Statistical Analysis Plan of the 'Automated Closed–loop versus Conventional Invasive Ventilation' trial (ACTiVE)

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INTRODUCTION

The ‘Automated Closed–loop versus Conventional Invasive Ventilation’ trial (ACTiVE) compares a fully automated closed–loop mode of ventilation to a conventional strategy of ventilation in intensive care unit (ICU) patients [1]. The primary objective of this study is to determine whether fully automated closed–loop mode of ventilation (‘automated’) is superior to a conventional ventilation strategy (‘conventional’) with regard to the number of ventilator–free days and alive at day 28. Enrollment of patients in ACTiVE already started and the study is planned to finish around the first trimester of 2025.

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 updated and finalized SAP of ACTiVE.

METHODS

Design

The protocol, with a detailed description of the study population, the two interventions and follow–up plan of ACTiVE was published before [1]. ACTiVE is registered in clinicaltrials.gov (study identifier NCT04593810) and is approved by the Institutional Review Board of the Amsterdam University Medical Centers, location Academic Medical Center, in Amsterdam, The Netherlands (2020_146). ACTiVE is an investigator–initiated international multicenter parallel pragmatic two–arm randomized clinical superiority trial, comparing a ventilation strategy with a fully automated closed–loop mode of ventilation ('automated') with a conventional ventilation strategy ('conventional') in ICU patients.

Randomization and blinding

Eligible patients are randomly allocated in a 1:1 ratio to the 'automated' or the 'conventional' strategy. The allocation sequence is computer–generated by an independent investigator using permuted blocks of different block sizes, with a maximum block size of eight and stratified per center. Randomization is performed by local investigators patient–by–patient employing a dedicated, password protected, SSL–encrypted website. Due to the nature of the intervention tested, blinding is not possible.

Outcomes

The primary outcome is the number of ventilator–free days and alive at day 28, defined as the number of days from day 1 to day 28 when the patient is alive and breathes without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. To calculate this endpoint all relevant data will be taken into account and collected, including all additional periods of ventilation during the first

28 days. In case of multiple extubations within day 28, only the last extubation will be considered for this endpoint. Patients who die before day 28 or are invasively ventilated for longer than 28 days are assigned to have zero ventilator–free days. The complete definition, as suggested [2], is shown in **Table 1**.

Secondary outcomes include (definition are described in **Table 1**):

- Quality of breathing in the first six hours, defined as the percentage of time spent within predefined zones of ventilation, analyzed breath–by–breath (definitions in **Table 1**) (in a subsample of patients from centers that can collect these data from an available communication port at the ventilator);
- Duration of ventilation in survivors;
- Incidence of new ARDS;
- Incidence of ventilator–associated pneumonia (VAP);
- Incidence of severe hypercapnia;
- Incidence of severe atelectasis, if a chest radiograph or other kind of imaging suitable for diagnosing atelectasis is obtained;
- Incidence of severe hypoxemia;
- Incidence of pneumothorax, if a chest radiograph or other kind of imaging suitable for diagnosing pneumothorax is obtained;
- Need for rescue strategies for severe hypoxemia or severe atelectasis;
- Incidence of extubation failure;
- ICU length of stay;
- Hospital length of stay;
- ICU mortality;
- Hospital mortality;
- 28–day mortality; and

- 90–day mortality.

Cleaning and closing of the database

The database will be locked as soon as all data are entered and all discrepant or missing data are resolved, after all efforts are employed to complete the database, 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 losses to follow–up for the primary outcome is anticipated. Complete–case analysis will be carried out for all the outcomes. However, if more than 5% of missing data is found for the primary outcome, a sensitivity analysis using multiple imputations and estimating–equation methods will be carried out. Multiple imputation will consider imputation models based on prognostic baseline and post-baseline variables under a missing at random assumption.

Sample size

The trial was designed to last until 1200 patients are enrolled. This number of patients was expected to be sufficient to show superiority of the 'automated' versus the 'conventional' strategy considering a difference of 1.5 in ventilator–free days at day 28, assuming a mean and common standard deviation in of 20 and 9, respectively [3,4], a two–sided alpha level of 5%, 80% of power, similar allocation of subjects to each group and corrected for 5% of dropouts.

Statistical analyses

All statistical analyses will be conducted on an intention–to–treat basis, with patients analysed according to their assigned treatment arms, except for cases lost to follow up or withdrawal of informed consent. In addition, a per–protocol analysis will be conducted. All analyses will be performed using a common two–sided superiority hypothesis test, with a significance level of 0.05 and presented with two–sided 95% confidence intervals. In addition to the unadjusted *p* values for secondary outcomes, a Holm–Bonferroni procedure will be applied to control for multiple testing [5]. Analyses will be performed using the software R (R Core Team, 2016, Vienna, Austria). A list of proposed tables and figures is in **Table 2**.

Trial profile

Patient flows will be represented in a CONSORT flowchart (**Figure 1).**

Baseline characteristics

A description of the baseline characteristics of the trial participants will be presented by treatment group (**Table 3**). Discrete variables will be summarized as numbers (%). Percentages will be calculated according to the number of trial participants for whom data are available. Where values are missing, the denominator will be stated in the table and no assumptions or imputations will be made. Continuous variables will be summarized by either means and standard deviations (SD) or medians and interquartile ranges (IQR), according to the observed distribution of the variable.

The ventilation strategies

The percentage of time with ventilation according to randomization over the first five days and the difference in ventilator variables among the groups from the pre–randomization until day five will be shown in line plots and compared using mixed–effect longitudinal models with patients and centers as random effect, the

variable of interest as the dependent variable and the moment of measurement, randomization group and an interaction of day and randomization group as fixed effects. Two *p* values will be reported: 1) *p* value for the group difference, reflecting the overall test for difference between groups across the five days; and 2) *p* values for the group x day interaction, evaluating if change over time differed by group. In addition, since it is expected that the baseline values will be similar between the groups, these will be exposed in the graphs but excluded from the models.

Daily ventilation variables and parameters will be reported according to pre–defined timeframes described in **Table 2**. Absolute differences between the groups with the respective 95% confidence interval will be calculated as mean difference from a mixed–effect linear model considering the centers as random effect to account for within–center clustering. All values will be calculated as mean from breath–by–breath data within the proposed timeframe. In addition, the highest will be reported.

Other daily characteristics

Daily variables, including sedation, transfusion and fluid therapy will be reported according to the description in **Table 2**. The percentage of patients under light sedation (defined as a RASS –2 to +1) and deep sedation (defined as a RASS –5 to –3) will be calculated and reported. Absolute differences between the groups with the respective 95% confidence interval will be calculated as mean differences from a mixed–effect linear model considering the centers as random effect to account for within–center clustering in continuous variables and as absolute differences derived from a generalized linear model considering a

binomial distribution with an identity-link and with centers as random effect to account for within–center clustering for categorical variables.

Primary outcome

The effect of 'automated' compared to 'conventional' ventilation on the ventilator–free days at day 28 will be presented as a common odds ratio, and presented as a two–sided 95% confidence interval calculated from a mixed-effect cumulative logistic model considering the centers as random effect to account for within–center clustering. Cumulative logistic models consider the ranking and ordinal structure of ventilator-free days. In this model, the cumulative log odds is modeled such that a parameter greater than 0 reflects an increase in the cumulative odds for the ventilator-free days outcome, which implies benefit. A potential advantage of this model is that, with multinomial sampling of independent subjects, the score test statistic from the model is similar to the Wilcoxon rank-sum test statistic [6], one of the most powerful tests to analyze ventilator-free days in a variety of scenarios [2]. This approach is being consistently used in trials in the critical care field [7,8]. To increase transparency, the data will be presented by group also as means ± standard deviations. Results will be presented in a table of outcomes (**Table 4**). A cumulative incidence plot will be used to plot the distribution of the outcome by group and with non-survivors coded as -1.

To support interpretation, a confidence distribution for the primary outcome using a normal approximation on the estimated log common odds ratio will be calculated [9]. The confidence distribution will be computed to provide the frequentist probability that the common odds ratio is greater than 1 [9]. In addition, the confidence distribution will be reported in a plot.

Secondary outcomes

The percentage of time spent in each ventilation zone and the maximum inspiratory pressure will be compared as the mean difference among the groups from a mixed-effect linear model considering the centers as random effect. Within the three comparisons of the ventilation zones, a Bonferroni correction for multiplicity will be applied and *p* value will be considered significant when < 0.017.

The effect of the intervention on binary outcomes will be assessed with absolute differences derived from a generalized linear model considering a binomial distribution with an identity-link and with centers as random effect to account for within–center clustering. The duration of ventilation in survivors, and the ICU– and hospital length of stay will be assessed with median difference from a mixed-effect median regression with centers as clustering effect. 28– and 90–day mortality will be compared using Kaplan–Meier curves, and hazard ratios with a 95% confidence interval will be calculated with (shared-frailty) Cox proportional hazard models with center included as frailty. The proportional hazard assumptions will be tested and alternative parametric survival models will be used if the proportionality assumption is not sustained. In addition, a Holm–Bonferroni correction to control the family–wise error rate to the *p* values for all 17 secondary outcomes will be done and presented in a Table.

Per–protocol analysis

The per–protocol analysis only considers those patients who were ventilated according to the originally allocated treatment study protocol. Patients will be included in the per–protocol analysis if receiving the correct mode of ventilation (INTELLiVENT-ASV when randomized for automated ventilation and conventional ventilation or any form or ‘semi–automated’ ventilation when

randomized for conventional ventilation) for more than 80% of the ventilation time for the first five days of ventilation after randomization.

Additional analysis

As additional analyses, the effect of the intervention on primary and secondary outcomes will be re–estimated using mixed–effect models incorporating adjustment for age, gender, prognostic score as well as for any observed baseline differences. These models will incorporate the underling distribution of each outcome as described above.

Subgroup analysis

The homogeneity of treatment effects on the primary outcome across subgroups will be examined via a test for treatment–by–subgroup interaction in the cumulative logistic model irrespective of whether there is evidence of a treatment effect. Results will be summarized by subgroup and presented as common odds ratio with two–sided 95% confidence intervals. Lack of a significant interaction will imply that the results are consistent across subgroups and that the overall effect estimated are the most appropriate estimates of treatment effect within each subgroup. The results will be presented in a forest plot with a solid line of reference in the number 1 and a dashed line of reference in the overall effect. The following subgroups will be assessed:

- Non–surgical vs. surgical admission;
- Neurologic vs. non-neurologic;
- Cardiac arrest vs. non–cardiac arrest;
- Hypoxemic respiratory failure ($PaO_2/FiO_2 \leq 200$) vs. non hypoxemic respiratory failure ($PaO_2 / FiO_2 > 200$);
- Body mass index > 30 kg/m^2 vs. body mass index ≤ 30 kg/m^2;

- Higher severity of illness vs. lower severity of illness (defined by the median of the severity score documented for the patient).

SUMMARY

ACTiVE is an investigator–initiated international multicenter parallel pragmatic two–arm randomized clinical superiority trial. This trial is comparing a ventilation strategy with ‘automated’ mode of ventilation with a ventilation strategy with ‘conventional’ mode in 1200 adults who are expected to need invasive ventilation beyond the first 24 hours. The primary outcome is ventilator–free days and alive at day 28. The here reported SAP was updated and finalized before completion of enrollment.

REFERENCES

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Table 1 – Definitions of secondary outcomes

Outcomes	Definition
Ventilator–free days at day 28	Start time: day of randomization (the same as the day of intubation due to the strict time for inclusion). Timeframe: 28 days. Successful extubation: > 24 hours without reintubation in a 28–day survivor. Interval reintubation: counted from the day of the last successful extubation if there were repeated intubation episodes in the first 28 days. Non–invasive ventilation: not counted. Tracheostomy: same as above (> 24 hours off positive pressure ventilation). 28–day non–survivors: 0 ventilator–free days even if extubated in the period. Death after 28 days: censored and considered the duration of ventilation only.
Percentage of time spent within predefined zones of ventilation for the first six hours	Percentage of time, measured in hours, spent in three pre–defined zones of ventilation. This analysis will take into account breath–by–breath data. The zones are: • Critical: if V_T ≥ 12 mL/kg PBW **OR** P_{max} ≥ 36 cmH_2O **OR** 51 ≤ $etCO_2$ < 25 mmHg **OR** SpO_2 < 85%; or • Acceptable: if 8 < V_T < 12 mL/kg PBW **AND/OR** 31 ≤ P_{max} < 36 cmH_2O **AND/OR** 25 ≤ $etCO_2$ < 31 mmHg or 46 ≤ $etCO_2$ < 51 mmHg **AND/OR** SpO_2 ≥ 98% or 85 ≤ SpO_2 < 93%; or • Optimal: if V_T ≤ 8 mL/kg PBW **AND** P_{max} < 31 cmH_2O **AND** 31 ≤ $etCO_2$ < 46 mmHg **AND** 93 < SpO_2 < 98% or SpO_2 ≥ 93% if FiO_2 ≤ 40%. If any of the options of the *critical* zone is present, the breath will be classified as *critical*. If all of the options of the *optimal* zone are present, the breath will be classified as *optimal*. If not in the *optimal* or in the *critical*, the zone is *acceptable*. The missing in any of the variables will be treated as following: • If all parameters are missing the zone is missing; or • If some parameters are missing but any of the available is within the *critical* zone, zone is *critical*; or • If some parameters are missing but any of the available is not within the *critical* zone, zone is missing.
Duration of ventilation in survivors	Duration, in days, between intubation and successfully extubation, defined as a patient breathing without invasive assistance of the mechanical ventilator 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.
Incidence of new ARDS	According to the Berlin definition[a] Only ARDS occurring after the first 48 hours of randomization will be considered and the degree of severity will be reported. ARDS can only be diagnosed once.
Incidence of VAP	New or progressive radiographic infiltrate 48 hours after randomization with a positive sputum culture plus at least one of the following:

	• Temperature > 38.5ºC; and/or • Leukocytosis (> 10,500 cells/mm3) or leucopenia (< 4,000 cells/mm3) Only VAP occurring after the first 48 hours of randomization will be considered and it can only be diagnosed once.
Incidence severe hypercapnia	$PaCO_2$ > 7.33 kPa (55 mmHg) combined with a pH < 7.35. Any severe hypercapnia occurring after the randomization will be considered.
Incidence of severe atelectasis	At least complete lobar atelectasis of a lung determined on chest radiograph or chest CT by a radiologist. Any severe atelectasis occurring after the randomization will be considered.
Incidence of severe hypoxemia	PaO_2 < 7.3 kPa (< 55 mmHg). Any severe hypoxemia occurring after the randomization will be considered.
Incidence of pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiograph or other kind of imaging suitable for diagnosis pneumothorax and with an intercostal catheter inserted. It can be scored twice (if a drain is removed and then placed again). Any pneumothorax occurring after the randomization will be considered.
Need for rescue strategies for severe hypoxemia or severe atelectasis	Need of one of the following: • Recruitment maneuvers (defined as increase of inspiratory pressure or the level of PEEP for at least 40 seconds); and/or • Prone positioning; and/or • Bronchoscopy (performed with indication to open atelectasis or when the pulmonologist noticed that he/she has removed sputum plugs during bronchoscopy). Any need for rescue occurring after the randomization will be considered and the maneuvers will be reported as a collapsed composite of need for rescue and also individually.
Incidence of extubation failure	Need of reintubation within 24 hours of extubation.
ICU length of stay	Number of days from randomization till ICU discharge. Counted from the day of the last ICU discharge if there were repeated readmissions.
Hospital length of stay	Number of days from randomization till hospital discharge.
ICU mortality	Any death occurring during ICU stay.
Hospital mortality	Any death occurring during hospital stay.
28–day mortality	Any death occurring during the first 28 days after randomization.
90–day mortality	Any death occurring during the first 90 days after randomization.

ARDS: acute respiratory distress syndrome; VAP: ventilator–associated pneumonia; ICU intensive care unit

[A] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.

Table 2 – List of proposed tables and figures

	Description
Main paper	
Table 1	Baseline characteristics of the included patients
Table 2	Primary and secondary outcomes
Figure 1	Participant flow diagram
Figure 2	Clinical outcomes for patients in the automated and conventional groups *A four panels figure showing: A) Cumulative distribution of ventilator-free days at day 28 in a cumulative proportion for each study group by day; B) Ventilator-free days at day 28 as horizontally stacked proportions by study group; C) Kaplan–Meier curve for the 28–day survival in both groups; and D) Kaplan–Meier curve for the 90–day survival in both groups.* *For panel C and D a hazard ratio and 95% confidence interval calculated from a (shared-frailty) Cox proportional hazard model will be presented.*
Figure 3	Subgroup analysis *A forest plot showing the common odds ratio and two–sided 95% confidence intervals with p value for interaction calculated via a test for treatment–by–subgroup interaction in the cumulative logistic model. A solid line of reference in the number 1 and a dashed line of reference in the overall effect will be shown.*
Online Supplement	
eTable 1	Zones of ventilation used to define the safety of ventilation
eTable 2	Additional baseline characteristics
eTable 3	Ventilatory variables in the first day of ventilation *Data is the mean of all measurements in each period and shown at the randomization, 1 hour, 3 hours, 6 hours, 12 hours and 24 hours*
eTable 4	Ventilatory variables in the first three days of ventilation *Data is the mean of all measurements in each period and shown at day 01, 02 and 03*
eTable 5	Daily ventilatory variables, vital signs and arterial blood gases in the first three days after randomization
eTable 6	Daily sedation, fluids and transfusion
eTable 7	Multiplicity adjustment for secondary outcome analyses *A table showing the observed p values for all the secondary outcomes and ordered from the lower until the higher and the corrected p values using a Holm–Bonferroni correction*
eTable 8	Primary and secondary outcomes after adjustment for baseline variables *Re–estimation of the effect of the intervention on primary and secondary outcomes using mixed–effect models incorporating adjustment for age, gender, prognostic score as well as for any observed baseline differences. These models will incorporate the underling distribution of each outcome as described in the secondary outcomes section.*
eFigure 1	Management of patients according to the allocated arm
eFigure 2	Mean tidal volume, PEEP, maximum airway pressure and driving pressure over the first day of ventilation *Line graph with hour 0, 1, 3, 6, 12 and 24 on the horizontal axis and the ventilator variables on the vertical axis with the mean in the period shown by treatment group. The mean will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.* *First day of ventilation defined as the first 24 hours after randomization. 12 and 24 hours when available.*
eFigure 3	Highest tidal volume, PEEP, maximum airway pressure and driving pressure over the first day of ventilation *Line graph with hour 0, 1, 3, 6, 12 and 24 on the horizontal axis and the ventilator variables on the vertical axis with the highest value in the period shown by treatment group. The highest value will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.* *First day of ventilation defined as the first 24 hours after randomization. 12 and 24 hours when available.*
eFigure 4	Mean tidal volume, PEEP, maximum airway pressure and driving pressure over the first five days of ventilation

	Line graph with day 1 to 5 on the horizontal axis and the ventilator variables on the vertical axis with the mean in the period shown by treatment group. The mean will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.
eFigure 5	Highest tidal volume, PEEP, maximum airway pressure and driving pressure over the first five days of ventilation *Line graph with day 1 to 5 on the horizontal axis and the ventilator variables on the vertical axis with the highest value in the period shown by treatment group. The highest value will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
eFigure 6	Mean respiratory rate, FiO_2, SpO_2 and $etCO_2$ over the first day of ventilation *Line graph with hour 0, 1, 3, 6, 12 and 24 on the horizontal axis and the ventilator variables on the vertical axis with the mean in the period shown by treatment group. The mean will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
eFigure 7	Highest respiratory rate, FiO_2, SpO_2 and $etCO_2$ over the first day of ventilation *Line graph with hour 0, 1, 3, 6, 12 and 24 on the horizontal axis and the ventilator variables on the vertical axis with the highest value in the period shown by treatment group. The highest value will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
eFigure 8	Mean respiratory rate, FiO_2, SpO_2 and $etCO_2$ over the first five days of ventilation *Line graph with day 1 to 5 on the horizontal axis and the ventilator variables on the vertical axis with the mean in the period shown by treatment group. The mean will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
eFigure 9	Highest respiratory rate, FiO_2, SpO_2 and $etCO_2$ over the first five days of ventilation *Line graph with day 1 to 5 on the horizontal axis and the ventilator variables on the vertical axis with the highest value in the period shown by treatment group. The highest value will be calculated based on breath–by–breath data and the data points will be reported with the 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period.*
eFigure 10	Confidence distribution for the primary outcome *Confidence distribution of the estimated common odds ratio of the primary outcome of Automated versus Conventional ventilation constructed using a normal approximation.* *A, The full confidence distribution of the estimated common odds ratio, with the dashed vertical line indicating the median value and the area highlighted in tan indicating the 95% confidence interval. The orange area is related to a common odds ratio lower than 1 (i.e., the intervention is associated with a lower number of ventilator-free days at day 28 vs standard care). The dotted line at a common odds ratio of 1 indicates no treatment effect. The figure demonstrates that the confidence probability that Automated ventilation is associated with a greater number of ventilator-free days at day 28 (to any extent) compared with Conventional ventilation is XX.X%.* *B, The cumulative confidence distribution of the estimated common odds ratio, with the y-axis corresponding to the confidence the common odds ratio is greater than or equal to the value on the x-axis. The blue-gray area indicates a beneficial intervention (i.e., common odds ratio greater than 1). The dashed vertical line indicates the median.*
eFigure 11	Percentage of breaths in pre–defined zones of ventilation and according to each parameter *Bar plot showing the percentage of total breaths measured in the proposed zones of ventilation*
eFigure 12	Heat map showing the ventilator zone in the first day of ventilation *Heat map showing ventilation zones every 2 hours. The zones will be given a numeric values (1 for optimal, 2 for acceptable and 3 for critical) and then all breaths within every two hours will be summarized using the mean and plotted in the heat map, with green for optimal, yellow for acceptable and red for critical*
eFigure 13	Heat map showing the ventilator zone in the first five days of ventilation *Heat map showing ventilation zones from day 1 to 5. The zones will be given a numeric values (1 for optimal, 2 for acceptable and 3 for critical) and then all breaths within every day will be summarized using the mean and plotted in the heat map, with green for optimal, yellow for acceptable and red for critical*

Table 3 – Baseline characteristics of the patients

	Automated (*n* =)	Conventional (*n* =)
Age, years		
Female sex		
BMI, kg/m^2		
BMI > 30 kg/m^2		
Prognostic score		
APACHE IV		
SAPS II score		
SOFA score		
Sepsis		
Hypoxemic respiratory failure		
Tobacco use		
Never		
Current		
Previous		
Former		
Reason of ICU admission		
Planned surgery		
Emergency surgery		
Medical		
Reason of intubation		
Airway protection		
Cardiac arrest		
Planned postoperative ventilation		
Depressed level of consciousness		
Respiratory failure		
Other		
Hours ventilated before randomization		
Ventilatory variables at randomization		
Mode of ventilation		
INTELLiVENT-ASV		
Pressure–controlled		
Volume–controlled		
SIMV (pressure or volume)		
Pressure support		
Other		
Tidal volume, mL/kg PBW		
Plateau pressure, cmH_2O		
Maximum airway pressure, cmH_2O		
Respiratory rate, bpm		
PEEP, cmH_2O		
Driving pressure, cmH_2O		
FiO_2		
Arterial blood gas at randomization		
PaO_2 / FiO_2, mmHg		
PaO_2 / FiO_2 ≤ 200 mmHg		
$PaCO_2$, mmHg		
Arterial pH		
SpO_2, %		
$etCO_2$, mmHg		

BMI: body mass index; SAPS: Simplified Acute Physiology Score; LIPS: Lung Injury Prediction Score; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit; ARDS: Acute Respiratory Distress Syndrome; PBW: predicted body weight; bpm: breaths per minute; PEEP: positive end-expiratory pressure

Table 4 – Primary and secondary outcomes

	Automated (*n* =)	Conventional (*n* =)	Effect Estimate (95% CI)	*p* value
Primary outcome				
Ventilator–free days at day 28			Common odds ratio	---
Median (IQR)				
Secondary outcomes				
Percentage of time spent in ventilation zones for the first 6 hours				
Critical			Mean difference	*
Acceptable			Mean difference	*
Optimal			Mean difference	*
Duration of ventilation in survivors, days			Median difference	---
Median (IQR)				
Acute respiratory distress syndrome			Absolute difference	---
Ventilator–associated pneumonia			Absolute difference	
Severe hypercapnia			Absolute difference	---
Severe atelectasis			Absolute difference	---
Severe hypoxemia			Absolute difference	---
Pneumothorax			Absolute difference	---
Need for rescue strategies			Absolute difference	---
Recruitment maneuvers			Absolute difference	---
Prone positioning			Absolute difference	---
Bronchoscopy for atelectasis			Absolute difference	---
Extubation failure			Absolute difference	
Length of stay				---
Intensive care unit			Median difference	---
Median (IQR)				
Hospital			Median difference	---
Median (IQR)				
Mortality				---
Intensive care unit			Absolute difference	---
Hospital			Absolute difference	---
28–day			Hazard ratio	---
90–day			Hazard ratio	---

* Bonferroni correction ($p < 0.017$ considered significant)

MODIFICATIONS FROM THE ORIGINAL ANALYSIS PLAN

ANALYSIS	ORIGINAL PLAN (*Trials* 2022;23:348-57)	UPDATE IN THE SAP (Closed in August 7, 2024)	INCLUDED IN THE NEW SAP (Updated in January 12, 2025)
Quality of breathing	Time spent within predefined zones of ventilation in a time frame of 24 h early after start of invasive ventilation	Percentage of time spent within predefined zones of ventilation in a time frame of 6 hours after randomization	---
Maximal inspiratory pressure	Maximal inspiratory pressure within 72 hours of extubation	It was impossible to collect the data in a reliable fashion	---
Pneumothorax definition	No need for an intercostal catheter	Needed of an intercostal catheter inserted to be coded as pneumothorax	---
Confidence distribution	Not described.	Not described.	To support interpretation, a confidence distribution for the primary outcome using a normal approximation on the estimated absolute difference will be calculated. The confidence distribution will be computed to provide the frequentist probability that the absolute difference is less than 0.10 In addition, the confidence distribution will be reported in a plot.

PROPOSED FIGURE 1