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High versus low positive end-expiratory pressure setting in patients receiving veno-venous extracorporeal membrane oxygenation support for severe acute respiratory distress syndrome: study protocol for the multicenter, randomized ExPress SAVER trial

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Abstract

- **Introduction**: While limiting the tidal volume to 6 mL/kg during veno-venous extracorporeal membrane oxygenation (V-V ECMO) to ameliorate lung injury in patients with acute respiratory distress syndrome (ARDS) is widely accepted, the best setting for positive end-expiratory pressure (PEEP) is still controversial. This study is being conducted to investigate whether a higher PEEP setting (15 cmH_2O) during V-V ECMO can decrease the duration of ECMO support needed in patients with severe ARDS, as compared with a lower PEEP setting.
- **Methods and analysis**: The study is an investigator-initiated, multicenter, open-label, two-arm, randomized controlled trial conducted with the participation of 21 intensive care units (ICUs) at academic as well as non-academic hospitals in Japan. The subjects of the study are patients with severe ARDS who require V-V ECMO support. Eligible patients will be randomized equally to the High PEEP group or Low PEEP group. Recruitment to the study will continue until a total of 210 ARDS patients requiring V-V ECMO support have been randomized. In the High PEEP group, PEEP will be set at 15 cmH_2O from the start of V-V ECMO until the trials for liberation from V-V ECMO (or until day 28 after the allocation), while in the Low PEEP group, the PEEP will be set at 5 cmH_2O. Other treatments will be the same in the two groups. The primary endpoint of the study is the number of ECMO-free days until day 28, defined as the length of time (in days) from successful libration from V-V ECMO to day 28. The secondary endpoints are mortality on day 28, in-hospital mortality on day 60, ventilator-free days during the first 60 days, and length of ICU stay.
- **Ethics and dissemination**: Ethical approval was obtained on September 27, 2022 (IRB at Hiroshima University hospital, C2022-0006). The results of this study will be presented at national and international medical congresses, and also published in a scientific journal.
- **Trial registration**: The Japan Registry of Clinical Trials jRCT1062220062. Registered on September 28, 2022
- **Protocol version:** January 7, 2023, version 3.0
- **Name and contact information for the trial sponsor:** Not applicable

- **Role of sponsor:** Not applicable

Keywords

acute respiratory distress syndrome, positive end-expiratory pressure, veno-venous extracorporeal membrane oxygenation, ventilator management, ExPress SAVER trial

Strengths and limitations of this study

- The ExPress SAVER trial is the first large multicenter RCT to investigate whether a high PEEP setting or low PEEP setting is more beneficial for ameliorating the lung injury in patients with severe ARDS requiring V-V ECMO.
- The result of this study will can help clarify the most beneficial mechanical ventilation strategies for severe ARDS patients receiving V-V ECMO support.
- Some limitations to the study design include study design as an open-label study and the endpoints assessed by ICU physicians. However, the criteria for liberation from ECMO are already set prior to the start of the study, and other outcomes, including the mortality on day 28 and in-hospital mortality on day 60, will be also evaluated as secondary endpoints.

INTRODUCTION

Background and rationale

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by widespread inflammatory lung injury, and is encountered in an estimated 23% of mechanically ventilated patients [1]. Of the three severity scales of ARDS categorized in the Berlin criteria, the reported mortality of severe ARDS, defined by a PaO_2/FIO_2 ratio (P/F ratio) of ≤100 mmHg, is as high as 45%, and these patients often need respiratory support with veno-venous extracorporeal membrane oxygenation (V-V ECMO) [2].

As compared with ventilation strategies in patients not requiring V-V ECMO, optimal strategies for patients requiring V-V ECMO support have received relatively little attention. Based on a previous prospective study conducted with the participation of 23 ECMO centers from 10 countries, a tidal volume of ≤6 mL/kg and plateau pressure not exceeding 30 cmH_2O have been widely accepted as lung protective strategies; however, there is still a large variability in the setting of positive end-expiratory pressure (PEEP); for example, the reported PEEP setting on day 1 of ECMO ranges from 5 to 20 cmH_2O [3]. Thus, the optimal settings for mechanical ventilation during ECMO in patients with ARDS have not been established yet.

A high PEEP setting can be beneficial for preventing lung injury by reducing atelectrauma. The ExPress trial conducted in mechanically ventilated ARDS patients not requiring ECMO support showed that a higher PEEP (approximately 15 cmH_2O on day 1) tended to improve the lung function and reduced the needed duration of mechanical ventilation [4]. The results of a previous systematic review and meta-analysis suggested that the beneficial effect of a higher PEEP setting may be more pronounced in the subgroup of patients with relatively more severe ARDS [5], which may imply that the effect may be most noteworthy in patients with severe ARDS who require ECMO support. In fact, a single-center RCT conducted in ARDS patients requiring V-V ECMO showed that the proportion of patients who could be successfully weaned from V-V ECMO was higher in the patient group in which a transpulmonary pressure-guided ventilation strategy, including a higher PEEP setting (approximately 15 cmH_2O), had been used, as compared with that in the conventional lung rest strategy group.

On the other hand, however, a high PEEP setting can also have a harmful influence on the hemodynamics by reducing the venous return [6], as well as on the lung condition by inducing lung injury due to overdistention [7] and increasing the mechanical power [16]. Considering that the PEEP setting during ECMO can be adjusted without limiting oxygenation, because oxygenation is mainly accomplished by ECMO rather than by mechanical ventilation, and patients with severe ARDS likely have concomitant right heart failure, a low PEEP setting, such as 5 cmH_2O, which is considered to be the minimum PEEP setting for patients with ARDS [8], may be more beneficial. While a recent guideline published by the Extracorporeal Life Support Organization (ELSO) recommends a PEEP setting of ≥10 cmH_2O during ECMO [9], the Consensus Conference 2014 recommends that "mechanical ventilation be adjusted to minimize the plateau pressure, while administering a minimum positive expiratory pressure" [10]. It remains unclear whether a higher or lower PEEP setting during V-V ECMO might be more beneficial for ameliorating the lung injury in severe ARDS patients [11].

Therefore, we designed this open-label, multicenter RCT to examine the beneficial effect of a higher PEEP setting (15 cmH_2O) as compared with a lower PEEP setting (5 cmH_2O) in severe ARDS patients requiring V-V ECMO support.

Aim and objectives

This study is being conducted to investigate whether a higher PEEP setting (15 cmH_2O) during V-V ECMO can decrease the duration of ECMO support needed in patients with severe ARDS, as compared with a lower PEEP setting (5 cmH_2O).

METHODS AND ANALYSIS

Trial design

The Expiratory Pressure for Severe ARDS requiring V-V ECMO Respiratory Support trial (ExPress SAVER trial) is a randomized controlled, parallel-group, open-label, multicenter, superiority trial that is proposed to be conducted in patients with severe ARDS requiring V-V ECMO. Eligible patients will be randomized equally to the High PEEP (15 cmH_2O) group or Low PEEP (5 cmH_2O) group.

Study setting

The study is an investigator-initiated, multicenter, open-label, two-arm, randomized trial conducted with the participation of 21 intensive care units (ICU) at academic as well as non-academic hospitals in Japan. The flow chart for patient recruitment into the trial is shown in Fig. 1. The study was conducted with the approval of the Institutional Review Boards of Hiroshima University Hospital (C2022-0006) and each of the other participating hospitals. Among the 21 participating hospitals, 12 were academic hospitals and 9 were non-academic hospitals. This 3-year study is planned to run from November 2022 until March 2026. The trial is registered in the jRCT (Japan Registry of Clinical Trials; https://jrct.niph.go.jp, trial registration number: jRCT1062220062).

Eligibility criteria

Patients will be included if they meet the following 3 criteria: (1) age between 18 and 80 years (male or female); (2) diagnosed as having severe ARDS at the timing of cannulation for ECMO; (3) V-V ECMO selected for respiratory support. The diagnosis of severe ARDS was made on the basis of the Berlin definition criteria (P/F ratio ≤ 100 mmHg) [12]. Respiratory support using ECMO is considered if the patients are assessed as having a high risk of mortality (≥50%) and is considered as being indicated when the risk is ≥80% in accordance with the guideline [13]. A P/F ratio of <150 mmHg on a high FIO_2 of >0.9 and/or a Murray score of 2–3 indicates a mortality risk of ≥50%, while a P/F ratio of <80 mmHg on a high FIO_2 of >0.9 and/or a Murray score of 3–4 indicates an 80% mortality risk.

Patients were excluded if they were cases of conversion from initial veno-arterial (V-A) ECMO, had been on a mechanical ventilation for longer than 7 days at the time of initiation of the ECMO support, had hemodynamic instability with a reduced left ventricular ejection fraction (<40%), had pneumothorax or air leak syndrome, had ARDS due to thoracic trauma, had ARDS due to extra-pulmonary triggers, are known to be pregnant, or are judged by the ICU attending doctors as being unsuitable to participate in this study based on their medical condition.

Since eligible patients are expected to be unconscious, the trial information will be given to a proxy in person by physicians before enrollment in the study, and both written and verbal informed consent will be obtained. When the patient becomes alert, the attending physicians will obtain informed consent. If enrollment is rejected, the data of that patient will not be used for the analyses. Physicians will attempt to obtain informed consent from the patient even if consent has already been provided by the proxy. Approval from the local ethical committee will be needed for ancillary studies of the patient data, unless this is waived based on prior approvals or the design of the studies.

Interventions

Explanation for the choice of comparators

There is poor evidence as to the optimal PEEP setting in ARDS patients requiring V-V ECMO support. In this study, which is being conducted to investigate beneficial effects of a high PEEP setting, we set the group with a low PEEP setting during ECMO as the control group. We will use 5 cmH_2O as a low PEEP setting, which is considered a the minimum PEEP for patients with ARDS, based on previous literature [8].

Intervention description

Within 24 hours after the start of V-V ECMO support, registration will be performed by electronic data capture (EDC) on a personal computer. Then, patients will be randomized to the High PEEP group and Low PEEP group. In the High PEEP group, the PEEP will be set at 15 cmH_2O from the start of V-V ECMO support until the trials for liberation from V-V ECMO (or until day 28 after the allocation), while in the Low PEEP group, the

PEEP will be set at 5 cmH_2O. Other treatments will be the same in the two groups.

In both groups, the invasiveness of mechanical ventilation, except for the PEEP, will be reduced for lung protection. The preset goals for oxygenation are a PaO2 of 55-65 mmHg. Accordingly, the tidal volume will be decreased to ensure that the plateau pressure does not exceed 30 cmH_2O. Also, the settings of FIO_2, respiratory rate and driving pressure were adjusted to less than 0.5, 10 times/min and 8 cmH_2O, respectively. Hypercapnia is allowed for lung protection ($PaCO_2 \geq 70$ mmHg).

After the lung function improves, the extracorporeal blood flow rate will be reduced stepwise to 2.0 liters per min. Thereafter, the gas flow will be tapered and finally switched off for 4-24 h. In the weaning trial, the settings of mechanical ventilation will be adjusted to match the following criteria: $FIO_2 \leq 0.6$ and plateau pressure ≤ 30 cmH_2O. If the arterial blood gases, including PaO2 >70 mmHg, and respiratory parameters remain stable, the ECMO system will be removed.

When the participant does not satisfy the eligibility criteria after registration before liberation from V-V ECMO, the intervention described above will be discontinued and the PEEP setting will be decided according to the clinical preference. Then, they will be excluded from the analyses and labelled as dropouts.

Relevant concomitant care permitted or prohibited during the trial

All treatments will be allowed, and there will be no prohibited treatments in either group.

Provisions for post-trial care

All patients who will suffer harm from participation in the trial will be covered by the Japanese public healthcare system.

Outcomes

The primary endpoint is ECMO-free days (EFDs) on day 28, defined as the number of days from successful weaning from V-V ECMO to day 28. The concept is similar to ventilator-free days (VFDs) [14]. EFDs are

typically defined as follows. EFD = 0, if the subject dies within 28 days after the start of ECMO support. EFDs = 28 - x in patients who are successfully liberated from ECMO x days after initiation of ECMO. EFD = 0, if the subject is on ECMO for >28 days (Figure 2). The 28-day time frame was initially chosen because most subjects with ARDS either die or are extubated by day 28 [15].

The secondary endpoints are the mortality rate on day 28, the in-hospital mortality on day 60, number of VFDs during the first 60 days, and length of ICU stay.

In the subgroup analysis, we propose to analyze the effects of high PEEP versus low PEEP setting separately according to indices of lung recruitability at the start of ECMO support. The indices of lung recruitability include the recruitment-to-inflation ratio (R/I) and the static lung compliance (Cst).

Participant timeline

The main timeline of this study is shown in Fig. 3.

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study.

Sample size

For the primary outcome measure, we assumed a mean number of EFDs of 10.5 days, with a standard deviation of 10 in the placebo group, based on past sample data of patients admitted to our ICU (53 cases from 2014 to 2021). Referring to the results of the ExPress trial [4], we set 4.0 days as a difference in the number of EFDs between the High PEEP group and Low PEEP group (10.5 days vs 6.5 days). It was estimated that a sample size of 100 per group would be needed to obtain at least 80% statistical power at a two-sided significance level of 5% by a Student's two-sample t-test. To compensate for the loss of participants to follow-up (5%), we decided to enroll 105 patients per group (total study sample, 210 subjects).

Recruitment

This study will be conducted with the participation of 19 ICUs in Japan. The ICU physicians at each hospital will provide the patients with adequate information about the study.

Assignment of interventions: allocation

Sequence generation

The randomization will be performed using stratified block randomization with a block size of two or four on the Electronic Data Capture (EDC) site. The randomization list was automatically generated with a random sequence in each hospital on the EDC, based on stratification according to the age of the subjects (≥60/<60 years). Therefore, stratification will be performed for two factors (facility and age). Once physicians input the inclusion of a new participant on the EDC site, his/her allocation is immediately noted on the EDC site.

Concealment mechanism

The results of the allocation will be shown on the EDC site of each hospital and researchers at one hospital will be blinded to the assignments and outcomes of the patients at the other hospitals.

Implementation

The allocation will be performed on the EDC. Clinicians and investigators will enroll patients and assign them to the High PEEP or Low PEEP group according to the allocation.

Assignment of interventions: Blinding

Due to the type of the study design, it is impossible to blind keep the investigators, patients, and care providers blinded to the group allocation. However, the data analysts will be kept blinded to the group allocation.

Data collection and management

Assessment and collection of outcomes will be performed by the ICU physicians at the participating hospitals. As for the mortality at 28 days, if a patient has been already discharged by 28 days, the outcome will be collected by a phone call to the patient's general practitioner or to any medical staff involved in the care of the patient after discharge from the ICU.

Patients included are expected to stay in the ICU until they are liberated from ECMO, which means the primary outcomes (EFDs at 28 days) of almost all included patients could be expected to be collected by ICU physicians without any extra effort. However, if a patient is transferred to another hospital before he/she is liberated from ECMO, the outcomes will be collected by a phone call to the patient's general practitioner or to any medical staff involved in the care of the patient.

Patient data will be stored as raw medical records at each participating hospital and remain anonymized on the EDC for at least 5 years. Changes in the EDC will be preserved on a log showing information about who changed the information and when.

All patient data will be anonymized in the EDC system. Only the chief investigator at each participating hospital, who has in his/her possession the original ID and password for accessing the EDC can input data on patients at his/her facility. The Statistician and Central Monitor will have exclusive access to all participants' data on the EDC.

Statistical methods

Statistical methods for primary and secondary outcomes

Statistical analyses will be performed using an intention-to-treat analysis with a full analysis set (FAS). FAS is defined as all subjects for whom there were no violations of the main eligibility criteria (selection and exclusion criteria) or conflicts with the discontinuation and dropout criteria. Student's t-test will be used to evaluate the significance of differences in the log-transformed values of the number of EFDs at 28 days. For analysis of the secondary endpoints, Fisher's exact test will be used to analyze differences in the categorical variables

(mortality on day 28 and in-hospital mortality on day 60), and Student's t-test will be used to analyze differences in the continuous variables (VFDs during the first 60 days and length of ICU stay).

Interim analyses

Safety monitoring will be conducted in a timely manner by the Safety Monitoring Committee, comprising Kei Suzuki, Yusuke Okazaki, and Yuya Yoshino of Hiroshima City North Medical Center Asa Citizens Hospital. If serious adverse events associated with the trial are identified, the chief investigator at the corresponding hospital will immediately report them to the director of that hospital and the Primary Investigator. The primary investigator will then take appropriate actions under the guidance of the Ethics Committee for Clinical Research of Hiroshima University and the Safety Monitoring Committee. The Safety Monitoring Committee will discontinue the study if a marked difference in safety is noted based on the severe adverse events. We do not propose to conduct any interim analysis of the efficacy.

Methods for additional analyses (e.g., subgroup analyses)

We propose to conduct a subgroup analysis to determine the effects of a high PEEP setting as compared with low PEEP setting separately according to the indices of lung recruitability at the start of ECMO support. The indices of lung recruitability include the R/I and Cst.

Methods of analysis to handle protocol non-adherence and any statistical methods to handle missing data

In this study, we will perform FAS analysis as the main analysis. Any patients with missing data on the primary or secondary outcomes will be excluded. The safety analysis will be performed including all patients, even if there are missing data.

Plans to give access to the full protocol, participant level-data and statistical code

Both the protocol and data will be available upon reasonable request and approval from the relevant authorities after the trial is completed.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The Principal Investigator and Study Coordinator is Shinichiro Ohshimo, Hiroshima University Hospital. The Data Manager is Mitsuaki Nishikimi, Hiroshima University Hospital. The Statistical Analysis Manager is Kunihiko Takahashi, Tokyo Medical and Dental University. The Certification of the Ethics Committee for Clinical Research is established at Hiroshima University Hospital as the Coordinating Center and Trial Steering Committee.

Composition of the data monitoring committee, its role and reporting structure

Central monitoring will be performed by the Data Monitoring Committee, which consist of Kazuya Kikutani, Assistant Professor, Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University. On-site monitoring will be performed at each hospital by monitors appointed by the Data Monitoring Committee if the committee judges that such monitoring is needed based on the results of central monitoring.

Adverse event reporting and harms

If serious adverse events associated with the trial are identified, the chief investigator at the corresponding hospital will immediately report them to the director of that hospital and to the Primary Investigator. The primary investigator will then take the appropriate actions under the guidance of the Ethics Committee for Clinical Research of Hiroshima University and the safety monitoring committee. All serious adverse events associated with the trial will be shared among all researchers by the Primary Investigator.

Frequency and plans for auditing trial conduct

An independent party will audit and report the results.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Any protocol modifications will be reviewed by the Ethical Committee for Clinical Research of Hiroshima University and then registered at jRCT (https://jrct.niph.go.jp). All relevant information will be shared among the researchers.

Dissemination plans

The results of this study will be presented at national and international medical congresses, and also published in a scientific journal.

DISCUSSION

The ExPress SAVER trial is the first large multicenter RCT being conducted to investigate whether a high PEEP setting or low PEEP setting is more beneficial for ameliorating the lung injury in patients with severe ARDS requiring V-V ECMO. As compared with ventilation strategies in the absence of V-V ECMO, those in patients needing ECMO have received relatively little attention, and the optimal PEEP setting in patients receiving ECMO has not been established yet. We believe that this trial can help clarify the most beneficial mechanical ventilation strategies for severe ARDS patients receiving V-V ECMO support.

In this study, we also plan to conduct a subgroup analysis according to the indices of lung recruitability at the start of ECMO support. Recently, several studies have reported on the heterogeneity of ARDS, and the most appropriate management for ARDS might differ according to the sub-clinical phenotype [16-18]. We consider it not surprising that the beneficial effects of high PEEP settings differ according to differences in the lung recruitability at the start of ECMO support. In this sub-group analysis, we will use R/I, which has been reported as a useful index of lung recruitability in several previous studies.

There are several limitations of the ExPress SAVER trial. Firstly, this is an open-label study and the endpoints will be assessed by ICU physicians. However, the criteria for liberation from ECMO are already set prior to the start of the study, and outcomes which cannot be influenced by the physicians' judgement, including the mortality on day 28 and in-hospital mortality on day 60, will be also evaluated as secondary endpoints. Secondly, we decided not to use novel monitoring devices for the PEEP setting, such as electrical impedance tomography (EIT) and esophageal balloon catheter for measuring the esophageal pressure, because these devices are used only at a limited number of ECMO centers in Japan. Both have the potential to help estimate the most appropriate PEEP setting for individual ARDS patients requiring ECMO, although the benefits of personalizing PEEP settings have not yet been established.

Trial status

This study protocol was approved by IRB at Hiroshima University hospital on September 27, 2022 (C2022-0006). This study protocol is version 3 made on January 7, 2023. The recruitment period is between November

15, 2022, and March 31, 2026. The first patient was randomized on November 18, 2022.

Declarations

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We acknowledge and honor all of our team members who consistently put themselves in harm's way during the COVID-19 pandemic. We dedicate this manuscript to them, as their vital contribution to knowledge about COVID-19 and sacrifices on the behalf of patients made it possible. We also want to thank all study participants for making this work possible.

Authors' contributions

Mitsuaki N and SO: conception and design of the study, interpretation of data, and drafting of the manuscript.

JH, KF, and YH: coordination and conduction of the study and interpretation of data.

TA and KT: drafting of the manuscript (statistical part) and statistical analysis.

JI, YO, TA, TI, TY, GS, KI, KK, Daisuke Konno, NH, TN, YM, Daisuke Kasugai, HK, TI, SK, HH, TI: conduction of the study and critical revision of the manuscript for important intellectual content.

TY, TO, KM, KS, Mitsunobu N, SI: supervision of the study and critical revision of the manuscript for important intellectual content.

NS: conception and design of the study, and supervision of the study.

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Availability of data and materials

The datasets in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Central ethical approval was confirmed by the Ethical Committee for Clinical Research of Hiroshima University (C2022-0006), and local ethical approval is not needed according to the Clinical Trials Act in Japan. Informed consent will be obtained from proxies and all study participants when they are alert.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig 1. Flow chart for patient recruitment into the ExPress SAVER trial

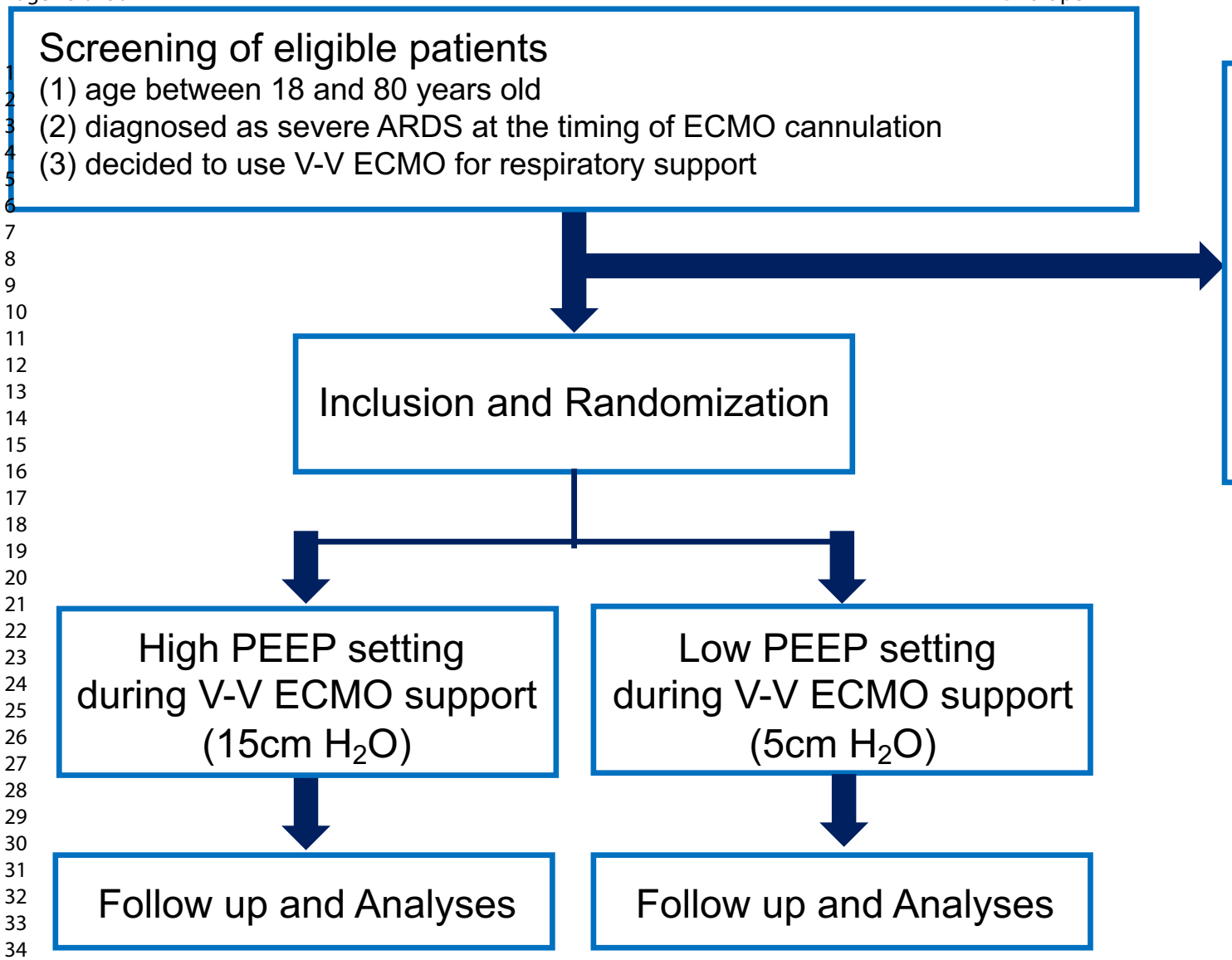
ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; EF: ejection fraction; ICU: intensive care unit; PEEP: positive end-expiratory pressure.

Fig 2. Calculation of ECMO-free days at 28 days

ECMO: extracorporeal membrane oxygenation; EFDs: ECMO-free days.

Fig 3. Time schedule for the trial

PEEP: positive end-expiratory pressure; ARDS: acute respiratory distress syndrome; SOFA score: Sequential Organ Failure Assessment score; ECMO: extracorporeal membrane oxygenation.



Day	1 (Initiation of ECMO support)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	EFDs
Patients No 1					Liberation																								23
Patients No 2						Liberation					Re-canulation												Liberation						5
Patients No 3					Death																								0
Patients No 4					Liberation			Death																					0

On ECMO support

Liberated from ECMO

	Trial period									
	Screening	Randomization	Post-Randomization						Follow up	
Time point	Decision of ECMO support	Day 1 (within 24 h after Initiated on ECMO)	Day 2	Day 3	Day 5	Day 7	Day 10	Liberated on ECMO	Day 28	Day 60
Enrolment										
Inclusion/ Exclusion criteria	X									
informed consent		X								
Allocation		X								
Interventions										
High PEEP		◆—	—	—	—	—	—	—◆		
Low PEEP		◆—	—	—	—	—	—	—◆		
Assessments										
Baseline: demographic data, medical history, trigger for ARDS, murray score, SOFA score		X								
Vital signs		X	X	X	X	X	X	X		
Ventilation data		X	X	X	X	X	X	X		
ECMO data		X	X	X	X	X	X	X		
Clinical laboratory data		X	X	X	X	X	X	X		
Chest CT		X								
Other treatments	X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X	X
Live status: death or alive									X	X

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 17

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	4
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

BMJ Open

High versus low positive end-expiratory pressure setting in patients receiving veno-venous extracorporeal membrane oxygenation support for severe acute respiratory distress syndrome: study protocol for the multicenter, randomized ExPress SAVER trial

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High versus low positive end-expiratory pressure setting in patients receiving veno-venous extracorporeal membrane oxygenation support for severe acute respiratory distress syndrome: study protocol for the multicenter, randomized ExPress SAVER trial

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Abstract

- **Introduction**: While limiting the tidal volume to 6 mL/kg during veno-venous extracorporeal membrane oxygenation (V-V ECMO) to ameliorate lung injury in patients with acute respiratory distress syndrome (ARDS) is widely accepted, the best setting for positive end-expiratory pressure (PEEP) is still controversial. This study is being conducted to investigate whether a higher PEEP setting (15 cmH_2O) during V-V ECMO can decrease the duration of ECMO support needed in patients with severe ARDS, as compared with a lower PEEP setting.
- **Methods and analysis**: The study is an investigator-initiated, multicenter, open-label, two-arm, randomized controlled trial conducted with the participation of 20 intensive care units (ICUs) at academic as well as non-academic hospitals in Japan. The subjects of the study are patients with severe ARDS who require V-V ECMO support. Eligible patients will be randomized equally to the High PEEP group or Low PEEP group. Recruitment to the study will continue until a total of 210 ARDS patients requiring V-V ECMO support have been randomized. In the High PEEP group, PEEP will be set at 15 cmH_2O from the start of V-V ECMO until the trials for liberation from V-V ECMO (or until day 28 after the allocation), while in the Low PEEP group, the PEEP will be set at 5 cmH_2O. Other treatments will be the same in the two groups. The primary endpoint of the study is the number of ECMO-free days until day 28, defined as the length of time (in days) from successful libration from V-V ECMO to day 28. The secondary endpoints are mortality on day 28, in-hospital mortality on day 60, ventilator-free days during the first 60 days, and length of ICU stay.
- **Ethics and dissemination**: Ethics approval for the trial at all the participating hospitals was obtained on September 27, 2022, by central ethics approval (IRB at Hiroshima University Hospital, C2022-0006). The results of this study will be presented at domestic and international medical congresses, and also published in scientific journals.
- **Trial registration**: The Japan Registry of Clinical Trials jRCT1062220062. Registered on September 28, 2022
- **Protocol version:** March 28, 2023, version 4.0

- **Name and contact information for the trial sponsor:** Not applicable
- **Role of sponsor:** Not applicable

Keywords

acute respiratory distress syndrome, positive end-expiratory pressure, veno-venous extracorporeal membrane oxygenation, ventilator management, ExPress SAVER trial

Strengths and limitations of this study

- This is the first randomized controlled trial (RCT) performed to investigate whether a high PEEP setting can shorten the ECMO-free days until day 28 as compared with a low PEEP setting in patients with severe ARDS requiring V-V ECMO.
- This study could be the largest randomized controlled trial conducted to date in patients with severe ARDS requiring V-V ECMO.
- This study includes a subgroup analysis for evaluating the outcomes by the index of lung recruitability.
- Some limitations of the study include its open-label study design and assessment of the endpoints by the attending ICU physicians.

INTRODUCTION

Background and rationale

Acute respiratory distress syndrome (ARDS) is a life-threatening condition characterized by widespread inflammatory lung injury, and is encountered in an estimated 23% of mechanically ventilated patients [1]. Of the three severity scales of ARDS categorized in the Berlin criteria, the reported mortality of severe ARDS, defined by a PaO_2/FIO_2 ratio (P/F ratio) of ≤100 mmHg, is as high as 45%, and these patients often need respiratory support with veno-venous extracorporeal membrane oxygenation (V-V ECMO) [2].

As compared with ventilation strategies in patients not requiring V-V ECMO, optimal strategies for patients requiring V-V ECMO support have received relatively little attention. Based on a previous prospective study conducted with the participation of 23 ECMO centers from 10 countries, a tidal volume of ≤6 mL/kg and plateau pressure not exceeding 30 cmH_2O have been widely accepted as lung protective strategies; however, there is still a large variability in the setting of positive end-expiratory pressure (PEEP); for example, the reported PEEP setting on day 1 of ECMO ranges from 5 to 20 cmH_2O [3]. Thus, the optimal settings for mechanical ventilation during ECMO in patients with ARDS have not been established yet.

A high PEEP setting can be beneficial for preventing lung injury by reducing atelectrauma. The ExPress trial conducted in mechanically ventilated ARDS patients not requiring ECMO support showed that a higher PEEP (approximately 15 cmH_2O on day 1) tended to improve the lung function and reduced the needed duration of mechanical ventilation [4]. The results of a previous systematic review and meta-analysis suggested that the beneficial effect of a higher PEEP setting may be more pronounced in the subgroup of patients with relatively more severe ARDS [5], which may imply that the effect may be most noteworthy in patients with severe ARDS who require ECMO support. In fact, a single-center RCT conducted in ARDS patients requiring V-V ECMO showed that the proportion of patients who could be successfully weaned from V-V ECMO was higher in the patient group in which a transpulmonary pressure-guided ventilation strategy, including a higher PEEP setting (approximately 15 cmH_2O), had been used, as compared with that in the conventional lung rest strategy group.

On the other hand, however, a high PEEP setting can also have a harmful influence on the hemodynamics by reducing the venous return [6], as well as on the lung condition by inducing lung injury due to overdistention [7] and increasing the mechanical power [8]. Considering that the PEEP setting during ECMO can be adjusted without limiting oxygenation, because oxygenation is mainly accomplished by ECMO rather than by mechanical ventilation, and patients with severe ARDS likely have concomitant right heart failure, a low PEEP setting, such as 5 cmH_2O, which is considered to be the minimum PEEP setting for patients with ARDS [9], may be more beneficial. While a recent guideline published by the Extracorporeal Life Support Organization (ELSO) recommends a PEEP setting of ≥10 cmH_2O during ECMO [10], the Consensus Conference 2014 recommends that "mechanical ventilation be adjusted to minimize the plateau pressure, while administering a minimum positive expiratory pressure" [11]. It remains unclear whether a higher or lower PEEP setting during V-V ECMO might be more beneficial for ameliorating the lung injury in severe ARDS patients [12].

Therefore, we designed this open-label, multicenter RCT to examine the beneficial effect of a higher PEEP setting (15 cmH_2O) as compared with a lower PEEP setting (5 cmH_2O) in severe ARDS patients requiring V-V ECMO support.

Aim and objectives

This study is being conducted to investigate whether a higher PEEP setting (15 cmH_2O) during V-V ECMO can decrease the duration of ECMO support needed in patients with severe ARDS, as compared with a lower PEEP setting (5 cmH_2O).

METHODS AND ANALYSIS

Trial design

The Expiratory Pressure for Severe ARDS requiring V-V ECMO Respiratory Support trial (ExPress SAVER trial) is a randomized controlled, parallel-group, open-label, multicenter, superiority trial that is proposed to be conducted in patients with severe ARDS requiring V-V ECMO. Eligible patients will be randomized equally to the High PEEP (15 cmH_2O) group or Low PEEP (5 cmH_2O) group.

Study setting

This 3-year study is expected to run from November 1, 2022, to March 31, 2026. The study is an investigator-initiated, multicenter, open-label, two-arm, randomized trial conducted with the participation of 20 intensive care units (ICU) at academic as well as non-academic hospitals in Japan. The flow chart for patient recruitment into the trial is shown in Fig. 1. Among the 20 participating hospitals, 11 were academic hospitals and 9 were non-academic hospitals. The trial is registered in the jRCT (Japan Registry of Clinical Trials; https://jrct.niph.go.jp, trial registration number: jRCT1062220062).

Eligibility criteria

Adult Patients (18-80 years old) with ARDS requiring V-V ECMO will be included. The diagnosis of severe ARDS was made on the basis of the Berlin definition criteria (P/F ratio ≤ 100 mmHg) [13]. Respiratory support using ECMO is considered if the patients are assessed as having a high risk of mortality (≥50%) and is considered as being indicated when the risk is ≥80% in accordance with the guideline [14]. A P/F ratio of <150 mmHg on a high FIO_2 of >0.9 and/or a Murray score of 2–3 indicates a mortality risk of ≥50%, while a P/F ratio of <80 mmHg on a high FIO_2 of >0.9 and/or a Murray score of 3–4 indicates an 80% mortality risk.

Patients were excluded if they were cases of conversion from initial veno-arterial (V-A) ECMO, had been on a mechanical ventilation for longer than 7 days at the time of initiation of the ECMO support, had hemodynamic instability with a reduced left ventricular ejection fraction (<40%), had pneumothorax or air leak syndrome, had ARDS due to thoracic trauma, had ARDS due to extra-pulmonary triggers, are known to be

pregnant, or are judged by the ICU attending doctors as being unsuitable to participate in this study based on their medical condition.

Since eligible patients are expected to be unconscious, the trial information will be given to a proxy in person by physicians before enrollment in the study, and both written and verbal informed consent will be obtained. When the patient becomes alert, the attending physicians will obtain informed consent. If enrollment is rejected, the data of that patient will not be used for the analyses. Physicians will attempt to obtain informed consent from the patient even if consent has already been provided by the proxy. An example of the participant consent form is shown in Supplemental Material. Approval from the local ethical committee will be needed for ancillary studies of the patient data, unless this is waived based on prior approvals or the design of the studies.

Interventions

Explanation for the choice of comparators

There is poor evidence as to the optimal PEEP setting in ARDS patients requiring V-V ECMO support. In this study, which is being conducted to investigate beneficial effects of a high PEEP setting, we set the group with a low PEEP setting during ECMO as the control group. We will use 5 cmH_2O as a low PEEP setting, which is considered a the minimum PEEP for patients with ARDS, based on previous literature [9].

Intervention description

Within 24 hours after the start of V-V ECMO support, registration will be performed by electronic data capture (EDC) on a personal computer. Then, patients will be randomized to the High PEEP group and Low PEEP group. In the High PEEP group, the PEEP will be set at 15 cmH_2O from the start of V-V ECMO support until the trials for liberation from V-V ECMO (or until day 28 after the allocation), while in the Low PEEP group, the PEEP will be set at 5 cmH_2O. Other treatments will be the same in the two groups.

In both groups, the invasiveness of mechanical ventilation, except for the PEEP, will be reduced for lung protection. The preset goals for oxygenation are a PaO2 of 55-65 mmHg. Accordingly, the tidal volume will be decreased to ensure that the plateau pressure does not exceed 30 cmH_2O. Also, the settings of FIO_2,

respiratory rate and driving pressure were adjusted to less than 0.5, 10 times/min and 8 cmH_2O, respectively. Hypercapnia is allowed for lung protection ($PaCO_2 \geq 70$ mmHg).

During the period of intervention, it is left to the charge of the ICU physicians to judge whether the lung injury has improved sufficiently to attempt a weaning trial from ECMO, based mainly on the findings of daily blood gas examinations (e.g. P/F ratio and PaCO2) and daily chest X-rays, and where needed, chest CT.

After the lung function improves, the sweep gas flow will be gradually tapered and finally switched off for 4-24 h. In the weaning trial, the settings for mechanical ventilation will be adjusted to achieve the following criteria: FIO2 ≤0.6 and plateau pressure ≤30 cmH2O. If the arterial blood gases and respiratory parameters remain stable (e.g., PaO2 >70 mmHg), the ECMO system will be disconnected.

When the participant does not satisfy the eligibility criteria after registration before liberation from V-V ECMO, the intervention described above will be discontinued and the PEEP setting will be decided according to the clinical preference. Then, they will be excluded from the analyses and labelled as dropouts.

Relevant concomitant care permitted or prohibited during the trial

All treatments will be allowed, and there will be no prohibited treatments in either group.

Provisions for post-trial care

All patients who will suffer harm from participation in the trial will be covered by the Japanese public healthcare system.

Outcomes

The primary endpoint is ECMO-free days (EFDs) on day 28, defined as the number of days from successful weaning from V-V ECMO to day 28. The concept is similar to ventilator-free days (VFDs) [15]. EFDs are typically defined as follows. EFD = 0, if the subject dies within 28 days after the start of ECMO support. EFDs = 28 - x in patients who are successfully liberated from ECMO x days after initiation of ECMO. EFD = 0, if the

subject is on ECMO for >28 days (Figure 2). The 28-day time frame was initially chosen because most subjects with ARDS either die or are extubated by day 28 [16]. We defined ECMO-free days as the primary endpoint, because we believe that it is a more appropriate index for evaluating improvement of lung injury as compared with mortality.

The secondary endpoints are the mortality rate on day 28, the in-hospital mortality on day 60, number of VFDs during the first 60 days, and length of ICU stay.

In the subgroup analysis, we propose to analyze the effects of high PEEP versus low PEEP setting separately according to indices of lung recruitability at the start of ECMO support. The indices of lung recruitability include the recruitment-to-inflation ratio (R/I) and the static lung compliance (Cst). Regarding the measurement for recruitability, we follow the method described in previous reports [17, 18]. In brief, all measurements were performed in the supine position after confirming a stable respiratory status in ventilated, deeply sedated patients (RASS ≤ -3). If necessary, neuromuscular blockade was also used to maintain adequate levels of sedation. To measure the R/I ratio, alveolar derecruitment was evaluated by the first expired volume immediately after lowering the PEEP level from 15 to 5 cmH2O.

Participant timeline

The main timeline of this study is shown in Fig. 3.

Patient and public involvement

There was no patient or public involvement in the design and conduct of this study.

Sample size

For the primary outcome measure, we assumed a mean number of EFDs of 10.5 days, with a standard deviation of 10 in the placebo group, based on past sample data of patients admitted to our ICU (53 cases from 2014 to 2021). Referring to the results of the ExPress trial [4], we set 4.0 days as a difference in the number of EFDs

between the High PEEP group and Low PEEP group (10.5 days vs 6.5 days). It was estimated that a sample size of 100 per group would be needed to obtain at least 80% statistical power at a two-sided significance level of 5% by a Student's two-sample t-test. To compensate for the loss of participants to follow-up (5%), we decided to enroll 105 patients per group (total study sample, 210 subjects).

Recruitment

This study will be conducted with the participation of 19 ICUs in Japan. The ICU physicians at each hospital will provide the patients with adequate information about the study.

Assignment of interventions: allocation

Sequence generation

The randomization will be performed using stratified block randomization with a block size of two or four on the Electronic Data Capture (EDC) site. The randomization list was automatically generated with a random sequence in each hospital on the EDC, based on stratification according to the age of the subjects (≥60/<60 years). Therefore, stratification will be performed for two factors (facility and age). Once physicians input the inclusion of a new participant on the EDC site, his/her allocation is immediately noted on the EDC site.

Concealment mechanism

The results of the allocation will be shown on the EDC site of each hospital and researchers at one hospital will be blinded to the assignments and outcomes of the patients at the other hospitals.

Implementation

The allocation will be performed on the EDC. Clinicians and investigators will enroll patients and assign them to the High PEEP or Low PEEP group according to the allocation.

Assignment of interventions: Blinding

Due to the type of the study design, it is impossible to blind keep the investigators, patients, and care providers blinded to the group allocation. However, the data analysts will be kept blinded to the group allocation.

Data collection and management

Assessment and collection of outcomes will be performed by the ICU physicians at the participating hospitals. As for the mortality at 28 days, if a patient has been already discharged by 28 days, the outcome will be collected by a phone call to the patient's general practitioner or to any medical staff involved in the care of the patient after discharge from the ICU.

Patients included are expected to stay in the ICU until they are liberated from ECMO, which means the primary outcomes (EFDs at 28 days) of almost all included patients could be expected to be collected by ICU physicians without any extra effort. However, if a patient is transferred to another hospital before he/she is liberated from ECMO, the outcomes will be collected by a phone call to the patient's general practitioner or to any medical staff involved in the care of the patient.

Patient data will be stored as raw medical records at each participating hospital and remain anonymized on the EDC for at least 5 years. Changes in the EDC will be preserved on a log showing information about who changed the information and when.

All patient data will be anonymized in the EDC system. Only the chief investigator at each participating hospital, who has in his/her possession the original ID and password for accessing the EDC can input data on patients at his/her facility. The Statistician and Central Monitor will have exclusive access to all participants' data on the EDC.

Statistical methods

Statistical methods for primary and secondary outcomes

Statistical analyses will be performed using an intention-to-treat analysis with a full analysis set (FAS). FAS is defined as all subjects for whom there were no violations of the main eligibility criteria (selection and exclusion criteria) or conflicts with the discontinuation and dropout criteria. Student's t-test will be used to evaluate the significance of differences in the log-transformed values of the number of EFDs at 28 days. For analysis of the secondary endpoints, Fisher's exact test will be used to analyze differences in the categorical variables (mortality on day 28 and in-hospital mortality on day 60), and Student's t-test will be used to analyze differences in the continuous variables (VFDs during the first 60 days and length of ICU stay).

Interim analyses

Safety monitoring will be conducted in a timely manner by the Safety Monitoring Committee, comprising Kei Suzuki, Yusuke Okazaki, and Yuya Yoshino of Hiroshima City North Medical Center Asa Citizens Hospital. Because this study is being conducted in the ICU, attempts will be made to identify signs of any serious adverse events as early as possible through daily chest X-rays and blood examinations. If serious adverse events associated with the trial are identified, the chief investigator at the corresponding hospital will immediately report them to the director of that hospital and the Primary Investigator. The primary investigator will then take appropriate actions under the guidance of the Ethics Committee for Clinical Research of Hiroshima University and the Safety Monitoring Committee. The Safety Monitoring Committee will discontinue the study if a marked difference in safety is noted based on the severe adverse events. We do not propose to conduct any interim analysis of the efficacy.

Methods for additional analyses (e.g., subgroup analyses)

We propose to conduct a subgroup analysis to determine the effects of a high PEEP setting as compared with low PEEP setting separately according to the indices of lung recruitability at the start of ECMO support. The indices of lung recruitability include the R/I and Cst.

Methods of analysis to handle protocol non-adherence and any statistical methods to handle missing data

In this study, we will perform FAS analysis as the main analysis. Any patients with missing data on the primary or secondary outcomes will be excluded. The safety analysis will be performed including all patients, even if there are missing data.

Plans to give access to the full protocol, participant level-data and statistical code

Both the protocol and data will be available upon reasonable request and approval from the relevant authorities after the trial is completed.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee

The Principal Investigator and Study Coordinator is Shinichiro Ohshimo, Hiroshima University Hospital. The Data Manager is Mitsuaki Nishikimi, Hiroshima University Hospital. The Statistical Analysis Manager is Kunihiko Takahashi, Tokyo Medical and Dental University. The Certification of the Ethics Committee for Clinical Research is established at Hiroshima University Hospital as the Coordinating Center and Trial Steering Committee.

Composition of the data monitoring committee, its role and reporting structure

Central monitoring will be performed by the Data Monitoring Committee, which consist of Kazuya Kikutani, Assistant Professor, Department of Emergency and Critical Care Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University. On-site monitoring will be performed at each hospital by monitors appointed by the Data Monitoring Committee if the committee judges that such monitoring is needed based on the results of central monitoring.

Adverse event reporting and harms

If serious adverse events associated with the trial are identified, the chief investigator at the corresponding hospital will immediately report them to the director of that hospital and to the Primary Investigator. The primary investigator will then take the appropriate actions under the guidance of the Ethics Committee for Clinical Research of Hiroshima University and the safety monitoring committee. All serious adverse events associated with the trial will be shared among all researchers by the Primary Investigator.

Frequency and plans for auditing trial conduct

An independent party will audit and report the results.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

Any protocol modifications will be reviewed by the Ethical Committee for Clinical Research of Hiroshima University and then registered at jRCT (https://jrct.niph.go.jp). All relevant information will be shared among the researchers.

Dissemination plans

The results of this study will be presented at national and international medical congresses, and also published in a scientific journal.

DISCUSSION

The ExPress SAVER trial is the first large multicenter RCT being conducted to investigate whether a high PEEP setting or low PEEP setting is more beneficial for ameliorating the lung injury in patients with severe ARDS requiring V-V ECMO. As compared with ventilation strategies in the absence of V-V ECMO, those in patients needing ECMO have received relatively little attention, and the optimal PEEP setting in patients receiving ECMO has not been established yet. We believe that this trial can help clarify the most beneficial mechanical ventilation strategies for severe ARDS patients receiving V-V ECMO support.

In this study, we also plan to conduct a subgroup analysis according to the indices of lung recruitability at the start of ECMO support. Recently, several studies have reported on the heterogeneity of ARDS, and the most appropriate management for ARDS might differ according to the sub-clinical phenotype [19-21]. We consider it not surprising that the beneficial effects of high PEEP settings differ according to differences in the lung recruitability at the start of ECMO support. In this sub-group analysis, we will use R/I, which has been reported as a useful index of lung recruitability in several previous studies.

There are several limitations of the ExPress SAVER trial. Firstly, this is an open-label study and the endpoints will be assessed by ICU physicians. However, the criteria for liberation from ECMO are already set prior to the start of the study, and outcomes which cannot be influenced by the physicians' judgement, including the mortality on day 28 and in-hospital mortality on day 60, will be also evaluated as secondary endpoints. Secondly, we decided not to use novel monitoring devices for the PEEP setting, such as electrical impedance tomography (EIT) and esophageal balloon catheter for measuring the esophageal pressure, because these devices are used only at a limited number of ECMO centers in Japan. Both have the potential to help estimate the most appropriate PEEP setting for individual ARDS patients requiring ECMO, although the benefits of personalizing PEEP settings have not yet been established.

Trial status

This study protocol was approved by IRB at Hiroshima University hospital on September 27, 2022 (C2022-0006). This study protocol is version 4 made on March 28, 2023. The recruitment period is between November

15, 2022, and March 31, 2026. The first patient was randomized on November 18, 2022.

Declarations

Acknowledgements

We acknowledge and honor all of our team members who consistently put themselves in harm's way during the COVID-19 pandemic. We dedicate this manuscript to them, as their vital contribution to knowledge about COVID-19 and sacrifices on the behalf of patients made it possible. We also want to thank all study participants for making this work possible.

Authors' contributions

Mitsuaki N and SO: conception and design of the study, interpretation of data, and drafting of the manuscript.

JH, KF, and YH: coordination and conduction of the study and interpretation of data.

Tatsuhiko A and KT: drafting of the manuscript (statistical part) and statistical analysis.

JI, YO, Toshiyuki A, Tokuji I, Tsukasa Y, GS, KI, KK, Daisuke Konno, NH, TN, YM, Daisuke Kasugai, HK, Tatsuhiko I, SK, HH, YI: conduction of the study and critical revision of the manuscript for important intellectual content.

Takeshi Y, TO, KM, KS, Mitsunobu N, SI: supervision of the study and critical revision of the manuscript for important intellectual content.

NS: conception and design of the study, and supervision of the study.

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Availability of data and materials

The datasets in this study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Central ethical approval for all participating hospitals was confirmed by the Ethical Committee for Clinical Research of Hiroshima University (C2022-0006), and local ethical approval is not needed according to the Clinical Trials Act in Japan. Informed consent will be obtained from proxies and all study participants when they are alert.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figure legends

Fig 1. Flow chart for patient recruitment into the ExPress SAVER trial

ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; EF: ejection fraction; ICU: intensive care unit; PEEP: positive end-expiratory pressure.

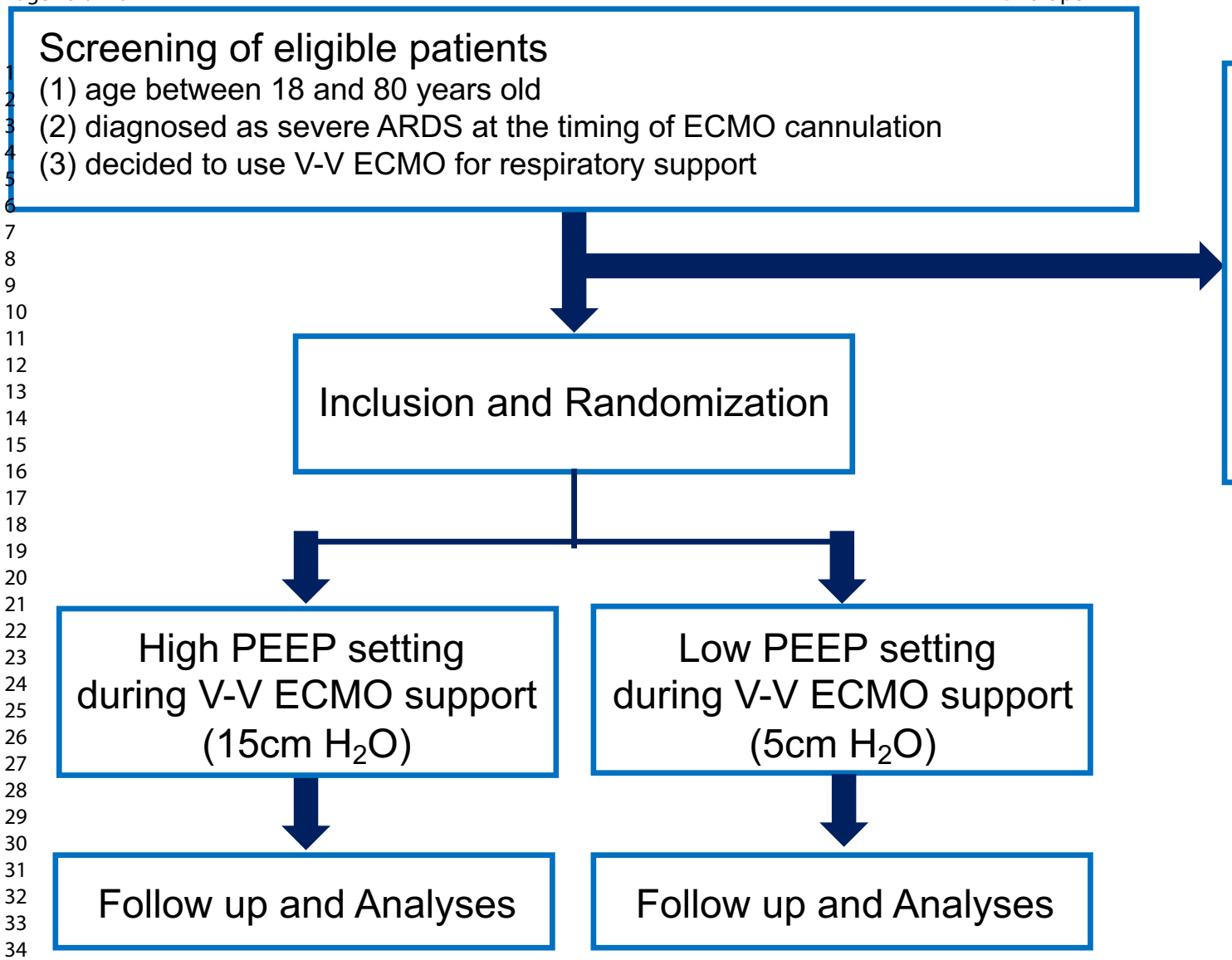
Fig 2. Calculation of ECMO-free days at 28 days

ECMO: extracorporeal membrane oxygenation; EFDs: ECMO-free days.

Fig 3. Time schedule for the trial

PEEP: positive end-expiratory pressure; ARDS: acute respiratory distress syndrome; SOFA score: Sequential Organ Failure Assessment score; ECMO: extracorporeal membrane oxygenation.

Supplemental material. Example of the participant consent form (in Japanese)



Day	1 (Initiation of ECMO support)	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	EFDs
Patients No 1					Liberation																								23
Patients No 2						Liberation					Re-canulation												Liberation						5
Patients No 3					Death																								0
Patients No 4					Liberation			Death																					0

On ECMO support

Liberated from ECMO

	Trial period									
	Screening	Randomization	Post-Randomization						Follow up	
Time point	Decision of ECMO support	Day 1 (within 24 h after Initiated on ECMO)	Day 2	Day 3	Day 5	Day 7	Day 10	Liberated on ECMO	Day 28	Day 60
Enrolment										
Inclusion/ Exclusion criteria	X									
informed consent		X								
Allocation		X								
Interventions										
High PEEP		◆—	—	—	—	—	—	—◆		
Low PEEP		◆—	—	—	—	—	—	—◆		
Assessments										
Baseline: demographic data, medical history, trigger for ARDS, murray score, SOFA score		X								
Vital signs		X	X	X	X	X	X	X		
Ventilation data		X	X	X	X	X	X	X		
ECMO data		X	X	X	X	X	X	X		
Clinical laboratory data		X	X	X	X	X	X	X		
Chest CT		X								
Other treatments	X	X	X	X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X	X	X
Live status: death or alive									X	X

第 4.0 版（2023 年 2 月 21 日）

研究に参加される患者さんへ

「急性呼吸窮迫症候群患者に対する体外式膜型肺管理中の至適呼気終末陽圧の検討：多施設前向き無作為化非盲検化比較試験」

についてのご説明

説明文書

第 4.0 版（2023 年 2 月 21 日作成）

広島大学病院　救急集中治療科

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第 4.0 版（2023 年 2 月 21 日）

目次

1. はじめに

（1） 同意について

今回、体外膜型肺（veno venous extracorporeal membrane oxygenation; V-V ECMO）による管理を必要とする急性呼吸窮迫症候群（Acute Respiratory Distress Syndrome; ARDS）の患者さんを対象に、高い圧での人工呼吸器管理と低い圧での人工呼吸器管理とでどちらが肺の病変を速やかに改善するのかを調べるための臨床研究を立案しました。この説明文書をよくお読みになり、この研究について十分にご理解いただいた上で、あなたの自由意思によりこの研究に参加するかどうかを決めてください。

一旦、参加することに同意をいただいた後でも、いつでも研究への参加をやめることができます。たとえ参加されなくても、途中で参加をとりやめられても今後の治療に不利益になることはありません。ただし、学会発表など結果が公表された後は状況によっては撤回ができない場合があります。参加を取りやめられた場合でも、場合によっては、患者さんの健康状態を確認するために検査を受けていただくことがあります。

この研究では、可能であれば患者さん本人から同意をいただきますが、患者さんは鎮静薬を使用して人工呼吸器管理をしている方を想定していますのでご自身で意思表示をすることは難しい場合が多く、その場合は代諾者の方にこの研究について説明を行い、本研究へのご協力について同意をいただきます。その場合、代諾者となる方は，患者さんの意思および利益を代弁できると考えられる者を選択することを基本としています。具体的には患者さんの配偶者，父母，成人の子，成人の兄弟姉妹若しくは孫，祖父母，同居の親族又はそれらの親近者に準ずると考えられる者，後見人です。人工呼吸器管理を必要とする患者さんの病気に対する治療法を検討するためにはどうしても代諾者の方から研究の同意を得て研究をせざるを得ないことをご理解ください。また、本研究を行うことであなたと同様な病気の患者さんにも有益となる可能性があります（代諾者の方がお読みになる場合には、「あなた」は「あなたのご家族」と読み替えてお読みください。）。

この研究にご協力頂けるようであれば、別紙の同意書にご署名をお願いいたします。

なお、この研究は広島大学臨床研究倫理審査委員会において、科学的、倫理的及び医学的妥当性の観点から審査を受け、承認されており、広島大学病院長の許可を得て実施されています。

（2） 臨床研究とは

この研究は、主に製薬会社や医療機器メーカーが厚生労働省に承認を得るために行う臨床試験、いわゆる‘治験’とは異なります。

広島大学病院では、最新の治療を患者さんに提供するために、病気の診断や治療について日々研究し、患者さんにより良い診断や治療の開発を試みています。さまざまな病気に対して、診療上重要であると考えられる治療法や診断方法などの有用性と安全性を調べるためには、患者さんやボランティアの方にご協力いただかざるを得ません。そのことを‘臨床研究’といい

ます。臨床研究は研究を目的としていますので、通常の治療と異なり研究的な側面があります。

今回実施する研究は、広島大学を中心として全国の V-V ECMO 管理に精通した数施設が参加している共同研究として実施しています。

共同研究機関の名称及び共同研究機関の研究責任者の氏名

（研究計画立案・プロトコル作成・解析担当　コアメンバー医師）

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済生会宇都宮病院　救急科・萩原　祥弘

前橋赤十字病院　救急科・中村　光伸

前橋赤十字病院　救急科・藤塚　健次

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名古屋大学医学部附属病院　救急・集中治療医学・春日井　大介

藤田医科大学　麻酔・侵襲制御医学講座・西田　修

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昭和大学病院　集中治療科　五十嵐友美
大阪大学医学部附属病院　麻酔・集中治療医学 吉田　健史

2.　研究の背景・目的・意義

患者さんの病気は急性呼吸窮迫症候群（Acute Respiratory Distress Syndrome; ARDS）という病気で体の中の酸素を保つために体外膜型肺（veno venous extracorporeal membrane oxygenation; V-V ECMO）による管理を必要とする状態です。

V-V ECMO による管理は通常の人工呼吸管理では血液の酸素が足りない ARDS の患者さんの酸素の値を保つことを可能にします。通常の人工呼吸管理では、病気に対する治療に反応して肺がよくなる前に命を落としてしまう程の重症な病態も、V-V ECMO による管理によって原因となる疾患に対する根本の治療の効果が出てきて肺が改善するまである程度待つことができます。

近年の V-V ECMO の登場は ARDS の患者さんの死亡率を改善させましたが、その死亡率はいまだに 50%におよび、V-V ECMO 管理開始後の最適な治療戦略はいまだ確立されておりません。V-V ECMO を必要とするほど重症な ARDS の患者さんは日本全国で見ても稀であることも理由の１つです。特に、V-V ECMO 管理中の最適な人工呼吸器の設定は解明されておらず、V-V ECMO 管理中の人工呼吸器の圧の設定に関しては高い圧か低い圧かどちらが肺にとっていいのかは明らかではありません。

以上の背景より、本研究は V-V ECMO 管理中の人工呼吸器の設定が高い圧で管理する群と低い圧で管理する群とでどちらがより早期に肺障害が改善するのかを調べることを目的とした研究です。これまでに同じような研究は国内外を見渡しても行われておらず、本研究の結果によって患者さんと同じ病気に苦しむ ARDS の患者さんの予後を良くする管理方法を確立できる可能性があります。

3.　研究の方法について

（1）　研究の参加基準

***患者さん本人から直接同意を得ることが難しい場合は、代諾者の方にこの研究について説明を行い、本研究へのご協力について同意をいただきます。代諾者の方がおられない場合は同意を得ずに研究を始める場合があります。**

●この研究に参加いただける方（以下の基準を**すべて**満たす方）

① 重症 ARDS と診断され、かつ V-V ECMO 管理を導入することが決定した研究参

加施設に入院している患者さん

② 同意時に 18 歳以上 80 歳以下の患者さん

●この研究に参加できない方（以下の**いずれか**の基準に該当する方）

① V-V ECMO 導入前にすでに別の種類の人工心肺管理をしている患者さん
② 気管挿管後 7 日以上経過している患者さん
③ 循環動態が不安定な患者さん
④ 気胸を合併している患者さん
⑤ 外傷による ARDS の患者さん
⑥ 肺以外が原因で ARDS となった患者さん
⑦ 妊娠及び授乳中の患者さん
⑧ 研究責任者または研究分担者が不適切と判断した患者さん

（2） 研究に使用する機器

本研究で特別に使用する機器や薬剤はありません。

【無作為化割付について】

この研究では、「無作為化割付（むさくいかわりつけ）」という方法により、参加者の方には 2 分の 1 の確率で高い人工呼吸器の設定圧で管理される群か、低い圧で管理される群かのいずれかのグループに分かれていただきます。

無作為化割付を行うことにより、性別や年齢、あるいは V-V ECMO の離脱までの期間に影響を及ぼしそうな特性が、グループ間で均等になることが期待できます。こうすることで、より公平に高い人工呼吸器の設定圧の効果を調べることができます。

（3） 研究の進め方

この研究全体の流れを図にしました。

同意取得の後、V-V ECMO での管理を開始します。V-V ECMO での管理中、割り付け結果に従い高い人工呼吸器の設定圧で管理されるか、低い圧で管理されます。設定圧での管理は医師が明らかに不適当と判断されない限り V-V ECMO の離脱(あるいは挿入 28 日後)まで継

続されます。また V-V ECMO の管理を終了した後も V-V ECMO 挿入後 60 日間の経過観察をします。

（4） 研究のスケジュールと検査項目

どちらの治療法にあたることになっても、あなたの体調に十分注意しながら研究を行います。それぞれの治療を行いますが、この研究では、通常の診療の範疇を超えて本研究のための血液検査や画像検査などは行いません。

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スケジュール表

項　目		同意取得時	集中治療室				集中治療室・病棟・転院 退院（自宅）	
時　期		ECMO 挿入方針決定	ECMO 挿入前	ECMO 挿入直後	ECMO 挿入後離脱までの各病日	ECMO 離脱時	第 28 病日	第 60 病日
選択・除外基準		●						
同意取得		●						
基本患者情報の確認			●					
侵襲・介入期間			←	―	―	→		
人工呼吸器の設定に関する情報		●	●	●	●	●		
人工呼吸器/V-V ECMO の設定に関する情報			●	●	●			
SOFA スコア			●	●	●			
基本バイタルサイン（血圧，心拍数，SpO_2 など）		●	●	●	●	●		
併用薬剤の確認		●	●		●			
臨床検査	末梢血検査		●		●			
	凝固検査		●		●			
	血液生化学検査		●		●			
	血液ガス検査		●	●	●	●		
	凝固検査		●		●			
エコー検査			●					
胸部 X 線検査			●					
胸部 CT			●					
転帰に関する情報の収集						●	●	●

4. 研究に参加することにより期待される利益及び予想される不利益

（1） 期待される利益

私たちは、患者さんがこの研究に参加し、どちらの治療法を受けられたとしても、これまで行われてきた治療と同じくらいか、それ以上の効果が得られると考えています。また、私たちは将来の V-V ECMO 管理を必要とする ARDS の患者さんのために、より有効でしかも合併症などお体に負担の少ない治療法を確立するための情報がこの研究を通じて得られることを期待しています。本研究の中で我々が立てている仮説の通り人工呼吸器の高い圧あるいは低い圧設定のどちらかの効果が認められた場合、結果的に該当の圧設定群に振り分けられれば、より病態の緩和が得られる可能性があります。

その他、この研究に参加することで得られる患者さんへの特別な利益はありませんが、将来の医学の発展のためご協力をお願いしています。

（2） 予想される不利益

この研究に参加していただいた場合に想定される不利益として、以下の【有害事象（副作用）及び不具合について】に記載されているような健康被害が生じる可能性があります。これらの有害事象は、すべての患者さんに起こるわけではありません。

この研究に参加されている間や終了後に、患者さんの身体に何らかの症状や不調がありましたら、すぐに研究責任者または研究分担者にご連絡ください。症状に応じて適切に対処します。

【有害事象（合併症）について】

本研究で行われる人工呼吸の高い圧に相当する 15cmH2O という設定値は日常臨床（V-V ECMO の管理をする場合も含めて）でも患者さんに対して行われています。これまで使用が全面的に禁止となるような有害事象は報告されていません。しかしながら高い胸腔内圧での管理に伴う循環不全を起こす可能性があります(頻度不明)。

また本研究で行われる低い圧での管理群で用いられる 5cmH2O という設定値も日常臨床において一般に使用される値です。使用が全面的に禁忌となるような有害事象は報告されていません。しかしながらなんらかのメカニカルトラブルや人工肺の突然の劣化などで V-V ECMO による血液の酸素化が不十分となった場合は 5cmH2O の圧では血液の酸素化が不十分となる可能性があります（頻度不明)。本研究ではあらかじめ設定された圧での管理が開始された後、ECMO 離脱まで設定された圧での管理を継続する予定ではありますが、臨床医の判断により設定された圧が明らかに臨床上有害であると判断した場合は圧を変更することを許容します。ここに記載した以外にも、未知の有害事象が発生する可能性は否定できません。合併症に関する最新の情報をお知りになりたいときは、いつでも研究責任者または研究分担者にお尋ね下さい。この研究に参加されている期間中、新たにあなたの研究継続の意思に影響を与えるような情報を入手した場合には、直ちにお知らせします。さらに研究を始めた後に、この

研究に関して重要な情報が得られた場合は、研究を続けることに関してあなたの意思を確認させていただき、再度同意をいただくことにしています。

5. あなたに守っていただきたい事項について

特にありません。

6. 研究を中止する場合があります

次のような場合、あなたが研究への参加に同意された後でも、研究を中止させていただくことがありますので、あらかじめご了承ください。

- 患者さんから研究参加の辞退の申し出や同意の撤回があった場合
- 担当医が割り付けられた設定圧での管理が臨床上不適切と判断した場合
- この研究の開始後に、参加基準を満たしていないことが判明した場合
- その他の理由により研究担当者が研究の中止が適当と判断した場合

また、以下の理由で患者さんについての研究を途中で中止することになった場合には、中止の理由をご説明し、その後は研究責任者または研究分担者があなたと相談しながら最善の治療をおこないます。なお、中止した場合でも、その後の患者さんの体調については必要な限り継続して観察をおこないます。

① 高い圧での管理あるいは低い圧での管理の安全性、有効性に関する重大な情報が得られた時。

② 目標対象者数を研究期間内に組み入れることが困難であると判断された時。

③ 倫理審査委員会により、実施計画等の変更指示があり、これを受け入れることが困難と判断された時。

④ 研究の倫理的妥当性又は科学的合理性を損なう又はそのおそれがある事実を知り、又は情報を得た場合であって、それが研究の継続に影響を与えると考えられる時。

⑤ 研究の実施の適正性又は研究結果の信頼を損なう又はそのおそれがある事実を知り、又は情報を得た時。

⑥ 研究の実施において、当該研究により期待される利益よりも予測されるリスクが高いと判断される時又は当該研究により十分な成果が得られた若しくは十分な成果が得られないと判断される時。

7. 研究に参加しない場合の治療法について

患者さんがこの研究に参加されない場合は、患者さんの病状、合併症などをもとに、可能な限り最適な治療を行います。

8. 研究終了後の対応について

参加期間終了後には、その時点で今後の治療法について相談し、最適な治療法を提供させていただきます。

9. 研究の参加予定期間

この研究は　　年 月 日（許可日）から　2026 年 5 月 30 日にかけて行います。あなたに参加していただく期間は 60 日です。

10. 研究の参加予定人数

全国 21 施設で 210 名、当院でおよそ 30 名の患者さんに参加いただく予定です。

11. 個人情報の保護について

この研究で得られた情報は、患者さんを特定できる情報（氏名、住所、電話番号等）は記載せず取りまとめられます。そして、この研究の成績をまとめて学会発表や学術論文として公表されることもありますが、いずれの場合も患者さんの名前等の個人的な情報は一切公表されませんので患者さんの個人情報は守られます。

また、患者さんの人権が守られながらきちんとこの研究が行われているかを確認するために、この研究の関係者（本院の職員、臨床研究倫理審査委員会の委員、厚生労働省等の職員、この研究事務局担当者、モニタリング担当者および監査担当者など）が患者さんの診療録などの医療記録を見ることがあります。このような場合でも、これらの関係者には、守秘義務があり、患者さんの個人情報は守られます。この研究で得られる情報の一部は、統計解析のため共同研究機関である東京医科歯科大学 生物統計学分野が見ることになります。情報を記号や通し番号に置き換えて（匿名化情報：個人情報を含む）取り扱いますので、患者さんの名前などの個人的な情報が直ちには判別できません。また、この研究で得られたデータを将来の研究に 2 次利用(出版・解析)する可能性があります。あなたの名前などの情報が第三者にわからないように処理したデータを、別途、臨床研究審査専門委員会で審査した上で使用します。

この研究は、他の施設との共同研究です。したがって、あなたのデータを他の施設のデータを含め WEB を通じて(広島病院 救急集中治療科研究事務局: 広島県広島市)で集約しますが、あなたの名前などの情報は記載せず、プライバシーに十分配慮して送付します。

本研究の統計解析責任者は以下の通りです。

東京医科歯科大学 生物統計学分野

教授　高橋邦彦

12.　研究に関する情報の公開について

患者さんからのご要望があれば、患者さんと患者さんのご家族がお読みになるという目的に限り、この研究の実施計画書をご覧いただくことができます。ご希望の場合は、研究責任者または研究分担者にご依頼ください。また、この研究の情報は、Japan Registry of Clinical Trials：jRCT のデータベースで公開しています。

（https://jrct.niph.go.jp）

13.　研究の資金源および利益相反について

この研究は、『日本救急医学会から支給された学会主導研究　助成金』の資金を用いて実施されます。

次に、利益相反※について説明いたします。この研究で利害関係が想定される企業・団体からの経済的な利益やその他の関連する利益は受けていませんので、本研究の実施に影響を及ぼすことはありません。なお、利害の衝突に関しては、各機関の利益相反管理委員会で審査を受けています。

（※）利益相反とは

臨床研究における、利益相反とは「主に経済的な利害関係によって公正かつ適正な判断が歪められてしまうこと、または、歪められているのではないかと疑われかねない事態」のことを指します。具体的には、製薬企業や医療機器メーカーから研究者へ提供される謝金や研究費、株式、サービス、知的所有権等がこれに当たります。このような経済的活動が、臨床研究の結果を特定の企業や個人にとって有利な方向に歪曲させるようなことが無いように利害関係を管理することが定められています。

14.　研究に参加された場合のあなたの費用負担について

この研究に参加することであなたに発生する費用について、説明します。すべて保険診療で行うため、治療に関わる費用には通常通り自己負担が生じます。今回の研究は人工呼吸器の設定値を比較する研究ですので通常の診療に加えての特別な費用は発生しません。また、この研究に関して、あなたへの謝礼の支払いはありません。

15.　研究中に健康被害が生じた場合の治療及び補償について

何か異常を感じた場合には、どんなことでも構いませんので遠慮なく直ちに研究責任者または

研究分担者に申し出てください。何らかの障害が起きた場合には、研究終了後であってもすみやかに適切な処置と治療をもって対応させていただきます。その際の医療処置にかかる費用は、健康保険によるあなたの自己負担となります。この点を十分にご理解いただき、研究への参加をご判断ください。

16. 研究終了後の結果の取り扱いについて

（1） 試料及びデータの保存方法並びに保管期間について

研究により得られた診療情報及び検体は、診療番号やお名前など個人を特定する情報がわからないように匿名化して保存されます。

診療情報は、データ解析され研究終了後５年間または結果の最終公表後３年間のいずれか遅い期間まで保存します。保存期間終了後は、匿名のまま適切に廃棄します。

（2） 研究成果の帰属について

この研究の結果として特許権等が生じる可能性がありますが、その権利は、大学に帰属し、あなたには帰属しません。また、その権利により経済的利益が生じる可能性がありますが、その権利もあなたには帰属しません。

17. データの二次利用について

この臨床研究のために集めたデータは、将来この研究とは別の研究に利用させていただく可能性があります。これを「データの二次利用」といいます。データの二次利用の際には、その研究に関する情報を開示し、データ使用の拒否権を行使できるようにします。また、個人を特定できない形で、改めて倫理審査委員会で承認を得てから利用します。

18. 研究代表者（責任者）の連絡先

この研究は、広島大学病院を中心として計 21 施設と共同で実施する研究です。この研究全体の連絡窓口は以下の通りです。

【研究代表者（責任者）】

職名： 准教授 氏名：大下 慎一郎

所属：救急集中治療科

住所：〒734-8551 広島県広島市南区霞 1-2-3

電話番号：082-257-5456

19. 研究に関する相談・問合せ先

この研究について何かお聞きになりたいことやわからないことや心配事がありましたら、遠慮なくおたずねください。

広島大学病院　救急集中治療科
職名：助教
担当者：錦見　満暁
連絡先：082-257-5456　（平日 9 時～17 時）
　　082-257-5586　　（夜間、休日）

20.　研究に関する苦情と相談窓口について

広島大学病院では研究に関する苦情とお問い合わせ窓口を設けています。この研究についてわからないことや心配なことなど疑問に思ったことがありましたら、いつでもご遠慮なく以下の相談窓口にお問い合わせください。

広島大学病院　患者支援センター　治験・臨床研究窓口
場所：診療棟 1 階　患者支援センター内
電話番号：082-257-5940（平日 9:00-17:00）

第 4.0 版（2023 年 2 月 21 日）

同　意　書

実施医療機関の長　殿

私は、「**急性呼吸窮迫症候群患者に対する体外式膜型肺管理中の至適呼気終末陽圧の検討：多施設前向き無作為化非盲検化比較試験**」の研究に参加するに当たり、説明担当者（研究責任者または研究分担者）から、下記のことについて十分に説明を受けて納得しましたので、自由意思によりこの研究に参加することに同意します。なお、説明文書及び同意書（写）を受領しました。

1. はじめに
2. 研究の背景・目的・意義
3. 研究の方法について
4. 研究に参加することにより期待される利益および予想される不利益
5. あなたに守っていただきたい事項について
6. 研究を中止する場合があります
7. 研究に参加しない場合の治療法について
8. 研究終了後の対応について
9. 研究の参加予定期間
10. 研究の参加予定人数
11. 個人情報の保護について
12. 研究に関する情報の公開について
13. 研究の資金源および利益相反について
14. 研究に参加された場合のあなたの費用負担について
15. 研究中に健康被害が生じた場合の治療及び補償について
16. 研究終了後の結果の取り扱いについて
17. データの二次利用について
18. 研究代表者（責任者）の連絡先
19. 研究に関する相談・問合せ先
20. 研究に関する苦情と相談窓口について

（研究責任者）職名：准教授　　氏名：　大下　慎一郎

（説明担当者）職名：　　連絡先（TEL）：082-257-5456

説明日　西暦　　年　　月　　日　　署名

（本人）同意日　西暦　　年　　月　　日　　署名

【本人氏名：　　】

（代諾者）同意日　西暦　　年　　月　　日　署名

研究対象者名：　　続柄：

第 4.0 版（2023 年 2 月 21 日）

同　意　撤　回　書

実施医療機関の長　殿

私は、「急性呼吸窮迫症候群患者に対する体外式膜型肺管理中の至適呼気終末陽圧の検討：多施設前向き無作為化非盲検化比較試験」の研究についての参加に同意いたしましたが、都合により同意を撤回いたします。

また、□　同意撤回前に収集された情報について、利用してもかまいません。

□　同意撤回前に収集された情報について、利用しないでください。
（いずれかに✔を入れてください）

（本人）同意撤回日　西暦　　年　　月　　日

署名

（代諾者）同意撤回日　西暦　　年　　月　　日　署名

研究対象者名：　　続柄：

私は、この同意の撤回について、確認いたしました。

（研究責任者）職名：　　氏名：

（確認者）　　職名：　　連絡先（TEL）：

同意撤回確認日　西暦　　年　　月　　日　署名

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	3
Protocol version	#3	Date and version identifier	3
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1, 17

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	3
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	4
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	5
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	7

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	8
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	8
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	11
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	12
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	8
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	18
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A