Critical Care and Resuscitation 25 (2023) 207–215

Contents lists available at ScienceDirect

Critical Care and Resuscitation

journal homepage: www.elsevier.com/locate/ccrj

Original Article

Protocol and statistical analysis plan for the identification and treatment of hypoxemic respiratory failure and acute respiratory distress syndrome with protection, paralysis, and proning: A type-1 hybrid stepped-wedge cluster randomised effectiveness-implementation study

Ken Kuljit S. Parhar, MD, MSc [a, b, c, *], Andrea Soo, PhD [a], Gwen Knight, BA [a], Kirsten Fiest, PhD [a, b, d], Daniel J. Niven, MD MSc PhD [a, b, d], Gordon Rubenfeld, MD, MSc [g], Damon Scales, MD, PhD [g], Henry T. Stelfox, MD, PhD [a, b, d], Danny J. Zuege, MD MSc [a, e], Sean Bagshaw, MD, MSc [e, f]

[a] *Department of Critical Care Medicine, University of Calgary & Alberta Health Services, Calgary, Alberta, Canada;* [b] *O'Brien Institute for Public Health, University of Calgary, Calgary, Alberta, Canada;* [c] *Libin Cardiovascular Institute, University of Calgary, Calgary, Alberta, Canada;* [d] *Department of Community Health Sciences, University of Calgary, Calgary, Alberta, Canada;* [e] *Critical Care Strategic Clinical Network, Alberta Health Services, Alberta, Canada;* [f] *Department of Critical Care Medicine, Faculty of Medicine and Dentistry, University of Alberta and Alberta Health Services, Edmonton, Canada;* [g] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto Ontario, Canada*

ARTICLE INFORMATION

Article history:
Received 24 October 2023
Accepted 30 October 2023

Keywords:
Acute respiratory distress syndrome
Hypoxemic respiratory failure
Mechanical ventilation
Cluster randomised stepped wedge trial
Statistical analysis plan

ABSTRACT

Objective: To describe a study protocol and statistical analysis plan (SAP) for the identification and treatment of hypoxemic respiratory failure (HRF) and acute respiratory distress syndrome (ARDS) with protection, paralysis, and proning (TheraPPP) study prior to completion of recruitment, electronic data retrieval, and analysis of any data.

Design: TheraPPP is a stepped-wedge cluster randomised study evaluating a care pathway for HRF and ARDS patients. This is a type-1 hybrid effectiveness-implementation study design evaluating both intervention effectiveness and implementation; however primarily powered for the effectiveness outcome.

Setting: Seventeen adult intensive care units (ICUs) across Alberta, Canada.

Participants: We estimate a sample size of 18816 mechanically ventilated patients, with 11424 patients preimplementation and 7392 patients postimplementation. We estimate 2688 sustained ARDS patients within our study cohort.

Intervention: An evidence-based, stakeholder-informed, multidisciplinary care pathway called Venting Wisely that standardises diagnosis and treatment of HRF and ARDS patients.

Main outcome measures: The primary outcome is 28-day ventilator-free days (VFDs). The primary analysis will compare the mean 28-day VFDs preimplementation and postimplementation using a mixed-effects linear regression model. Prespecified subgroups include sex, age, HRF, ARDS, COVID-19, cardiac surgery, body mass index, height, illness acuity, and ICU volume.

Results: This protocol and SAP are reported using the Standard Protocol Items: Recommendations for Interventional Trials guidance and the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. The study received ethics approval and was registered (ClinicalTrials.gov-NCT04744298) prior to patient enrolment.

Abbreviations: ARDS, Acute Respiratory Distress Syndrome; BMI, Body Mass Index; CFS, Composite Fidelity Score; CI, Confidence Interval; FiO2, Fraction of Inspired Oxygen; HRF, Hypoxemic Respiratory Failure; ICU, Intensive Care Unit; ICC, Intraclass Correlation Coefficient; IQR, Interquartile range; LOS, Length of Stay; LPV, Lung protective ventilation; MV, Mechanically ventilated; PaO2, Partial pressure of oxygen; PF ratio, PaO2/FiO2; PEEP, Positive End Expiratory Pressure; PBW, Predicted Body Weight; RTs, Respiratory Therapists; SAP, Statistical analysis plan; SD, Standard Deviation; TFA, Theoretical Framework of Acceptability; VFDs, Ventilator Free Days; VV-ECMO, Veno-venous Extracorporeal Membrane Oxygenation.

* Corresponding author at: Department of Critical Care Medicine. University of Calgary, ICU Administration, Ground Floor, McCaig Tower, Foothills Medical Center, 3134 Hospital Drive NW, Calgary, Alberta, T2N 5A1, Canada. Tel.: +1403 944 0735; fax: +1403 283 9994.
E-mail address: ken.parhar@albertahealthservices.ca (K.K.S. Parhar).

https://doi.org/10.1016/j.ccrj.2023.10.008

Conclusions: TheraPPP will evaluate the effectiveness and implementation of an HRF and ARDS care pathway.

1. Introduction

Hypoxemic respiratory failure (HRF) and acute respiratory distress syndrome (ARDS) are common among intensive care unit (ICU) patients and associated with considerable morbidity, mortality, and health care resource utilisation.[1–7] Potentially life-saving therapies for HRF and ARDS such as lung protective ventilation (LPV), neuromuscular blockade (paralysis), and prone positioning are available but are not consistently provided.[1,2,8–13] Guidelines endorsing these therapies exist; however, implementation is extremely inconsistent due to challenges with ARDS diagnosis and ineffective knowledge translation.[1,11,14–21] Moreover, there is frequent use of unproven, invasive, or resource-intensive therapies (e.g. extracorporeal membrane oxygenation; inhaled pulmonary vasodilators) rather than proven and less resource-intensive therapies (e.g. prone positioning).[1,2,22]

The Institute of Medicine recommends standardised care processes to improve the reliability and safety of care.[23] A recent systematic review with over 5000 patients demonstrated that the pooled relative risk of mortality among HRF and ARDS patients was reduced by 23% when using standardised pathways.[24] However, these studies were limited by high methodological bias, omitting evidence-informed treatments, or poor implementation fidelity. To address this gap, we rigorously developed an evidence-based, stakeholder-informed, multidisciplinary standardised care pathway called Venting Wisely using a modified Delphi consensus process[25] and evidence-based guidelines.[14,15,26] The pathway standardises the diagnosis and management of patients with HRF and ARDS, with the goal of reducing practice variation and improving adherence to evidence-informed therapy. Over 700 clinicians from diverse ICUs were surveyed to validate the pathway and identify barriers and facilitators to pathway adherence using implementation science.[27–29] A corresponding implementation strategy was specifically designed to target these barriers. A single-centre before-and-after pilot study demonstrated the feasibility and acceptability of the pathway.[30]

The identification and treatment of HRF and ARDS with protection, paralysis, and proning (TheraPPP) study is a type-1 hybrid stepped-wedge cluster randomised effectiveness-implementation study involving 17 adult ICUs. Here we describe the study protocol and provide a detailed pre-specified statistical analysis plan (SAP) for the TheraPPP study prior to completion of recruitment, electronic data retrieval, and data analysis.

2. Objectives

The specific objectives of this study are to evaluate the clinical effectiveness and implementation of the pathway using a pragmatic registry-based cluster randomised stepped-wedge type 1 implementation study and a process evaluation. We hypothesise that the pathway will increase adherence to life-saving therapies, improve patient outcomes, and save costs within the health care system.

3. Methods

3.1. Study reporting and ethics

This protocol (see Appendix S1 for the full protocol, version 2.5, February 14, 2023) and SAP (See Appendix S2 for the full SAP, version 1.0, February 22, 2022)[31] are reported in accordance with Guidelines for the Content of Statistical Analysis Plans in Clinical Trials[32] (for checklist see Appendix S3) as well as in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidance (for checklist see Appendix S4).[33] This manuscript is consistent with other published protocols and SAPs.[34,35] Study methods will be conducted and reported in accordance with standards for reporting stepped wedge cluster randomised trials (CONSORT, SW-CRT extension),[36] and standards for reporting implementation studies (StaRI)[37] and their replication (TIDieR).[38] Qualitative work will be reported using the Standards of Reporting of Quality Research guidelines (SRQR) and the consolidated criteria for reporting qualitative research (COREQ).[39,40]

The study 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. The findings of this study will be disseminated through international conference presentations as well as publication in a peer-reviewed journal. The authorship of the final publication will be attributed using international standards.[41] The use of professional writers is not planned. Deidentified data will be made available to researchers upon reasonable request. The proposed use of data must be approved by the study steering group; a signed and executed data access agreement between institutions will be needed; and local ethics approval will be required.

3.2. Study design

The study is designed as an effectiveness-implementation hybrid study design (type 1).[42] This study design evaluates both clinical effectiveness and implementation of the pathway, but is primarily powered by the primary clinical effectiveness outcome. Implementation will occur via a pragmatic registry-based stepped wedge cluster randomised implementation study.

3.3. Population

3.3.1. Inclusion criteria

All patients admitted to the adult ICU will be screened for eligibility for the pathway. All mechanically ventilated patients admitted to the ICU will be included in the study and receive the pathway intervention.

3.3.2. Exclusion criteria

There are no exclusion criteria for entry into the pathway; however, not all steps will be applicable to all patients.

For the process evaluation and assessment of acceptability, the target population includes clinicians (physicians, respiratory therapists (RTs), registered nurses, and nurse practitioners) who participated in the intervention.

3.4. tudy 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 (Appendix S1, Protocol Attachment 2). One ICU (Calgary) served as

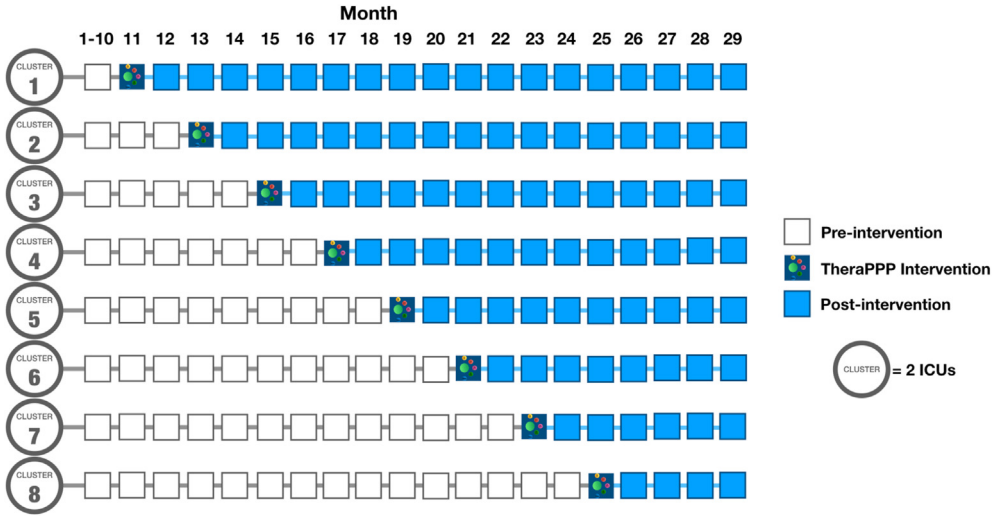

Fig. 1. Stepped-wedge cluster randomisation allocation schedule.

the setting for a pilot study (completed in September 2020). The remaining 16 ICUs will participate in the full study.

3.5. Randomisation

The unit of randomisation 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 Fig. 1). Sites will be randomised using a computer-generated random number sequence by a blinded investigator. Details of the randomisation method are held securely in the statistics master file. Two sites will be selected at any time. ICU sites will be deferred from a randomisation 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 randomised and notified four to eight weeks prior to the initiation schedule to prevent contamination.

3.6. Intervention

The intervention is a comprehensive, evidence-based, stakeholder-informed pathway for the diagnosis and management of HRF called Venting Wisely. Although the pathway contains 46 elements, it focuses on five key steps (Fig. 2). See Appendix S1, Protocol section 6.8 for details on the intervention, and Attachments 1 and 3 for the full 46-element Venting Wisely pathway. The five steps include:

Step 1 All mechanically ventilated patients will have their height measured and documented.
Step 2 All mechanically ventilated patients will be screened for HRF daily.
Step 3 For patients with HRF, lung protective ventilation (LPV) will be initiated (limit tidal volumes to 6–8 mL/kg predicted body weight (PBW), plateau pressure to $\leq$30 cm H_2O, and driving pressure $\leq$18).
Step 4 Paralysis. For patients with worsening HRF, neuromuscular blockade will be considered when the PF ratio is $\leq$ 150.
Step 5 Patients with a worsening PF ratio despite steps 1–4 will be considered for prone positioning if the PF ratio is $\leq$150 and the FiO2 is $\geq$ 0.60.

3.7. Implementation of the intervention

Implementation will include eight key strategies including education, decision-support, reminders, audits and feedback, training, champions, implementation support, and empowerment (see Appendix S1, Protocol section 6.9, and Attachment 4 for a detailed strategy). Implementation strategies were informed by an

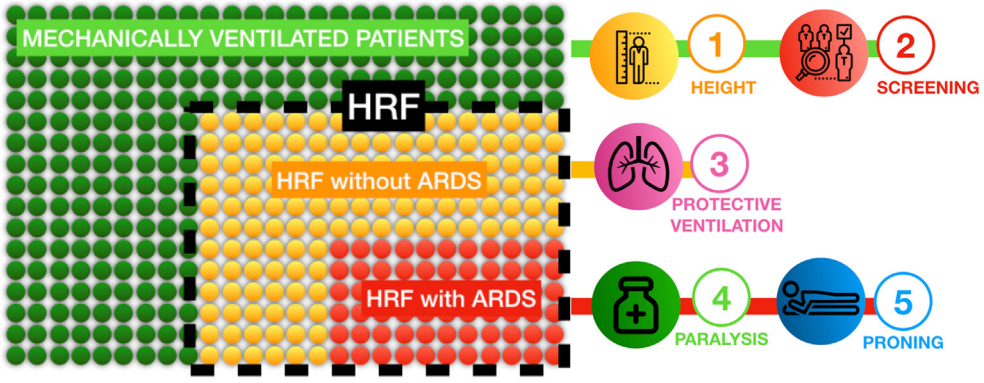

Fig. 2. Five key steps of the *Venting Wisely* pathway.

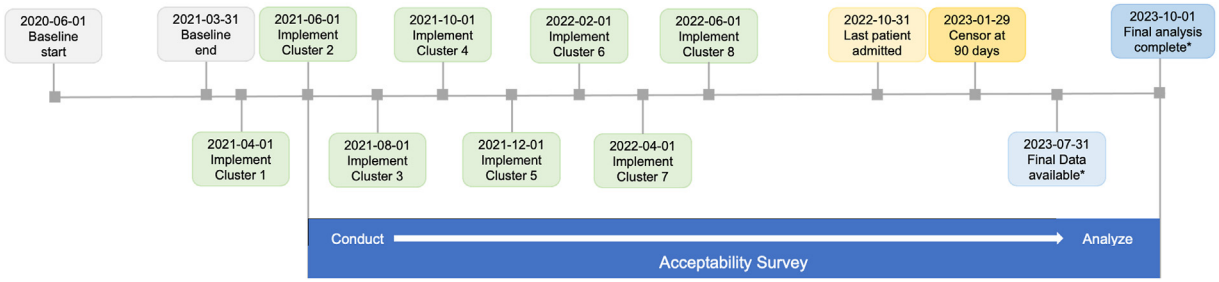

Fig. 3. Study Timeline. * = estimated date.

assessment of contextual barriers and facilitators, using the Theoretical Domains Framework and the Behaviour Change Wheel.[27–29] Implementation will be delivered by a multidisciplinary group of pathway champions (nurses, RTs, and physicians). A readiness assessment will be conducted prior to implementation at each site. Tailoring of the intervention and implementation will be conducted during the 1-month implementation transition phase for each ICU based upon individual ICU characteristics (patient volumes, staffing), readiness, and local contextual factors (e.g. RT availability at night).

3.8. Study duration

See Fig. 3 for details of the study timeline. There will be a 10-month baseline data collection period at the beginning of the study common to all sites. The intervention will be implemented in 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 analysed. Once implemented, the cluster will continue to receive the intervention for the remainder of the study. The total study duration will be 29 months.

Table 1
Outcomes.

Outcome	Population
Clinical effectiveness	
28-day ventilator free days (VFDs)	Primary
28-day hospital, ICU, and hospital survival	Secondary
Ventilator duration	Secondary
Driving pressure	Secondary
Mechanical power	Secondary
ICU and hospital LOS	Secondary
Utilisation of VV-ECMO	Secondary
Implementation – Fidelity	
Composite Fidelity Score (CFS)	Primary
Height ever documented	Secondary
Tidal volume ≤ 8 ml/kg predicted body weight	Secondary
Plateau pressure measured	Secondary
Receiving neuromuscular blockade	Secondary
Receiving prone ventilation	Secondary
Implementation – Acceptability	
Composite Acceptability Score	Secondary
Intervention coherence[a]	Secondary
Opportunity costs[a]	Secondary
Perceived effectiveness[a]	Secondary
Self-efficacy[a]	Secondary
Affective attitude[a]	Secondary
Burden[a]	Secondary
Ethicality[a]	Secondary

CFS = composite fidelity score. ICU = intensive care unit. LOS = length of stay. Pts = patients. PEEP = positive end expiratory pressure. TFA = theoretical framework of acceptability. VV ECMO = veno venous extracorporeal membrane oxygenation. VFDs = ventilator free days.
See Appendix S1, Protocol Attachment 8 and Appendix S2, SAP Supplementary Table 3 for Outcome definitions, details on eligible patients, calculations, time-points and reporting of results, and references.
[a] Denotes that this outcome is part of the Composite Acceptability Score.

3.9. Outcome measures

This study is a hybrid effectiveness and implementation study type 1, and therefore it is powered by the primary clinical effectiveness outcome. Pathway implementation will be assessed through a process evaluation as part of the hybrid trial using multimethods to quantitatively evaluate the fidelity of the intervention and qualitatively assess acceptability among clinicians. The process evaluation will provide vital information on why the implementation may or may not have worked as anticipated (type III error), identify opportunities for iteratively improving pathway fidelity, and provide insights for future sustainability and scalability.

The primary clinical effectiveness 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. Secondary clinical effectiveness outcomes are listed in Table 1.

The primary implementation outcome is a composite fidelity score (CFS) that awards points for up to five key fidelity indicators that are met and is reported as a percentage. Secondary implementation outcomes for fidelity and acceptability among clinicians are listed in Table 1. The composite fidelity score measures are routinely charted within the electronic health record.

To evaluate acceptability outcomes, invitations to participate in acceptability survey and focus groups will be sent to clinicians (nurses, physicians, and RTs) two to six months postimplementation in each cluster. The secondary acceptability outcomes assess clinician perceptions about the pathway and are based on the seven component constructs of the theoretical framework of acceptability (TFA) (see Table 1).[43] Expanded details about the survey are in Appendix S1 (Protocol section 7.1.2, 7.2.2, 8.2.1, and Attachment 9 & 12). The assessment of acceptability through focus groups will be reported in a separate, detailed study protocol.

4. Sample size

The study is a type 1 hybrid effectiveness-implementation design and therefore is primarily powered by the effectiveness outcome.[42] We do, however, also provide sample size calculations for the implementation outcomes to estimate the effect sizes and precision of the estimates that can be detected.

4.1. Clinical effectiveness sample size

The design of the cluster randomised stepped wedge TheraPPP trial incorporated several considerations. The study balances the detection of a meaningful clinical difference in the primary

Table 2
Ventilator free days (primary clinical effectiveness outcome) and composite fidelity score (primary implementation outcome) detectable differences.

Ventilator free days (VFDs) (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
Composite Fidelity Score (CFS) (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. 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 S2, SAP Supplementary Table 1 for details on criteria for sustained HRF, ARDS definition 1 and 2, and sustained ARDS.

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 the 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.

With the considerations above, the final study design included a ten-month baseline data collection period, eight clusters with two ICUs per cluster, the and implementation of the pathway in one cluster every two months, followed by a four-month post-implementation period following the last cluster. Using historical ICU admission rates in Alberta from 2018 to 2019, we estimate a total of 18816 mechanically ventilated patients will be included in this study, with 11424 patients preimplementation and 7392 patients postimplementation. Based on this, a baseline mean VFDs of 21 (standard deviation (SD) 10), an intraclass correlation coefficient (ICC) = 0.15), a 90% power, and a two-sided $\alpha = 0.05$, we estimate an ability to detect a difference of 0.9 VFDs (see Table 2).

Given that ARDS is an important subgroup of patients within this cohort that would receive most pathway steps, we wanted to ensure sufficient patient recruitment from this subgroup of interest. To estimate the ARDS population within this cohort as well as the ICC, we applied a local population-based incidence of ARDS that was derived using standardised screening.[2] We estimate this will generate a sample size of 2688 sustained ARDS patients within our TheraPPP study cohort and provide the ability to detect a minimum difference of 2.4 VFDs (11–13.4 mean 28-day VFDs) (with a 90% power and a two-sided $\alpha = 0.05$, ICC = 0.01) within this subgroup. The minimal clinically important difference of 2.4 days is similar to other ARDS trials.[44–46] The ICC was estimated to be 0.011 (95% confidence interval (CI) 0.00–0.20).[2] 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 (standardised mean difference increase of 3.48 (2.43–4.54) days).[24]

4.2. Implementation sample size

Given this is a type 1 hybrid study, we also estimated the detectable difference in our primary implementation outcome Composite Fidelity Score [CFS%]. Using a baseline CFS of 20%, a standard deviation of 32%, 18816 patients, an ICC of 0.31, 90% power, and a two-sided $\alpha = 0.05$), we estimate the study could detect a difference of 2.6% in mechanically ventilated patients (see Table 2).

To improve the reliability of these estimations, we conducted several sensitivity analyses, which we present in Table 2 and provide an expanded rationale in Appendix S2 (SAP sections 5.5.1 & 5.5.2).

The power calculation was performed using the Stata function "stepped wedge".[47,48]

4.3. Acceptability survey sample size

We estimate up to a total of 1000 survey responses from clinicians. Based on our pilot study and previous work,[25] we anticipate a conservative response rate of 50% (625 surveys completed of 1250 distributed), which will provide a 95% binomial CI of ±3.9 %.

5. Statistical analysis

5.1. 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 nonintervention site or vice versa, see Appendix S2 (SAP section 7.4) for details.

5.2. Analysis plan

Baseline patient characteristics and how they will be reported are presented in Appendix S2 (SAP Supplementary Table 2). Categorical data will be summarised by frequencies and percentages. Continuous data will be summarised 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.

Clinical outcomes will be analysed at the patient level. For the primary analysis, we will compare the mean 28-day VFDs pre-implementation and postimplementation using a mixed effects linear regression model to account for clustering of patients within the site.

The analysis of VFDs has a number of considerations, including its bimodal nature as well as the presence of competing risks for each of its components. There is no single best analysis method for

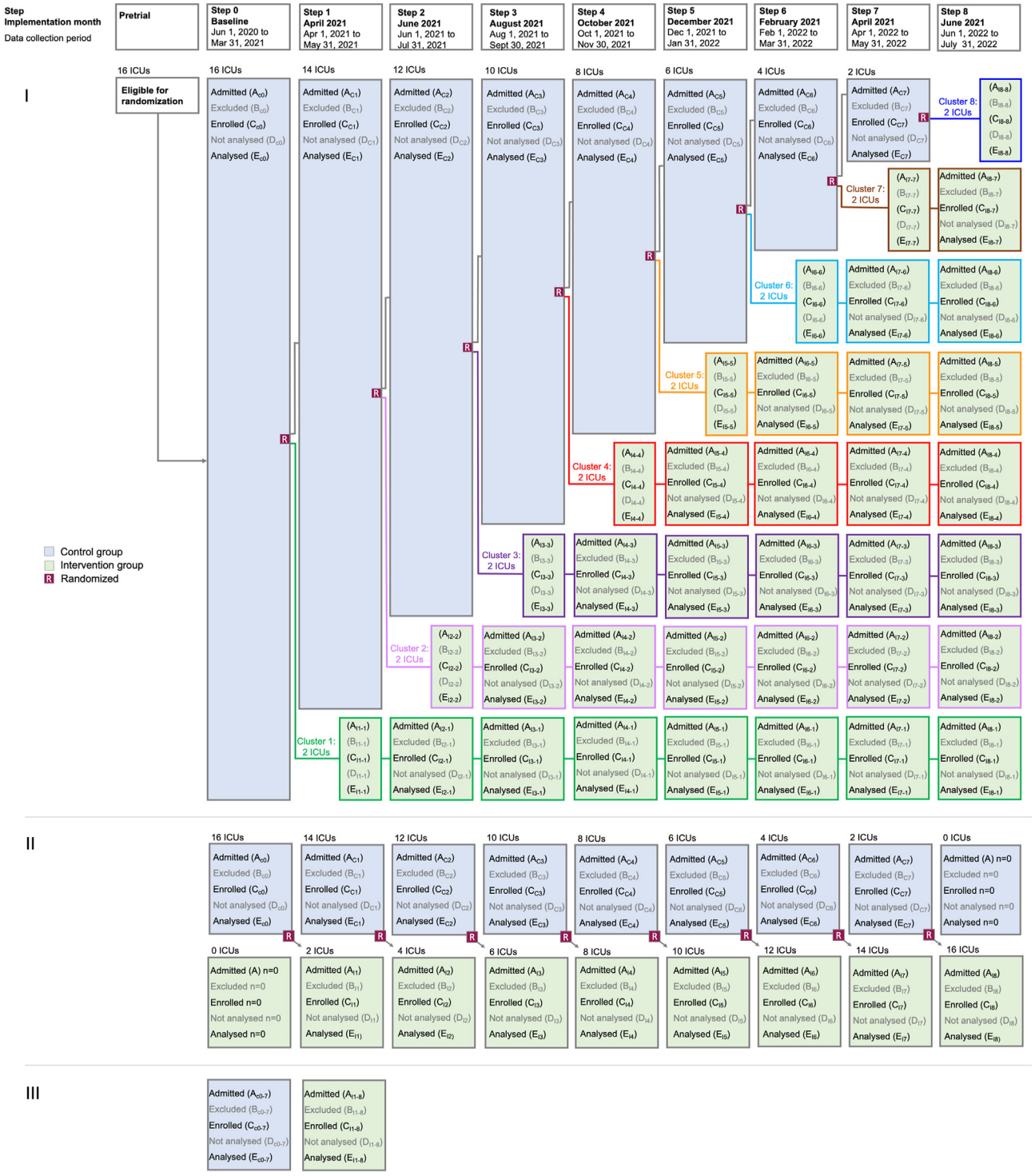

Fig. 4. CONSORT diagram. I = patients by step. II = patients by cluster. III = patients at trial level. Admitted (A) = the number of patients admitted. Excluded (B) = the number of patients who were excluded, e.g. not mechanically ventilated. Enroled (C) = the number of patients who were enrolled. (C = 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 analysed (E = C - D). $_c$ = control. $_I$=intervention. In each box, the symbols represent the analysis status (A, B, C, D, E), whether it is the control ($_c$) or intervention ($_I$) group, the step of the stepped wedge (0–8), and in section I, the intervention groups, which cluster 1–8 For example, $A_{I5\text{-}2}$ 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 ($_{\text{-}2}$).

VFDs.[49,50] The parametric T-Test provides the opportunity to adjust for baseline variables (both continuous and categorical) through linear regression, the T-Test's modelling analog, and provide effect estimates. An alternative approach would be to conduct a competing risk analysis using a Fine and Gray competing risk regression using the two mutually exclusive endpoints of successful extubation or death. The use of a nonparametric test such as the Wilcoxon rank sum was not ideal for our study as it could only be stratified by a single categorical variable and could not adjust for continuous variables, also would not provide effect estimates. We hypothesised that our intervention would either influence the duration of mechanical ventilation only or have a week to moderate impact on mortality in addition to a benefit on duration. Based on simulation studies for 28-day VFDs and the hypothesised outcomes above, the T-test had the same or higher power than a Fine and Gray competing risk regression.[50] A recent modelling study on VFDs confirms that a T-test/linear regression-based approach is simple and easy to interpret, but it also performed similarly (if not better) in estimating group means compared to other models[49] Given how close the power is between the T-Test method and the Fine and Gray competing risk regression method, we planned to conduct the T-test/linear regression as our primary analysis and the competing risk analysis as a sensitivity analysis (see sensitivity analysis section below and Appendix S2, SAP section 8.2.1). In addition to this, we have preplanned to report the separate components of VFDs (ventilator duration and mortality) as secondary outcomes.

Secondary clinical outcomes will be similarly compared preimplementation and postimplementation using mixed-effects linear or logistic regression models, as appropriate. To account for the competing risk of death, we will also analyse ICU and hospital LOS using time-to-event analyses censored at 90 days after mechanical ventilation for hospital LOS (no censoring is required for ICU LOS) using Fine and Gray competing risk regression since we have two mutually exclusive potential endpoints (discharge or death). Assumptions for the competing risk analysis will be assessed using the same method as the analysis for VFDs. 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 assess for potential collinearity among adjustment factors by examining the variance inflation factors (VIF), and if there is evidence of collinearity (eg. VIF >5), a variable will be considered for exclusion from the models. 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. The threshold for the entire analysis of primary and secondary outcomes will be two-sided using a 5% significance level ($\alpha = 0.05$). Measures of association will be reported using differences in means or odds ratios with a 95% CI as appropriate. There is only one primary clinical effectiveness outcome; therefore, no adjustment for multiplicity is required. For secondary outcomes, we will report the false discovery rate to account for the multiplicity of testing. All analysis will be conducted using the statistical analysis software R.

Adherence will be presented using the CFS score preimplementation and postimplementation (Appendix S2, SAP Supplementary Table 3) of the intervention (mean, median, interquartile range (IQR), p-value). Time trends in the CFS will be presented for all mechanically ventilated patients, patients with HRF, and patients with ARDS (definition 2, see Appendix S2, SAP Supplementary Table 1 for definition). Fidelity process of care indicators will also be used to improve pathway adherence through monthly audits and feedback reports.

The timing of the final analysis is presented in Fig. 3 and described in Appendix S2 (SAP section 5.8). This SAP version 1 (February 22, 2022) was added to ClinicalTrials.gov and posted publicly on a preprint server prior to the retrieval of electronic data and before any analyses had been conducted.[31]

Details of protocol deviation definitions, patient transfer to a nonstudy site, and loss to follow-up are presented in Appendix S2 (SAP sections 6.2 & 7.4). The number of ICUs, number of eligible patients, and exclusions will be detailed in the CONSORT flow diagram (see Fig. 4).

Acceptability survey data will be presented as aggregated frequencies with proportions. The data will be stratified by participant profession, years of experience, and type of institution. Differences will be compared using Fisher's exact test or Chi-squared test for

Table 3
Ventilator free days (primary clinical effectiveness outcome) and composite fidelity score (primary implementation outcome) subgroup analyses.

Subgroup	Directionality
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 vs non-HRF	HRF patients most likely to improve VFDs as eligible to get more elements of the pathway
ARDS vs non-ARDS (ARDS definition 2)	ARDS patients most likely to improve VFDs as eligible to get more elements of the pathway
Females vs males	Females most likely to improve VFDs given lower baseline CFS
Covid positive vs Covid negative	Covid patients most likely most likely to improve VFDs as eligible to get more elements of the pathway
Cardiac surgery vs non-cardiac surgery patients	Non cardiac surgery patients most likely to improve VFDs as eligible to get more elements of the pathway
Average height of patients (3 categories: quartile 1, quartile 2 & 3, quartile 4)	Lower quartile height patients most likely to improve VFDs given lower baseline lung protective strategies
Severity of HRF in first 24 h of MV (Severe vs moderate vs mild)	Severe HRF patients most likely to improve VFDs as eligible to get more elements of the pathway
Age >60 vs 60 and under	Age >60 patients most likely to improve VFDs as mortality at presentation is higher
Weight by BMI classifications (<18.5, 18.5 to <25, 25 to <30, >30)	Higher BMI patients 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

Subgroup analyses will be conducted for both the primary effectiveness outcome (28-day VFDs) and also the primary implementation outcome (CFS).
ARDS = acute respiratory distress syndrome. BMI = body mass index. CFS = composite fidelity score. HRF = hypoxemic respiratory failure. ICU = intensive care unit. LOS = length of stay. MV = mechanically ventilated. Pts = patients. PEEP = positive end expiratory pressure. SOFA = sequential organ failure assessment. VFDs = ventilator free days. See Appendix S2, SAP for details of subgroup analyses.

categorical variables, or the Wilcoxon rank-sum test or Kruskal-Wallis test for Likert scale data, as appropriate. An expanded method for focus group analysis will be reported separately. Additional details on both the survey methodology and focus groups are available in Appendix S1 (Protocol, section 7.1.2, 7.2.2, 8.2.1, and Attachment 9, 10, 12, 13).

5.3. Sensitivity analysis

As a sensitivity analysis, we will analyse 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.[50] Schoenfeld-type residuals will be used to assess the proportional subdistribution hazard assumption.[51,52] Additional sensitivity analyses are presented in Appendix S2 (SAP section 7.4, 8.2.1).

5.3.1. Subgroup analysis

A full list of subgroups for analyses is presented in Table 3 and 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 secondary analyses, we will report the false discovery rate.

5.3.2. Cost-effectiveness analysis

Full details of the statistical analysis plan for the economic analysis will be provided in a separate protocol.

6. Data access

Demographic, clinical, and outcome data to evaluate effectiveness and fidelity will be collected via TRACER, which prospectively captures data for all patients admitted to Alberta ICUs using an integrated bedside electronic medical record.[53] Surveys will be administered via Qualtrics, an online survey tool. Additional details of data access, handling, storage, and encryption can be found in Appendix S1 (Protocol section 7 and Attachment 7).

CRediT authorship contribution statement

All authors are members of the Scientific Steering Group. Members provided input and approved the statistical analysis plan. KP, GK and AS wrote the first draft of the manuscript. All authors contributed to editing and final approval of the accepted version.

Funding

We have received funding from the Canadian Institutes of Health Research (CIHR) (427774) and the Health Innovation Implementation and Spread (HIIS 2) grant from Alberta Health and Alberta Health Services (2020). The funders had no role in study design, data collection, decision to publish or preparation of the manuscript..

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2023.10.008.

References

[1] Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA 2016;315(8):788–800.
[2] Parhar K, Zjadewicz K, Soo A, Sutton A, Zjadewicz M, Doig L, et al. Epidemiology, mechanical power, and 3-year outcomes in acute respiratory distress syndrome patients using standardized screening. An observational cohort study. Annals of the American Thoracic Society 2019;16(No. 10):1263–72.
[3] Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med 2005;353(16):1685–93.
[4] Villar J, Blanco J, Anon JM, Santos-Bouza A, Blanch L, Ambros A, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med 2011;37(12):1932–41.
[5] Cheung AM, Tansey CM, Tomlinson G, Diaz-Granados N, Matte A, Barr A, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. Am J Respir Crit Care Med 2006;174(5):538–44.
[6] Hernu Rw F, Thiolliere F, Martin O, Richard JC, Schmitt Z, Wallon G, et al. An attempt to validate the modification of the American-European consensus definition of acute lung injury/acute respiratory distress syndrome by the Berlin definition in a university hospital. Intensive Care Med 2013;39:2161–70.
[7] Sadana D, Kaur S, Kesavan S, Saini I, Banerjee K, Siuba M, et al. Mortality associated with acute respiratory distress syndrome, 2009-2019: a systematic review and meta-analysis. Critical Care and Resuscitation 2022;24(4):341–51.
[8] Walkey AJ, Goligher EC, Del Sorbo L, Hodgson CL, Adhikari NKJ, Wunsch H, et al. Low tidal volume versus non-volume-limited strategies for patients with acute respiratory distress syndrome. A systematic review and meta-analysis. Annals of the American Thoracic Society 2017;14(Supplement_4):S271–9.
[9] Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med 2000;342(18):1301–8.
[10] Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev 2013;(2):CD003844.
[11] Alhazzani W, Alshahrani M, Jaeschke R, Forel JM, Papazian L, Sevransky J, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. Crit Care 2013;17(2):R43.
[12] Guérin C, Reignier J, Richard J-C, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368(23):2159–68.
[13] Al-Bassam W, Parikh T, Neto A, Idrees Y, Kubicki M, Hodgson C, et al. Pressure support ventilation in intensive care patients receiving prolonged invasive ventilation. Critical Care and Resuscitation 2021;23(4):394–402.
[14] Fan E, Del Sorbo L, Goligher EC, Hodgson CL, Munshi L, Walkey AJ, et al. An official American thoracic society/European society of intensive care medicine/society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195(9):1253–63.
[15] Chiumello D, Brochard L, Marini JJ, Slutsky AS, Mancebo J, Ranieri VM, et al. Respiratory support in patients with acute respiratory distress syndrome: an expert opinion. Crit Care 2017;21(1):240.
[16] Guerin C, Beuret P, Constantin JM, Bellani G, Garcia-Olivares P, Roca O, et al. A prospective international observational prevalence study on prone positioning of ARDS patients: the APRONET (ARDS Prone Position Network) study. Intensive Care Med 2018;44(1):22–37.
[17] Munshi L, Del Sorbo L, Adhikari NKJ, Hodgson CL, Wunsch H, Meade MO, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. Annals of the American Thoracic Society 2017;14(Supplement_4):S280–8.
[18] Ferguson ND, Frutos-Vivar F, Esteban A, Fernandez-Segoviano P, Aramburu JA, Najera L, et al. Acute respiratory distress syndrome: underrecognition by clinicians and diagnostic accuracy of three clinical definitions. Crit Care Med 2005;33(10):2228–34.
[19] Frohlich S, Murphy N, Doolan A, Ryan O, Boylan J. Acute respiratory distress syndrome: underrecognition by clinicians. J Crit Care 2013;28(5):663–8.
[20] Herasevich V, Yilmaz M, Khan H, Hubmayr RD, Gajic O. Validation of an electronic surveillance system for acute lung injury. Intensive Care Med 2009;35(6):1018–23.
[21] Kalhan R, Mikkelsen M, Dedhiya P, Christie J, Gaughan C, Lanken PN, et al. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. Crit Care Med 2006;34(2):300–6.
[22] Li X, Scales DC, Kavanagh BP. Unproven and expensive before proven and cheap - extracorporeal membrane oxygenation vs. Prone position in ARDS. Am J Respir Crit Care Med 2018;197(8):991–3.
[23] To Err is Human. In: Kohn JMC Linda T, Donaldson Molla S, editors. Building A safer health system. 1 ed. Washington, DC: National Academy Press; 1999. p. 287.

[24] Parhar KKS, Stelfox HT, Fiest KM, Rubenfeld GD, Zuege DJ, Knight G, et al. Standardized management for hypoxemic respiratory failure and ARDS: systematic review and meta-analysis. Chest 2020;158(6):2358–69.
[25] Parhar KKS, Zjadewicz K, Knight GE, Soo A, Boyd JM, Zuege DJ, et al. Development and content validation of a multidisciplinary standardized management pathway for hypoxemic respiratory failure and acute respiratory distress syndrome. Crit 2021;3(5):e0428.
[26] Cavalcanti AB, Suzumura EA, Laranjeira LN, Paisani DM, Damiani LP, Guimaraes HP, et al. Effect of lung recruitment and titrated positive end-expiratory pressure (PEEP) vs low PEEP on mortality in patients with acute respiratory distress syndrome: a randomized clinical trial. JAMA 2017;318(14):1335–45.
[27] Atkins L, Francis J, Islam R, O'Connor D, Patey A, Ivers N, et al. A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci : ISCUS 2017;12(1):77.
[28] Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci : ISCUS 2011;6:42.
[29] Michie S, Atkins L, West R. The Behaviour change Wheel: a guide to designing interventions. London: Silverback Publishing; 2014.
[30] Parhar KKS. Treatment of hypoxemic respiratory failure and ARDS with protection, paralysis, and proning (TheraPPP) pathway. ClinicalTrials.gov Identifier: 2023. NCT040700532019 [updated June 18, Available from: https://ClinicalTrials.gov/show/NCT04070053 [Accessed 28 June 2023].
[31] Parhar KKS, Soo A, Knight G, Fiest K, Niven DJ, Rubenfeld G, et al. 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. medRxiv 2023. 2023.03.17.23287218.
[32] Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the content of statistical analysis plans in clinical trials. JAMA 2017;318(23):2337–43.
[33] Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158(3):200–7.
[34] Young PJ, Al-Fares A, Aryal D, Arabi YM, Ashraf MS, Bagshaw SM, et al. Protocol and statistical analysis plan for the mega randomised registry trial comparing conservative vs. liberal oxygenation targets in adults with nonhypoxic ischaemic acute brain injuries and conditions in the intensive care unit (Mega-ROX Brains). Critical Care and Resuscitation 2023;25(1):53–9.
[35] Maia S, Kawano-Dourado L, Zampieri F, Damiani L, Nakagawa RH, Gurgel RM, et al. High flow nasal catheter therapy versus non-invasive positive pressure ventilation in acute respiratory failure (RENOVATE trial): protocol and statistical analysis plan. Critical Care and Resuscitation 2022;24(1):61–79.
[36] Hemming K, Taljaard M, Grimshaw J. Introducing the new CONSORT extension for stepped-wedge cluster randomised trials. Trials 2019;20(1):68.
[37] Pinnock H, Barwick M, Carpenter CR, Eldridge S, Grandes G, Griffiths CJ, et al. Standards for reporting implementation studies (StaRI): explanation and elaboration document. BMJ Open 2017;7(4):e013318.
[38] Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.
[39] O'Brien BC, Harris IB, Beckman TJ, Reed DA, Cook DA. Standards for reporting qualitative research: a synthesis of recommendations. Acad Med 2014;89(9):1245–51.
[40] Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care 2007;19(6):349–57.
[41] ICMJE. Recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals. 2019.
[42] Curran GM, Bauer M, Mittman B, Pyne JM, Stetler C. Effectiveness-implementation hybrid designs: combining elements of clinical effectiveness and implementation research to enhance public health impact. Med Care 2012;50(3):217–26.
[43] Sekhon M, Cartwright M, Francis JJ. Acceptability of healthcare interventions: an overview of reviews and development of a theoretical framework. BMC Health Serv Res 2017;17(1):88.
[44] Tomazini BM, Maia IS, Bueno FR, Silva MVAO, Baldassare FP, Costa ELV, et al. COVID-19-associated ARDS treated with DEXamethasone (CoDEX): study design and rationale for a randomized trial. Revista Brasileira de terapia intensiva 2020;32(3):354–62.
[45] Rice TW, Wheeler AP, Thompson BT, deBoisblanc BP, Steingrub J, Rock P, et al. Enteral omega-3 fatty acid, γ-linolenic acid, and antioxidant supplementation in acute lung injury. JAMA, J Am Med Assoc 2011;306(14):1574–81.
[46] Hodgson CL, Cooper DJ, Arabi Y, King V, Bersten A, Bihari S, et al. Maximal recruitment open lung ventilation in acute respiratory distress syndrome (pharlap). A phase II, multicenter randomized controlled clinical trial. Am J Respir Crit Care Med 2019;200(11):1363–72.
[47] Hemming K, Girling AJ. A menu driven facility for sample size for power and detectable difference calculations in stepped wedge randomised trials. STATA J 2014;14:363–80.
[48] Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials 2007;28(2):182–91.
[49] Granholm A, Kaas-Hansen B, Lange T, Munch M, Harhay M, Zampieri F, et al. Use of days alive without life support and similar count outcomes in randomised clinical trials – an overview and comparison of methodological choices and analysis methods. BMC Med Res Methodol 2023:23.
[50] Yehya N, Harhay MO, Curley MAQ, Schoenfeld DA, Reeder RW. Reappraisal of ventilator-free days in critical care research. Am J Respir Crit Care Med 2019;200(7):828–36.
[51] Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94(446):496–509.
[52] Zhou B, Fine J, Laird G. Goodness-of-fit test for proportional subdistribution hazards model. Stat Med 2013;32(22):3804–11.
[53] Brundin-Mather R, Soo A, Zuege DJ, Niven DJ, Fiest K, Doig CJ, et al. Secondary EMR data for quality improvement and research: a comparison of manual and electronic data collection from an integrated critical care electronic medical record system. J Crit Care 2018;47:295–301.