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Protocol and Statistical Analysis Plan for the Mode of Ventilation During Critical Illness (MODE) Trial

Kevin P. Seitz, MD,
Bradley D. Lloyd, RRT-ACCS,
Li Wang, MS,
Matthew S. Shotwell, PhD,
Edward T. Qian, MD,
Roger K. Richardson, RRT-ACCS, JM,
Jeffery C. Rooks, RRT, MMHC,
Vanessa Hennings-Williams, RRT-ACCS, MBA,
Claire E. Sandoval, RRT-ACCS,
Whitney D. Richardson, RRT,
Tracy Morgan, RRT,
Amber N. Thompson, RRT-ACCS,
Pamela G. Hastings, RRT-ACCS,
Terry P. Ring, RRT-ACCS, MBA,
Joanna L. Stollings, PharmD,
Erica M. Talbot, MD,
David J. Krasinski, MD,
Bailey Decoursey, MD,
Kevin W. Gibbs, MD,
Wesley H. Self, MD, MPH,
Amanda S. Mixon, MD, MSPH,
Todd W. Rice, MD,
Matthew W. Semler, MD,

CORRESPONDENCE TO: Kevin P. Seitz, MD; kevin.seitz@vumc.org.
Drs Shotwell and Casey contributed equally to this manuscript.

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Additional information: The e-Appendix is available online under “Supplementary Data.”

Jonathan D. Casey, MD

Department of Medicine (K. P. S., E. T. Q., T. W. R., M. W. S., and J. D. C.), Division of Allergy, Pulmonary and Critical Care Medicine; the Department of Emergency Medicine (B. D. L. and W. H. S.); the Department of Biostatistics (L. W. and M. S. S.); the Department of Respiratory Care (R. K. R., J. C. R., V. H.-W., C. E. S., W. D. R., T. M., A. N. T., P. G. H., and T. P. R.); the Department of Pharmaceutical Services (J. L. S.); the Department of Medicine (E. M. T., D. J. K., and B. D.), Vanderbilt University Medical Center, Nashville, TN; the Section on Pulmonary, Critical Care, Allergy, and Immunology (K. W. G.), Wake Forest School of Medicine, Winston-Salem, NC; the Vanderbilt Institute for Clinical and Translational Research (W. H. S.), Vanderbilt University Medical Center, Nashville, TN; the Department of Medicine, Division of General Internal Medicine and Public Health (A. S. M.), Vanderbilt University Medical Center, Nashville, TN; and the VA Tennessee Valley Healthcare System, Geriatric Research, Education, and Clinical Center (A. S. M.), Nashville, TN.

Abstract

BACKGROUND: For every critically ill adult receiving invasive mechanical ventilation, clinicians must select a mode of ventilation. The mode of ventilation determines whether the ventilator directly controls the tidal volume or the inspiratory pressure. Newer hybrid modes allow clinicians to set a target tidal volume; the ventilator controls and adjusts the inspiratory pressure. A strategy of low tidal volumes and low plateau pressure improves outcomes, but the optimal mode to achieve these targets is not known.

RESEARCH QUESTION: Can a cluster-randomized trial design be used to assess whether the mode of mandatory ventilation affects the number of days alive and free of invasive mechanical ventilation among critically ill adults?

STUDY DESIGN AND METHODS: The Mode of Ventilation During Critical Illness (MODE) trial is a cluster-randomized, multiple-crossover pilot trial being conducted in the medical ICU at an academic center. The MODE trial compares the use of volume control, pressure control, and adaptive pressure control. The study ICU is assigned to a single-ventilator mode (volume control vs pressure control vs adaptive pressure control) for continuous mandatory ventilation during each 1-month study block. The assigned mode switches every month in a randomly generated sequence. The primary outcome is ventilator-free days to study day 28, defined as the number of days alive and free of invasive mechanical ventilation from the final receipt of mechanical ventilation to 28 days after enrollment. Enrollment began November 1, 2022, and will end on July 31, 2023.

RESULTS: This manuscript describes the protocol and statistical analysis plan for the MODE trial of ventilator modes comparing volume control, pressure control, and adaptive pressure control.

INTERPRETATION: Prespecifying the full statistical analysis plan prior to completion of enrollment increases rigor, reproducibility, and transparency of the trial results.

CLINICAL TRIAL REGISTRATION: The trial was registered with clinicaltrials.gov on October 3, 2022, before initiation of patient enrollment on November 1, 2022 (ClinicalTrials.gov identifier: NCT05563779).

Keywords

artificial respiration; critical illness; feasibility studies; respiratory failure

Approximately 2 to 3 million critically ill adults receive invasive mechanical ventilation in an ICU each year.[1–3] Although clinical trials have demonstrated that the use of smaller tidal volumes and lower plateau pressures can improve the outcomes of critically ill adults receiving invasive mechanical ventilation,[4,5] the optimal ventilator mode to achieve these targets remains unknown.

The tidal volume and the inspiratory airway pressure are directly related. For patients receiving invasive mechanical ventilation, delivering larger tidal volumes generates higher airway pressures, and conversely, increasing airway pressures usually generates higher tidal volumes. Ventilator modes allow clinicians to control either the volume ("volume control" mode) or the pressure ("pressure control" mode) administered during inspiration.[6] By controlling one variable, each mode provides indirect control over the other variable, which varies in a proportion dictated by the patient's unique respiratory physiology. Modern ventilators also offer hybrid modes such as adaptive pressure control, a pressure-targeted mode in which a clinician sets a target tidal volume (eg, pressure-regulated volume control) and the ventilator achieves that target by titrating the inspiratory pressure over multiple breaths to account for changes in patient effort and respiratory physiology.

Volume control, pressure control, and adaptive pressure control all can achieve low tidal volume and low plateau pressures, the key components of lung protective ventilation, a strategy proven to improve outcomes for critically ill adults receiving mechanical ventilation.[7–9] Each mode differs, however, in the specifics of how it delivers inspiratory pressure, volume, and flow. For example, volume control directly controls tidal volumes but permits more breath-to-breath variability in inspiratory pressure, increasing the risk for barotrauma. Pressure control directly controls inspiratory pressure but allows more breath-to-breath variability in tidal volume, which could result in more exposure to excessive tidal volumes.[10] Adaptive pressure control automatically titrates inspiratory pressures to reach a target tidal volume, which could provide both the benefits and harms of volume control and pressure control.[11] These differences could theoretically affect pulmonary physiology, patient comfort, sedation requirements, risk of ventilator-induced lung injury, and clinical outcomes.[12] No studies have found conclusive benefit from any mandatory mode of ventilation.[13,14] Furthermore, the only clinical trials comparing modes of mechanical ventilation among critically ill adults have been small and occurred when deep sedation and paralysis were common and spontaneous awakening and breathing trials had not yet become routine practice.[15,16]

Given the absence of evidence regarding the ideal mode of mechanical ventilation, significant variation in the choice of mode exists in current clinical practice. Observational cohort studies in the United States and internationally have demonstrated that volume control, pressure control, and adaptive pressure control are each used routinely in the management of critically ill adults.[7,8,17] Because the mode of mechanical ventilation must be set for every critically ill patient receiving mechanical ventilation and the relationship

between the commonly used modes and patient outcomes remains uncertain, a large, randomized trial at multiple centers is needed to inform the optimal mode of mechanical ventilation for critically ill adults.[18–20] Before such a trial can be conducted, additional data are needed regarding the feasibility of assigning the mode of mechanical ventilation for critically ill adults, of maintaining adherence to group assignment, and of using days alive and free of ventilation as a primary outcome for a trial comparing ventilator modes.[14,21–23] To address this lack of preliminary data, we designed the Mode of Ventilation During Critical Illness (MODE) trial as a prospective, randomized pilot trial comparing modes of continuous mandatory ventilation among critically ill adults in a medical ICU.

Methods and Analysis

This manuscript was written by the MODE trial investigators, in accordance with Standard Protocol Items: Recommendations for Interventional Trials guidelines (e-Appendix 1, section 1). In this manuscript, we describe key elements of the trial protocol and statistical analysis plan.

Supplementary materials in e-Appendix 1 provide additional background on design decisions (sections 2, 19, 22), mode monitoring and management (sections 3, 4, 12, 15, 23, 24), institutional protocols and management of critically ill adults receiving invasive mechanical ventilation (sections 5–11), a complete list of data elements (section 13), additional outcome definitions (section 14), details of the interim analysis (section 16), and secondary analysis considerations (sections 17, 18).

Study Design

The MODE trial is a prospective, cluster-randomized, multiple-crossover trial being conducted in the medical ICU at a single center. This trial compares use of volume control vs pressure control vs adaptive pressure control among patients receiving invasive mechanical ventilation in the study ICU. Consistent with the goals of a pragmatic trial, delivery of the intervention is embedded in routine clinical care and managed by bedside clinicians. The primary outcome is the number of days alive and free of invasive mechanical ventilation to study day 28 after enrollment. Feasibility measures are reported to inform the conduct of a subsequent multicenter trial. The trial protocol was approved by the Vanderbilt University Medical Center institutional review board (IRB# 220446) on July 21, 2022, and was registered with ClinicalTrials.gov[24] (NCT05563779) on October 3, 2022, before initiation of patient enrollment on November 1, 2022.

Study Site and Population

The trial is being conducted in the medical ICU at a tertiary-care teaching hospital. Patients are enrolled in the trial or excluded from the trial at the time of first receipt of invasive mechanical ventilation in the study ICU, using the criteria outlined in Table 1.

The inclusion criteria are:

1. Age ≥ 18 years
2. Receiving mechanical ventilation through an endotracheal tube or tracheostomy

3. Admitted to the study ICU.

The exclusion criteria are:

1. Patient is pregnant.
2. Patient is incarcerated.
3. Patient receiving invasive mechanical ventilation at place of residence before hospital admission. This criterion is intended to exclude patients who are receiving chronic positive-pressure ventilation through an invasive airway at a long-term acute care facility, at a nursing facility, or at home. This criterion does not exclude patients who began to receive invasive mechanical ventilation previously during this episode of acute illness in another location, such as the ED, hospital ward, operating room, another ICU, or another hospital.
4. Patient receiving extracorporeal membrane oxygenation at the time of admission to the study ICU.

Randomization and Treatment Allocation

During each 1-month period of the 9 months of enrollment in the MODE trial, the study ICU is assigned to use one of the three modes of mechanical ventilation (volume control vs pressure control vs adaptive pressure control) (Fig 1). Each month, the ICU will switch between the three modes in a randomly generated sequence. The order of the study group assignments was generated by computerized randomization using permuted blocks of three to minimize the impact of seasonal variation. Patients will be analyzed in the group to which they were assigned at enrollment (intention-to-treat) even if they remain in the study ICU during a transition from one month to the next (“crossover”).

Washout Periods

The last 3 days of each month are an analytic washout period during which the study ICU continues to use the assigned ventilator mode, but new patients are not included in the primary analysis. The 3-day washout period will reduce the number of patients who experience a “crossover” from one assigned mode to another assigned mode in the 72-hour time window when feasibility outcomes of adherence are assessed.

Study Interventions

Ventilator Mode: The MODE trial compares volume control, pressure control, and adaptive pressure control (Table 2). On initiation of invasive mechanical ventilation, nearly all patients require a ventilator mode that initiates breaths at a set frequency (mandatory mode of ventilation). The three most commonly used modes of mandatory ventilation are volume control, pressure control, and adaptive pressure control. Each of these modes provides continuous mandatory ventilation, in which every inspiratory effort by a patient triggers a machine-cycled breath delivered by the ventilator, and a set minimum respiratory rate is maintained by machine-triggered breaths as needed.[6]

For patients enrolled in the MODE trial, clinicians are instructed to use the assigned mode beginning at the first receipt of invasive mechanical ventilation in the study ICU and ending

at the first of (1) extubation from mechanical ventilation, (2) transfer out of the study ICU, (3) treating clinician deciding that optimal care requires a different mode (with completion of a ventilator mode modification sheet), or (4) end of the 1-month study block (e-Appendix 1, section 15). Any patients who remain mechanically ventilated during a "crossover" from one month to the next will, after the "crossover," have their mode of ventilation determined by the clinical team. The treating team may opt to continue the mode assigned during the prior month, use the mode assigned to the current month, or use any other mode they believe would be best for the patient. If a patient is enrolled, extubated, and reintubated during the same study block, the study protocol will determine the ventilator mode until they meet one of the criteria listed above. The study protocol does not determine the ventilator mode during periods in which the patient is not receiving a mandatory mode of ventilation (eg, use of pressure support ventilation such as during a spontaneous breathing trial), is not physically located in the study ICU (eg, during transport), or is undergoing an invasive procedure (eg, bronchoscopy).

In the study ICU, respiratory therapists typically have primary responsibility for determining the initial settings for invasive mechanical ventilation and titrating the settings to achieve clinical goals (eg, arterial oxygen saturation, PCO_2, target tidal volume, target plateau pressure). To set and titrate mechanical ventilators, respiratory therapists use standard-of-care clinical protocols jointly developed by respiratory therapy and physician leaders. For patients enrolled in the MODE trial, respiratory therapists employ preexisting clinical protocols dictating how each study group (volume control, pressure control, and adaptive pressure control) should be set and titrated (e-Appendix 1, section 5).

Ventilator Mode Modification Sheet: If at any time, any member of the clinical team, such as a respiratory therapist, advanced practice provider, or physician, determines a specific mandatory mode of ventilation is needed for the optimal treatment of any specific patient, they may use that mode of mechanical ventilation. In these cases, a one-page mode modification sheet is completed documenting the date, time, reason for modification, and the mode of ventilation chosen. Anticipated examples of conditions for which treating clinicians may elect to override the assigned mode include refractory hypoxemia, persistently high peak pressures (> 40 cm H_2O), dyssynchrony not amenable to changes within the assigned mode, excessive work of breathing, barotrauma, inability to limit tidal volumes delivered, or intrinsic positive end-expiratory pressure. If the condition that precipitated the mode modification sheet resolves, clinicians are encouraged to return to the assigned study mode and complete a new mode modification sheet if subsequent changes to the ventilator mode are required. Strategies used to monitor and improve adherence to the assigned study mode are included in e-Appendix 1 (sections 3, 4).

Co-Interventions: For all patients, regardless of group assignment, existing ventilator protocols in the study ICU will be used to target a tidal volume of 6 mL/kg predicted body weight and a plateau pressure less than 30 cm H_2O, while maintaining a respiratory rate less than 35 breaths/min and pH of greater than 7.15, with a target of 7.30 to 7.45.[5] This lung protective ventilation strategy is the existing standard of care in the study unit for all patients because the strategy has been shown to improve outcomes in patients with ARDS,[5,25] and

studies in surgical patients and those without ARDS on mechanical ventilation have shown benefit or been indeterminate across most patient populations.[26–28]

On each day of mechanical ventilation, all patients in the study ICU are assessed for safety of a spontaneous awakening trial and spontaneous breathing trial, and if safe, these procedures are performed, per the existing unit clinical protocols. As such, the spontaneous awakening trial and spontaneous breathing trial procedures are handled in the same way for each patient, regardless of study group assignment. For patients who have passed a spontaneous awakening trial and spontaneous breathing trial, the decision to discontinue invasive mechanical ventilation is made by the treating clinicians. Additional details regarding clinical practice guidelines in use are provided in e-Appendix 1 (sections 6–12).

Blinding

Consistent with prior trials evaluating mechanical ventilation settings,[5,29] patients and clinicians in the MODE trial are not blinded to trial group assignment.

Data Collection

Trial personnel collect data by two methods to minimize observer bias. First, trial personnel review the electronic health record at least twice daily to confirm eligibility criteria and enrollment status for new patients, monitor adherence to the assigned ventilator mode, and screen for the occurrence of adverse events (e-Appendix 1, section 3). Trial personnel manually collect data on baseline characteristics, study management, and clinical outcomes.

Second, structured data recorded in routine clinical care is exported from the institution's electronic health record into an Enterprise Data Warehouse. This method of data collection has been validated and used in prior pragmatic trials at this site.[29,30]

The primary outcome is collected by both manual chart review and automated data collection for confirmation. Discordance between manual and automated data will be reviewed and manually adjudicated by a second investigator. The list of all variables collected is available in e-Appendix 1 (section 13).

Outcomes

Primary Outcome: The primary outcome is the number of ventilator free days (VFDs) through day 28 after enrollment. VFDs will be defined as the number of whole calendar days alive and free of invasive mechanical ventilation from the final receipt of invasive mechanical ventilation through day 28 after enrollment.[31,32] Patients who die before hospital discharge on or before day 28 will receive 0 VFDs. Patients whose final receipt of invasive mechanical ventilation occurs on the day of enrollment (day 1) and survive to day 28 will receive 27 VFDs. Additional detail is provided in e-Appendix 1 (section 20).

Additional Outcomes: Feasibility outcomes, exploratory efficacy and safety outcomes, and clinical outcomes were prespecified and are described in Table 3.

Statistical Analysis and Reporting

Sample Size Estimation and Power Calculation: The objectives of this trial are to demonstrate the feasibility of comparing modes of invasive mechanical ventilation in critically ill adults using a cluster-randomized, multiple-crossover design and to collect preliminary data to inform a subsequent multicenter trial using a similar study design. To assess whether adherence to trial group assignment can be maintained across "crossovers" in the assigned mode of mechanical ventilation, we will need to observe two end-of-period "crossovers" into each mode while maintaining an equal number of treatment blocks for each mode. Doing so will require a total of 9 months. Based on data from a prior trial in the same ICU,[33] we anticipate an average of 75 patients will be enrolled per month. In 9 months, we expect to enroll an estimated 675 patients, of whom 69 will be enrolled during washout periods and excluded from the primary analysis. As a result, approximately 606 patients will be included in the primary analysis.

Although the sample size was determined to demonstrate feasibility of the cluster-crossover design, we anticipate this pilot will be the largest randomized trial of ventilator modes to date, and as such, we plan to compare VFDs to day 28 (primary outcome) among groups. In a prior cluster-randomized cluster-crossover trial in the same ICU,[33] mechanically ventilated patients experienced a median of 22 VFDs (interquartile range, 0–25 VFDs) and an intracluster, intraperiod correlation of 0.01. With 606 patients (202 in each group) in the primary analysis, a SD in the primary outcome of VFDs of 11 days, and a two-sided alpha of 0.05, the MODE trial will have 80% statistical power to detect an absolute difference between groups in the primary outcome of 3 VFDs.

Data and Safety Monitoring Board and Interim Analysis

An independent Data Safety and Monitoring Board (DSMB) oversees conduct of the MODE trial. The DSMB is composed of three physicians with expertise in critical care medicine, pulmonary medicine, biostatistics, and clinical trials. On March 22, 2023, the DSMB conducted a single, planned interim analysis for safety after the first 3 months of enrollment. The DSMB recommended that the trial continue without modification. Details of the safety analysis are provided in the e-Appendix 1 (section 16). Given that the goal of the study is to demonstrate feasibility rather than demonstrating efficacy, there was no early stopping criterion for efficacy or futility.

Statistical Analysis Principles

Statistical analyses will be completed using R (R foundation for Statistical Computing), and analyses will be done at the level of an individual patient during an individual hospitalization in an intention-to-treat fashion.

Main Analysis of the Primary Outcome—The sole prespecified primary outcome of VFDs will be compared among the three trial groups in an intention-to-treat fashion among all patients enrolled in the trial except those enrolled during one of the 3-day washout periods. We will compare the primary outcome of VFDs between the trial groups using a proportional odds model with independent variables of group assignment (volume control, pressure control, or adaptive pressure control) and time. Time (in days) will be treated as a

continuous variable with values ranging from 1 (first day of enrollment) to 272 (final day of enrollment) and will be analyzed using restricted cubic splines with multiple knots to allow for nonlinearity resulting from seasonality or secular trends. A *P* value threshold of .05 will be considered significant evidence of an overall difference across treatment groups. In addition to assessing for overall differences across the three groups, we will estimate the differences between each pair of modes by extracting ORs with 95% CIs from the model. Sensitivity analyses of the primary outcome are described in e-Appendix 1 (section 18).

Analysis of Effect Modification for the Primary Outcome

We will examine whether prespecified baseline variables modify the effect of study group on the primary outcome using tests of statistical interaction in a proportional odds model. Independent variables will include study group assignment, the potential effect modifier of interest, the interaction between the two (eg, study group and shock), and time. Continuous variables will be analyzed using restricted cubic splines to allow for nonlinear relationships. Significance will be determined by the *P* value for the interaction term(s), with values less than .05 considered significant evidence of an interaction.

In accordance with the Instrument for Assessing the Credibility of Effect Modification Analyses recommendations, we prespecified the following baseline variables as potential modifiers of the effect of study group on the primary outcome and hypothesized the direction of the effect modification for each in e-Appendix 1 (section 17):

1. Age (continuous variable)
2. Duration of invasive mechanical ventilation before enrollment (0 min; 1–360 min; > 360 min)
3. Pre-enrollment FIO_2 (continuous variable).
4. Sequential Organ Failure Assessment score[34] at enrollment (continuous variable)
5. Shock receiving vasopressors (yes, no)
6. Indications for intubation (categories are not mutually exclusive)
    a. Hypoxemic respiratory failure (yes, no)
    b. Hypercarbic respiratory failure (yes, no)
    c. Altered mental status or airway protection (yes, no)
7. COPD (yes, no)

Analysis of the Exploratory Outcomes

Each of the exploratory outcomes will be compared between groups in an intention-to-treat fashion with an approach similar to that used for the primary outcome. A logistic model will be used for binary outcomes, and a proportional odds model for ordinal and continuous outcomes. All models will include independent covariates of group assignment and time.

Trial Status

The MODE trial is an ongoing trial comparing volume control vs pressure control vs adaptive pressure control for critically ill adults receiving invasive mechanical ventilation. Patient enrollment began on November 1, 2022, and is anticipated to conclude on July 31, 2023.

Ethics and Dissemination

Waiver of Informed Consent

Volume control, pressure control, and adaptive pressure control are all common approaches to controlled mechanical ventilation for critically ill adults. All represent standard-of-care treatments in current clinical practice. Because the study involves minimal incremental risk and obtaining informed consent would be impracticable, this trial was approved by the Vanderbilt University Medical Center institutional review board with a waiver of informed consent (#220446). Additional rationale is provided in e-Appendix 1 (section 20).

Protocol Changes

All changes to the trial protocol will be distributed to the institutional review board and recorded on ClinicalTrials.Gov as per Standard Protocol Items: Recommendations for Interventional Trials guidelines (e-Appendix 1, section 21).

Data Handling

Privacy protocols and data handling are reported in e-Appendix 1 (section 22).

Dissemination Plan

Investigators will submit the MODE trial results to a peer-reviewed journal for consideration of publication, and results will be presented at scientific conferences.

Conclusion

The MODE trial will provide the best evidence to date regarding the effect of mode of mechanical ventilation on the clinical outcomes of critically ill adults and will provide data regarding the feasibility for a definitive multicenter trial. To aid in the transparency and interpretation of trial results, this protocol and statistical analysis plan has been finalized before the conclusion of patient enrollment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Role of sponsors:

The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

ABBREVIATIONS:

DSMB	Data Safety and Monitoring Board
MODE	Mode of Ventilation During Critical Illness
VFD	ventilator-free days

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Take-home Points

Study Question:

Can a cluster-randomized trial design be used to assess whether the mode of mandatory ventilation affects the number of days alive and free of invasive mechanical ventilation among critically ill adults?

Results:

This manuscript describes the protocol and statistical analysis plan for the Mode of Ventilation During Critical Illness (MODE) trial of ventilator modes comparing volume control, pressure control, and adaptive pressure control.

Interpretation:

Prespecifying the full statistical analysis plan prior to before completion of enrollment increases rigor, reproducibility, and transparency of the trial results.

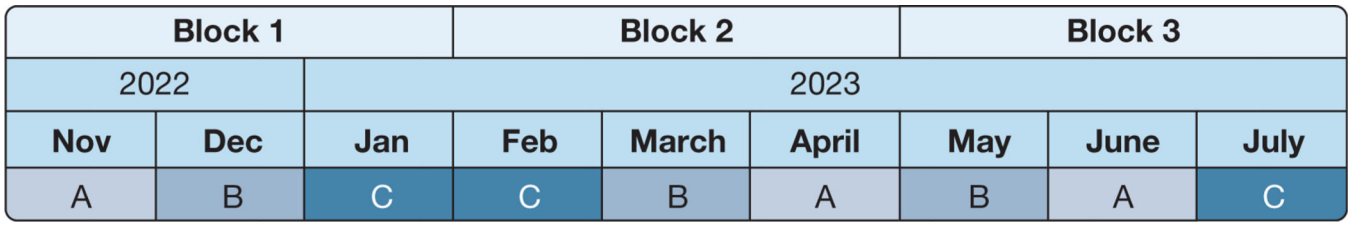

Figure 1 –.

Group assignment during the MODE trial. For each of the 1-month study periods, the study unit is randomly assigned to a study mode for continuous mandatory ventilation. The letters ‘A,’ ‘B,’ and ‘C’ each correspond to one of the three study modes.

TABLE 1]

Standard Protocol Items: Recommendations for Interventional Trials Checklist

	Study Period			
Activity/Assessment	**Allocation and Enrollment**	**On-Study**		**Final Outcome Assessment**
Timepoint	First receipt of invasive mechanical ventilation in the study unit	Receiving invasive mechanical ventilation in the study unit	Hospitalized but not receiving invasive mechanical ventilation in the study unit	Discharge or 28 d after enrollment
Eligibility screening	X			
Enrollment	X			
Allocation	X			
Interventions				
Volume control	X	X		
Pressure control	X	X		
Adaptive pressure control	X	X		
Screening for indications for mode modification	X	X		
Assessments				
Baseline variables	X			
Adverse events		X	X	X
On-study variables	X	X	X	
Clinical outcomes		X	X	X

TABLE 2]

Characteristics of the Modes of Mechanical Ventilation

Group Assignment	Volume Control	Pressure Control	Adaptive Pressure Control
Ventilator mode designation	Volume control	Pressure control	Pressure-regulated volume control
Control variable[a]	Volume	Pressure	Pressure
Breath sequence	Continuous mandatory ventilation	Continuous mandatory ventilation	Continuous mandatory ventilation
Targeting scheme	Set-point (clinician sets target volume)	Set-point (clinician sets target inspiratory pressure)	Adaptive (clinician sets target volume and ventilator titrates pressure to achieve target volume)

[a]Taxonomy of ventilator mode characteristics as per Chatburn et al.[6]

TABLE 3]

Feasibility and Exploratory Outcomes

Feasibility Outcomes	
Prespecified feasibility outcomes focus on adherence to group assignment and separation between groups in mode of mechanical ventilation.	
1	Exposure to assigned study mode in the first 3 days: proportion of time in the assigned mode while receiving invasive mechanical ventilation in the study ICU between enrollment and 72 hours after enrollment (including time spent in spontaneous modes such as during a spontaneous breathing trial)
2	Adherence to study mode in the first 3 days: proportion of time in the assigned mode while receiving invasive mechanical ventilation in the study ICU with a mandatory mode between enrollment and 72 hours after enrollment (excluding time spent in spontaneous modes such as during a spontaneous breathing trial)
3	Time from enrollment to initiation of assigned mode of mechanical ventilation
4	Receipt of a “mode modification sheet” completed by treating clinicians
Exploratory Efficacy and Safety Outcomes	
Exploratory outcomes for efficacy and safety were prespecified to provide intermediate measures that may be affected by the intervention (ventilator mode) and may affect the primary outcome (ventilator-free days to study day 28) but in this study are not meaningful in isolation. Additional outcomes are listed below, with definitions available in e-Appendix 1 (section 14).	
1	Median exhaled tidal volume (mL/kg predicted body weight) on each study day
2	Exhaled tidal volumes above target range: proportion of recorded breaths with exhaled tidal volume values above the target range (> 8 mL/kg predicted body weight) on each study day
3	Hypoxemia during mechanical ventilation: episodes of hypoxemia during mechanical ventilation: S_{PO_2} < 85% for more than 5 minutes
4	Severe acidemia during mechanical ventilation: episodes of severe acidemia during mechanical ventilation: pH < 7.1 on blood gas
5	Number of blood gas laboratory tests per day while receiving mechanical ventilation
6	Pneumomediastinum or pneumothorax during course of mechanical ventilation
7	SOFA score daily on the first 7 study days
8	Delirium and coma-free days to day 28
Exploratory Clinical Outcomes	
Exploratory Clinical Outcomes	
1	ICU-free days to study day 28
2	Hospital-free days to study day 28
3	In-hospital mortality to study day 28

SOFA, Sequential Organ Failure Assessment; S_{PO_2}, oxygen saturation.