	nonARDS
Hematoma, epidural	ARDS	nonARDS
Hematoma, epidural, surgery for	ARDS	nonARDS
Hematoma, subdural	ARDS	nonARDS
Hematoma, subdural, surgery for	ARDS	nonARDS
Hematomas	ARDS	nonARDS
Hemorrhage (for gastrointestinal bleeding GI-see GI system) (for trauma see Trauma)	ARDS	nonARDS
Hemorrhage, intra/retroperitoneal	ARDS	nonARDS
Hemorrhage, postpartum (female only)	ARDS	nonARDS
Hemorrhage/hematoma-intracranial, surgery for	ARDS	nonARDS
Hemorrhage/hematoma, intracranial	ARDS	nonARDS
Hemorrhage/hemoptysis, pulmonary	ARDS	nonARDS
Hemothorax	ARDS	nonARDS
Hepatic failure, acute	ARDS	nonARDS
Hepato-renal syndrome	ARDS	nonARDS
Hernia-hiatal, esophageal surgery for	ARDS	nonARDS
Herniorrhaphy	ARDS	nonARDS
Hip replacement, total (non-traumatic)	ARDS	nonARDS
Hydrocephalus, obstructive	ARDS	nonARDS
Hypertension-pulmonary, primary/idiopathic	ARDS	nonARDS
Hypertension, uncontrolled (for cerebrovascular accident-see Neurological System)	ARDS	nonARDS
Hyperthermia	ARDS	nonARDS
Hyperthyroid storm/crisis	ARDS	nonARDS
Hypoglycemia	ARDS	nonARDS
Hypothermia	ARDS	nonARDS
Hypothyroid/myxedema	ARDS	nonARDS
Hypovolemia (including dehydration. Do NOT include shock states.)	ARDS	nonARDS
Hysterectomy for cancer with or without lymph node dissection	ARDS	nonARDS
Hysterectomy for other benign neoplasm/fibroids	ARDS	nonARDS
Infarction, acute myocardial (MI)	nonARDS	nonARDS
Infection/abscess, other surgery for	ARDS	ARDS
Inflammatory bowel disease	ARDS	nonARDS
Inflammatory bowel disease, surgery for	ARDS	nonARDS
Kidney-pancreas transplant	ARDS	nonARDS
Kidney transplant	ARDS	nonARDS
Knee replacement, total (non-traumatic)	ARDS	nonARDS
Laminectomy/spinal cord decompression (excluding malignancies)	ARDS	nonARDS
Leukemia, acute lymphocytic	ARDS	nonARDS
Leukemia, acute myelocytic	ARDS	nonARDS
Leukemia, chronic lymphocytic	ARDS	nonARDS
Leukemia, chronic myelocytic	ARDS	nonARDS
Leukemia, other	ARDS	nonARDS
Liver-small bowel transplant	ARDS	nonARDS
Liver transplant	ARDS	nonARDS
Lung transplant, bilateral	ARDS	nonARDS
Lung transplant, single	ARDS	nonARDS
Lupus, systemic	ARDS	nonARDS
Lymph node dissection, pelvic or retroperitoneal (male)	ARDS	nonARDS
Lymphoma, Hodgkins	ARDS	nonARDS
Lymphoma, non-Hodgkins	ARDS	nonARDS
Lymphoma, non-Hodgkins; surgery for (including staging)	ARDS	nonARDS
Mastectomy (all)	ARDS	nonARDS
Meningitis	ARDS	nonARDS
Metabolic/endocrine medical, other	ARDS	nonARDS
Metabolic/endocrine surgery, other	ARDS	nonARDS
Mitral valve repair	nonARDS	nonARDS
Mitral valve replacement	nonARDS	nonARDS
Monitoring, hemodynamic (pre-operative evaluation)	ARDS	nonARDS
Musculoskeletal medical, other	ARDS	nonARDS
Myasthenia gravis	ARDS	nonARDS
Near drowning accident	ARDS	nonARDS
Neoplasm-cranial, surgery for (excluding transphenoidal)	ARDS	nonARDS
Neoplasm-spinal cord surgery or other related procedures	ARDS	nonARDS
Neoplasm, neurologic	ARDS	nonARDS
Nephrectomy (other reasons)	ARDS	nonARDS
Nephrectomy for neoplasm	ARDS	nonARDS

Neurologic medical, other	ARDS	nonARDS
Neurologic surgery, other	ARDS	nonARDS
Neuromuscular medical, other	ARDS	nonARDS
Nontraumatic coma due to anoxia/ischemia	ARDS	nonARDS
Obesity-morbid, surgery for	ARDS	nonARDS
Obstruction-airway (i.e. acute epiglottitis, post-extubation edema, foreign body, etc.)	ARDS	nonARDS
Obstruction due to neoplasm ,surgery for; (with or without ileal-conduit)	ARDS	nonARDS
Obstruction due to nephrolithiasis, surgery for (with or without ileal-conduit)	ARDS	nonARDS
Obstruction/other, surgery for (with or without ileal-conduit)	ARDS	nonARDS
Oophorectomy with/without salpingectomy with/without lymph node dissection	ARDS	nonARDS
Orchiectomy with/without pelvic lymph node dissection	ARDS	nonARDS
Orthopedic surgery, other	ARDS	nonARDS
Overdose, alcohols (bethanol, methanol, ethylene glycol)	ARDS	nonARDS
Overdose, analgesic (aspirin, acetaminophen)	ARDS	nonARDS
Overdose, antidepressants (cyclic, lithium)	ARDS	nonARDS
Overdose, other toxin, poison or drug	ARDS	nonARDS
Overdose, sedatives, hypnotics, antipsychotics, benzodiazepines	ARDS	nonARDS
Overdose, street drugs (opiates, cocaine, amphetamine)	ARDS	nonARDS
Palsy, cranial nerve	ARDS	nonARDS
Pancreatitis	ARDS	ARDS
Pancreatitis, surgery for	ARDS	nonARDS
Pancytopenia	ARDS	nonARDS
Papillary muscle rupture	ARDS	nonARDS
Parathyroidectomy	ARDS	nonARDS
Pelvic relaxation (cystocele, rectocele, etc.)	ARDS	nonARDS
Pelvis/extremity trauma	ARDS	ARDS
Pelvis/extremity trauma, surgery for	ARDS	ARDS
Pelvis/face trauma	ARDS	ARDS
Pelvis/face trauma, surgery for	ARDS	ARDS
Pelvis/hip only trauma	ARDS	ARDS
Pelvis/hip only trauma, surgery for	ARDS	ARDS
Pelvis/multiple trauma	ARDS	ARDS
Pelvis/multiple trauma, surgery for	ARDS	ARDS
Pelvis/spinal trauma	ARDS	ARDS
Pelvis/spinal trauma, surgery for	ARDS	ARDS
Pericardial effusion/tamponade	ARDS	nonARDS
Pericardiectomy (total/subtotal)	ARDS	nonARDS
Pericarditis	nonARDS	nonARDS
Peritoneal lavage	ARDS	nonARDS
Peritonitis	ARDS	nonARDS
Peritonitis, surgery for	ARDS	nonARDS
Pneumonia, aspiration	ARDS	ARDS
Pneumonia, bacterial	ARDS	ARDS
Pneumonia, fungal	ARDS	nonARDS
Pneumonia, other	ARDS	ARDS
Pneumonia, parasitic (i.e. Pneumocystis pneumonia)	ARDS	nonARDS
Pneumonia, viral	ARDS	ARDS
Pneumothorax	nonARDS	nonARDS
Poisoning, carbon monoxide, arsenic, cyanide	ARDS	nonARDS
Pre-eclampsia/eclampsia (female only)	ARDS	nonARDS
Prostatectomy, suprapubic; for benign prostatic hypertrophy	ARDS	nonARDS
Prostatectomy, suprapubic; for cancer	ARDS	nonARDS
Pulmonary valve surgery	nonARDS	nonARDS
Renal bleeding	ARDS	nonARDS
Renal failure, acute	ARDS	nonARDS
Renal infection/abscess	ARDS	nonARDS
Renal neoplasm, cancer	ARDS	nonARDS
Renal obstruction	ARDS	nonARDS
Respiratory- medical, other	ARDS	nonARDS
Respiratory surgery, other	ARDS	nonARDS
Restrictive lung disease (i.e. sarcoidosis, pulmonary fibrosis)	ARDS	nonARDS
Rhabdomyolysis	ARDS	nonARDS
Rhythm disturbance (atrial, supraventricular)	nonARDS	nonARDS
Rhythm disturbance (conduction defect)	nonARDS	nonARDS
Rhythm disturbance (ventricular)	nonARDS	nonARDS
Scleroderma	ARDS	nonARDS
Seizures-intractable, surgery for	ARDS	nonARDS
Seizures (primary-no structural brain disease)	ARDS	nonARDS
Sepsis, cutaneous/soft tissue - other	ARDS	ARDS
Sepsis, GI - other	ARDS	ARDS

Sepsis, GU/UTI (including bladder) - other	ARDS	ARDS
Sepsis, gynecologic	ARDS	ARDS
Sepsis, other	ARDS	ARDS
Sepsis, pulmonary - other	ARDS	ARDS
Sepsis, unknown	ARDS	ARDS
Shock, cardiogenic	nonARDS	nonARDS
Shunt-portosystemic, surgery for	ARDS	nonARDS
Shunts and revisions	ARDS	nonARDS
Skin surgery, other	ARDS	nonARDS
Smoke inhalation	ARDS	nonARDS
Spinal cord only trauma	ARDS	nonARDS
Spinal cord only trauma, surgery for	ARDS	nonARDS
Spinal cord sugery, other	ARDS	nonARDS
Spinal/extremity trauma	ARDS	nonARDS
Spinal/extremity trauma, surgery for	ARDS	nonARDS
Spinal/face trauma	ARDS	nonARDS
Spinal/face trauma, surgery for	ARDS	nonARDS
Spinal/multiple trauma	ARDS	ARDS
Spinal/multiple trauma, surgery for	ARDS	ARDS
Splenectomy	ARDS	nonARDS
Subarachnoid hemorrhage/arteriovenous malformation	ARDS	nonARDS
Subarachnoid hemorrhage/intracranial aneurysm	ARDS	nonARDS
Subarachnoid hemorrhage/intracranial aneurysm, surgery for	ARDS	nonARDS
Tamponade, pericardial	nonARDS	nonARDS
Thoracotomy for benign tumor (i.e. mediastinal chest wall mass, thymectomy)	ARDS	nonARDS
Thoracotomy for bronchopleural fistula	ARDS	nonARDS
Thoracotomy for esophageal cancer	ARDS	nonARDS
Thoracotomy for lung cancer	ARDS	nonARDS
Thoracotomy for other malignancy in chest	ARDS	nonARDS
Thoracotomy for other reasons	ARDS	nonARDS
Thoracotomy for pleural disease	ARDS	nonARDS
Thoracotomy for thoracic/respiratory infection	ARDS	nonARDS
Thrombectomy (with general anesthesia)	ARDS	nonARDS
Thrombectomy (without general anesthesia)	ARDS	nonARDS
Thrombocytopenia	ARDS	nonARDS
Thrombosis, vascular (deep vein)	ARDS	nonARDS
Thrombus,arterial	ARDS	nonARDS
Thyroid neoplasm	ARDS	nonARDS
Thyroidectomy	ARDS	nonARDS
Thyroidectomy and parathyroidectomy	ARDS	nonARDS
Toxicity, drug (i.e., beta blockers, calcium channel blockers, etc.)	ARDS	nonARDS
Tracheostomy	ARDS	nonARDS
Transphenoidal surgery	ARDS	nonARDS
Transplant, other	ARDS	nonARDS
Trauma medical, other	ARDS	ARDS
Trauma surgery, other	ARDS	ARDS
Tricuspid valve surgery	nonARDS	nonARDS
Tumor removal, intracardiac	nonARDS	nonARDS
TURP, transurethral prostate resection for benign prostatic hypertrophy	ARDS	nonARDS
TURP, transurethral prostate resection for cancer	ARDS	nonARDS
Ulcer disease, peptic	ARDS	nonARDS
Vascular medical, other	ARDS	nonARDS
Vascular surgery, other	ARDS	nonARDS
Vasculitis	ARDS	nonARDS
Ventricular Septal Defect (VSD) Repair	nonARDS	nonARDS
Ventriculostomy	ARDS	nonARDS
Weaning from mechanical ventilation (transfer from other unit or hospital only)	ARDS	nonARDS
Whipple-surgery for pancreatic cancer	ARDS	nonARDS

Table 5. Scientific Steering Group

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