Effect of PERMISSive Lung-protective Ventilation on Outcome in Critically Ill Invasively Ventilated Patients (PERMISS) – statistical analysis plan of the feasibility and safety *pilot* randomized clinical trial

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SAP version: v1.0, 03-07-2026
Protocol version: V3.0
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INTRODUCTION

The study 'Effects of PERMISSive Lung–protective Ventilation on Outcome in Critically Ill Invasively Ventilated Patients (PERMISS)—a feasibility and safety *pilot* study for a randomized clinical trial' compares permissive lung–protective ventilation (LPV) with conventional lung–protective ventilation in critically ill invasively ventilated patients. The primary objective is to evaluate the feasibility of permissive LPV with regard to the difference in the respiratory rate (RR). Secondary objectives are to assess the safety of permissive LPV, with regard to the occurrence of unacceptable hypercapnia and severe hypoxemia and ventilator–associated complications, and to assess the protocol compliance and the feasibility of collecting data. PERMISS pilot has completed the recruitment phase and is schedule to complete patients' follow up in September 2026. To prevent outcome reporting bias and data-driven analysis results, the International Conference on Harmonization of Good Clinical Practice (ICH-GCP) recommends that clinical trials should be analyzed according to a pre-specified detailed Statistical Analysis Plan (SAP). This document presents the finalized SAP of PERMISS pilot.

METHODS

Trial design

The PERMISS pilot study is an investigator–initiated, multicenter, randomized, feasibility and safety pilot study comparing a permissive LPV strategy with low RR to conventional LPV with higher RR in adult critically ill invasively ventilated patients. The trial was approved by the Human Research Ethics Committee of Leiden Den Haag Delft (METC LDD, approval number NL-009624.P25.028) and was registered at ClinicalTrials.gov (NCT07077174). The protocol, with a detailed description of the study population, the two interventions and follow-up, was previously published [1].

Randomization and blinding

Randomization takes place using the Castor EDC platform (www.castoredc.com). Eligible patients are randomly assigned in a 1:1 ratio to permissive LPV, or to conventional LPV. The allocation sequence is computer–generated, using the Castor randomization module with permuted blocks of different block sizes, with a maximum block size of 8 and stratified per center. Due to the nature of the intervention, blinding is not possible.

Definitions

- Unacceptable hypercapnia: $PaCO_2$ > 70 mmHg (9.3 kPa) and pH < 7.20.
- Severe hypoxemia: PaO_2 < 60 mmHg (8 kPa).
- Ventilator-associated complications:
    1. Air leaks: any subcutaneous emphysema, pneumothorax or pneumomediastinum, confirmed by a radiologist on a chest computed tomography (CT) or chest radiograph (CXR);
    2. Severe atelectasis: one or more completely collapsed lobes on a CT or CXR confirmed by a radiologist;
    3. Ventilator–associated pneumonia: new or progressive radiographic infiltrate plus at least two of the following: fever (tympanic temperature > 38.5 ^{0}C), leukocytosis or leucopenia or purulent secretions, confirmed with microbiological culture.
    4. Acute cor pulmonale: defined as the association of right ventricle dilatation (ratio of right over left ventricle surface >0.6) and septal dyskinesia assessed by echocardiography.
- Protocol deviations: provided reason for deviation from the study protocol.
- Reasons for not lowering the RR:

1. RR needed to be increased because of hypercapnia;
2. metabolic acidosis;
3. spontaneous breathing;
4. clinical decision of the attending physician;
5. other.

- Compliance with the protocol: the proportion of patients in whom the measured RR was reduced by at least 2 breaths/min from baseline within 6 hours after randomization.
- Ventilator-free days at day 28 (VFD-28): Start time is the day of randomization, the timeframe is 28 days, successful extubation is considered as >24 hours without reintubation. VFD-28 is counted from the day of the last successful extubation if there were repeated intubation episodes in the first 28 days. Periods of non-invasive ventilation are not counted. If a patient is tracheostomized, > 24 hours off from positive pressure ventilation are needed to consider the patient ventilator-free. In non survivors at day 28, VFD-28 is considered 0, even if extubated within the period. Patients not died and not extubated at day 28 are censored and considered having 28 VFD-28.
- Duration of ventilation in survivors: duration, in days, between randomization and successful extubation, defined as the patient breathing without invasive assistance of the mechanical ventilation for at least 24 consecutive hours. All relevant data will be taken into account and collected, including all additional periods of ventilation during the first 28 days. Only patients surviving the first 28 days will be considered.
- ICU length of stay (LOS) among survivors: number of days from randomization till ICU discharge. Counted from the day of the last ICU discharge if there were

repeated readmissions within the same hospital admission. Only patients surviving to ICU discharge will be considered.

- Hospital LOS among survivors: number of days from randomization till hospital discharge. Only patients surviving to hospital discharge will be considered.
- 28-day mortality: death for any cause occurring during the first 28 day after randomization.
- 90-day mortality: death for any cause occurring during the first 90 day after randomization.

Outcomes

The primary outcome is the difference in the measured RR between groups from randomization to extubation or death or day 28, whichever comes first. To evaluate this endpoint all collected data at pre-specified time points will be considered.

Secondary safety outcomes are (definitions described in the previous section):

- Occurrence of unacceptable hypercapnia;
- Occurrence of severe hypoxemia;
- Occurrence of ventilator-associated complications.

Secondary feasibility outcomes are:

- Compliance with the protocol: the goal of the intervention in the permissive LPV group is to reduce the RR as much as possible and as close as possible to the target RR. Therefore, compliance with the intervention is defined as a reduction in measured RR at 6 hours after randomization compared with baseline. The magnitude of intervention delivery is further described by the difference between baseline RR and measured RR, and by the difference between measured RR and target RR;
- Compliance with data collection.

Exploratory clinical endpoints are:

- Ventilator-free days at day 28 (VFD-28);
- Mortality in the Intensive Care Unit (ICU), in hospital, at day 28 and day 90;
- Duration of ventilation among survivors;
- Hospital and ICU length of stay (LOS).

Cleaning and closing of the database

The database will be locked as soon as all data is entered and all discrepant or missing data are resolved, and we consider that the remaining issues cannot be fixed. At this step, the data will be reviewed before database locking. After that, the study database will be locked and exported for the statistical analysis. At this stage, permission for access to the database will be removed for all investigators, and the database is locked and archived.

Missing data

No or minimal data losses for the primary outcome are anticipated. Complete-case analysis will be carried out for all outcomes. Missing data for the primary outcome consists only of unrecorded RR measurements at scheduled time points in patients who were still under invasive ventilation. If more than 10% of missing data is found for the primary outcome, a sensitivity analysis using multiple imputation and estimating-equations methods will be carried out. Multiple imputation will consider imputation models based on baseline and post-baseline variables under the missing at random assumption. Additionally, the counts and proportions of non-missing observations for primary, secondary and clinical explorative outcomes will be reported as part of the evaluation of the compliance with data collection.

Sample size

Assuming an expected mean difference of 7.5 breaths/min, with a standard deviation

(σ) of 10, accepting a probability of type II error of 10% (power = 90%) and a probability of type I error of 5% (α = 0.05), and accounting for a drop-out rate of 10%, a total of 84 patients (42 per group) are required to detect a significant mean reduction of RR with a two-sample t-test. As a pilot study, recruitment may be stopped early if additional inclusions are unlikely to yield new relevant information on feasibility, data completeness, or key parameter variability, as determined by the steering committee in accordance with the Data Safety Monitoring Board.

Statistical analysis

All analyses will be conducted on a modified intention-to-treat basis, with patients analyzed according to their intended assignment arm, except for participants lost to follow-up or withdrawal of informed consent. No per-protocol analyses will be conducted. All analyses with be conducted with a two-sided superiority hypothesis testing at a significant level of 0.05 and presented with two-sided 95% confidence intervals (95% CI). No multiplicity adjustment is planned. Analyses will be performed using the R software (R Core Team, 2016, Vienna, Austria). **Table 1** reports a list of proposed tables and figures.

Trial profile

Patients' flow will be presented in a CONSORT flowchart (**Figure 1**).

Baseline characteristics

A description of the baseline characteristics of trial participants will be presented by treatment group (**Table 2**). A description of ventilation and arterial blood gas (ABG) parameters before randomization will be presented by treatment group (**Table 2**). Categorical variables will be expressed as counts and percentages; when values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be reported as means and standard deviations,

or medians and interquartile ranges (IQR), according to the observed distribution.

Primary outcome

The primary outcome is the overall difference in RR between the permissive and conventional LPV groups from randomization to first extubation or death or 28 days, whichever occurs first. This will be evaluated with a linear mixed-effects model with randomization group, time from randomization in hours, and their interaction as fixed effects, and a random intercept and random slope for time per patient. A random effect for hospitals will not be included as it is expected that the number of patients per center will be small due to the pilot nature of the trial. The primary estimate of interest is the overall mean group difference averaged across all timepoints, derived as the marginal contrast between groups, and reported with 95% CI and *p* value. The time and group × time interaction coefficients, with 95% CI and *p* values, of the primary model will be reported to evaluate the rate of change in RR over time and its difference between groups. Estimated marginal means and mean difference in RR between groups with 95% CI and *p* values at pre-specified timepoints (hour 1, 2, 3, 4, 5, 6, and day 1, 2, 3, 4, 5) will be reported (**Table 3**). Line plots showing mean (95% CI) RR per group before randomization to day 5, and bar plots showing the delta RR (RR at timepoint – RR at baseline) per group to day 5 will be constructed.

Secondary safety outcomes

Safety outcomes will be reported as incidence (the count and proportion of patients experiencing each event during the ventilation period) per randomization group, with exact 95% CI (Clopper-Pearson method). Safety outcomes are unacceptable hypercapnia, severe hypoxemia, and ventilator-associated complications (**Table 3**). Ventilator-associated complications will be reported as composite and individually (air leaks, severe atelectasis, ventilator-associated pneumonia, and acute cor pulmonale).

The between-group difference in incidence will be reported as absolute difference (AD) with 95% CI and *p* values. Safety outcomes will be reported as exploratory, acknowledging the that the study is underpowered for such outcomes.

Secondary feasibility outcomes

Regarding compliance with the protocol, this is defined as the proportion of patients in whom the measured RR was reduced by at least 2 breaths/min from baseline within 6 hours after randomization, reported as counts and percentages.

Additional measures to analyze the magnitude of the intervention delivery are:

1. Magnitude of RR reduction: the estimated marginal mean difference from a mixed-effects linear model, with 95% CI and *p* values, between the measured RR at pre specified timepoints (hour 1, 2, 3, 4, 5, 6, and day 1, 2, 3, 4, 5) and the baseline RR in the intervention group. The maximum drop from baseline to the nadir of the measured RR will be reported;
2. Proximity to the target RR: the estimated marginal mean difference from a mixed-effects linear model, with 95% CI and *p* values, between the measured RR at pre-specified timepoints (hour 1, 2, 3, 4, 5, 6, and day 1, 2, 3, 4, 5) and the target RR;
3. Achievement of target RR: the proportion of patients reaching a measured RR equal to the target RR ±2 breaths/min within 6 hours after randomization, reported as counts and percentages;
4. Reasons for not further reducing RR: counts and percentages of reasons for not lowering the RR in the intervention group including hypercapnia, metabolic acidosis, spontaneous breathing, clinical decision by the treating physician, or other reasons.

Regarding compliance with data collection, counts and percentages of missing and

non-missing values will be reported.

Exploratory clinical outcomes

VFD-28 will be presented as common odds ratio (OR), with 95% CI, from a cumulative logistic model. In this model the cumulative log odds are modeled such as a parameter greater than 0 reflects an increase in the probabilities of being in a higher VFD-28 category. To inform the large RCT, VFD-28 will also be presented as median (IQR). A cumulative incidence plot will be created to present the distribution of VFD-28 by group. Day-28 and day-90 mortality will be compared using Kaplan-Meier curves and reported as hazard ratios (HR) with 95% CI calculated from a Cox proportional hazard model. ICU and hospital mortality will be assessed with ADs (95% CI) . Duration of ventilation in survivors, and ICU and hospital LOS will be assessed with median difference (95% CI).

Ventilator and blood gas parameters

Relevant ventilator and blood gas will be evaluated with a linear mixed-effects model with randomization group, time from randomization in hours, and their interaction as fixed effects, and a random intercept and random slope for time per patient and reported as the overall mean group difference averaged across all timepoints and reported with 95% CI and *p* value. Estimated marginal means and mean difference with 95% CI and *p* values will also be reported at pre-specified timepoints (hour 6, and day 1, 2, 3, 4, 5). Pre-randomization values will be presented descriptively but not included in the model. Line plots showing observed variables mean (95% CI) per group before randomization to day 5 will be constructed.

Other daily characteristics

Additional daily variables, including sedation, analgesia, nutrition, Richmond Agitation-Sedation Scale (RASS) and bicarbonate administration will be reported in each group

according to the study day.

Sensitivity analyses

The analysis on the primary outcome will be repeated according to the mode of ventilation (controlled mode vs. spontaneous mode) and considering only the first 5 days after randomization.

REFERENCES

1. The PERMISS investigators. Effect of PERMISSive-Lung-Protective Ventilation on Outcomes in Critically Ill Invasively Ventilated Patients (PERMISS) – a Feasibility and Safety Randomized Clinical Trial *(in progress)*

Table 1. List of proposed tables and figures*	
Main paper	
Table 1	Demographic, clinical, ventilator and blood gas characteristics of included patients at baseline by study group.
Table 2	Primary outcome and secondary safety outcomes
Figure 1	Participants' flow diagram
Figure 2	RR, ΔRR (measured at specific timepoint - baseline), V_T/PBW, Mechanical Power (MP), Minute Volume (MV), ΔP, P_{peak} and P_{plat} from baseline to day 5 in the permissive and conventional LPV groups
Figure 3	$PaCO_2$, pH, PaO_2, $etCO_2$ from baseline to day 5 in the permissive and conventional LPV groups
Supplement	
Table S1	Coefficients of the primary outcome regression model
Table S2	Secondary feasibility outcomes in the permissive LPV group
Table S3	Ventilator parameters in the first 6 hours after randomization according to study group
Table S4	Ventilator parameters in the first 5 days after randomization according to study group
Table S5	Metabolic and ABG parameters in the first 6 hours after randomization according to study group
Table S6	Metabolic and ABG parameters in the first 5 days after randomization according to study group
Table S7	Summary of overall and marginal mean, mean differences and *p* values in MP, V_T/PBW, MV, P_{Peak}, P_{plat}, ΔP, $PaCO_2$, pH, PaO_2 according to study group
Table S8	Summary of non-missing and missing observations for ventilator and ABG parameters, and for follow-up clinical outcomes
Table S9	Feasibility of ABG collection in the first 6 hours after randomization
Table S10	Unacceptable hypercapnia and severe hypoxemia occurrence in the first 6 hours and in the first 5 days after randomization according to study group
Table S11	Exploratory clinical outcomes
Table S12	Daily clinical assessment in the first 5 days after randomization according to study group
Table S13	Ventilator parameters under controlled ventilation in the first 6 hours after randomization according to study group
Table S14	Ventilator parameters under spontaneous ventilation in the first 6 hours after randomization according to study group
Table S15	Ventilator parameters under controlled ventilation in the first 5 days after randomization according to study group
Table S16	Ventilator parameters under spontaneous ventilation in the first 5 days after randomization according to study group
Table S17	Sensitivity analysis of the primary outcome according to controlled or spontaneous mode of ventilation
Table S18	Sensitivity analysis of the primary outcome considering only the first 5 days after randomization
Figure S1	Individual patient trajectories of RR from baseline to day 5 according to study group
Figure S2	Percentage of patients under controlled vs spontaneous modes of

	ventilation in the first 6 hours according to study group
Figure S3	Percentage of patients under controlled vs spontaneous modes of ventilation in the first 5 days according to study group
Figure S4	Additional ventilator parameters from baseline to day 5 in the permissive and conventional lung-protective ventilation groups
Figure S5	Additional metabolic and ABG parameters from baseline to day 5 in the permissive and conventional lung-protective ventilation groups
Figure S6	Sedation and analgesia in the first 5 days after randomization according to study group
Figure S7	Cumulative distribution of VFD-28 and cumulative incidence of VFD-28
Figure S8	ICU, hospital, 28-day and 90-day mortality forest plots
Figure S9	Cumulative incidence of being alive and ICU free at day 28
Figure S10	Cumulative incidence of being alive and hospital free at day 28
Figure S11	RR, V_T/PBW, MP, ΔP, P_{peak} and P_{plat} under controlled ventilation from baseline to day 5 in the permissive and conventional lung-protective ventilation groups
Figure S12	RR, V_T/PBW, P_{supp}, P_{peak} under spontaneous ventilation in the first 5 days in the permissive and conventional lung-protective ventilation groups

**The final order and number of tables and figures in the supplement may change according to the reference in the main paper.*

Table 2. Patients' baseline characteristics		
Characteristic*	**Permissive LPV (n =)**	**Conventional LPV (n =)**
Demographics and clinical characteristics		
Age, years		
Gender, male		
BMI, kg/m^2		
PBW, kg		
APACHE IV		
SOFA score		
SAPS II score		
Type of ICU admission: - Medical - Surgical elective - Surgical emergent		
Reason for intubation: - Respiratory failure - Cardiac arrest - Postoperative ventilation - Decreased consciousness - Airway protection - Other		
Cause of respiratory failure: - Pneumonia; - Sepsis - ARDS - Atelectasis - Pulmonary edema - Aspiration pneumonia - Neuromuscular disease - Other		
Comorbidities: - Cardiovascular - COPD gold I or II - Kidney failure - None of the above		
Ventilator variables		
Mode: - Pressure control; - Volume control; - Pressure support; - Other		
V_T/PBW, mL/kg		
RR set, breaths/min		
RR measured, breaths/min		
P_{peak}, cmH_2O		
P_{plat}, cmH_2O		
PEEP, cmH_2O		

P_{insp} (if pressure control) , cmH_2O		
$EtCO_2$, mmHg		
FiO_2, %		
P/F ratio		
SpO_2, %		
Metabolic and ABG parameters		
pH		
$PaCO_2$, mmHg		
PaO_2, mmHg		
HCO_3^-, mmoL/L		
Lactate, mmoL/L		
SaO_2, %		

**n(%) or median (IQR).*
Abbreviations: .

Table 3. Primary and secondary safety outcomes				
	Permissive LPV	**Conventional LPV**	**Estimate (95% CI)**	***P* value**
Primary outcome				
Overall RR mean difference, breaths/min			MD:	
Marginal means at pre-specified timepoints, breaths/min				
- day 0, hour 1			MD:	
- day 0, hour 2			MD:	
- day 0, hour 3			MD:	
- day 0, hour 4			MD:	
- day 0, hour 5			MD:	
- day 0, hour 6			MD:	
- day 1			MD:	
- day 2			MD:	
- day 3			MD:	
- day 4			MD:	
- day 5			MD:	
Secondary safety outcomes				
Unacceptable hypercapnia, n (%)			RD:	
Severe hypoxemia, n(%)			RD:	
Ventilator associated complications, n(%)				
- composite			RD:	
- air leaks			RD:	
- severe atelectasis			RD:	
- VAP			RD:	
- Acute cor pulmonale			RD:	

Figure 1. Proposed Figure 1

