Effect of Automated Closed-Loop Ventilation vs Protocolized Conventional Ventilation on Ventilator-Free Days in Critically Ill Adults – statistical reanalysis plan of the ACTiVE trial using a Bayesian framework

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1. Purpose

The aim of this reanalysis is to use a Bayesian framework to complement the frequentist results of the ACTiVE trial [1], characterize the range of plausible treatment effects and assess posterior probabilities of benefit, harm and clinical equivalence of the treatment effect.

2. Materials and Methods

2.1 Study Type

Post hoc Bayesian re-analysis of the ACTiVE trial. The ACTiVE trial was registered at www.clinicaltrials.gov (NCT NCT04593810). The study protocol of the original study was approved by the Institutional Review Board of the Academic Medical Center, Amsterdam, The Netherlands, and subsequently published [2].

2.2 Design of the original trial

ACTiVE was an investigator-initiated, international, multicenter, parallel, randomized control, superiority, clinical trial conducted in 7 ICUs in The Netherlands and Switzerland. It included adults under invasive mechanical ventilation for less than 1 hour in the ICU and expected to require invasive mechanical ventilation for 24 hours or longer. Two ventilation strategies were compared. Patients randomized to the “closed-loop ventilation” group received mechanical ventilation via the INTELLiVENT adaptive support ventilation (ASV) mode throughout the intervention period (from randomization to extubation, 28 days or death); patients assigned to the “conventional ventilation” group received mechanical ventilation with volume- or pressure-control mode or pressure-support ventilation with protective settings adjusted by clinicians. Primary endpoint was the number of ventilator-free days at day 28 (VFD-28) after randomization and sample size was powered on demonstrating superiority. Secondary endpoints included ventilation quality, duration of invasive ventilation among survivors, ICU and hospital length of stay, ICU and hospital mortality, and mortality at day 28 and day 90.

2.3 Data management

The ACTiVE database is protected and de-identified. Data are stored in archives of the Academic Medical Center, Amsterdam, The Netherlands.

2.4 Outcomes

The primary outcome of this analysis will be the primary outcome of the main trial, ventilator-free days at day 28 (VFD-28), defined as the number of days that a patient was alive and free of invasive ventilation, calculated from the moment of randomization, if the period of unassisted breathing lasted at least 24 consecutive hours. Patients who died or received invasive ventilation for more than 28 days were considered to have 0 VFD-28. The secondary outcomes will be key secondary outcome of the main trial, 28-day mortality and duration of ventilation among survivors.

2.5 Sample Size

All patients included in the ACTiVE trial will be analyzed.

2.6 Missing values management

Complete-case analysis.

2.7 Analysis Plan

The primary analysis will be based on the modified intention to treat population, where all the patients will be included and analyzed by the treatment group to which they were randomized, except for withdrawals. Difference of treatment effect between the two groups will be assessed at an individual patient-level data. Estimates will be obtained by fitting a hierarchical Bayesian cumulative logistic regression model for VFD-28 as an ordinal outcome, a hierarchical Bayesian logistic regression model for 28-day mortality as a dichotomous outcome, and a hierarchical Bayesian linear regression model for ventilation duration as a

continuous outcome. The randomization group will be entered in the model as a fixed effect and hospitals as random effects. The effect of the intervention on VFDs will be reported as odds ratio (OR) with 95% Credible Interval (95%CrI). The cumulative log odds will be modelled such that a parameter greater than 0 (or an OR > 1) reflects an increase in the cumulative odds for VFD-28, which implies benefit. The model will assume proportional effects across the ordinal VFDs scale. The effect of the intervention on 28-day mortality will be reported as OR with 95%CrI, and P(OR<1) will be considered as probability of benefit. The effect of the intervention on ventilation duration will be reported as mean difference (MD) with 95%CrI, and P(MD < 0) will be considered as probability of benefit. All analysis will be performed using R (R Core Team, 2016, Vienna, Austria).

2.8 Priors definition

Previously published recommendations on Bayesian analysis will be followed for defining priors, as well as the methodology from studies applying a Bayesian framework in related clinical fields [3–7].

For primary and secondary outcomes, we will adopt a neutral, a pessimistic and an optimistic prior informed by the available literature. To enhance the sensitivity of our analysis, we will incorporate an additional prior derived from an online survey eliciting intensive care physicians' opinions and a priori knowledge on the effect of INTELLiVENT-ASV.

2.8.1 Derivation of the literature-based priors

We informed our literature-based priors from a recent Cochrane systematic review and metanalysis investigating the clinical efficacy of closed-loop ventilation systems [8]. We then identified three RCTs [9–11] that enrolled ICU patients comparable to those in the ACTiVE trial, randomized to INTELLiVENT-ASV versus conventional ventilation strategies (**Table 1**). We

prioritized information derived from studies investigating INTELLiVENT-ASV to align with the ACTiVE trial, and to account for the substantial differences between INTELLiVENT-ASV and ASV modes (e.g., QUICK-WEAN algorithm, closed-loop monitoring of SpO_2 and $EtCO_2$).

The meta-analysis by Rose et al. concluded, with moderate certainty of evidence, that closed-loop systems probably reduce the duration of mechanical ventilation compared with non-automated systems (relative reduction 24%, 95% confidence interval [CI] 18%–30%) and probably result in little or no difference in mortality (risk ratio 0.94, 95% CI 0.82–1.07) [8]. In a subgroup analysis, INTELLiVENT-ASV was associated with a 16% reduction in ventilation duration (95%CI 7% to 24%). Accordingly, there is reasonable prior evidence supporting a modest reduction in ventilation duration and probably no mortality benefit with INTELLiVENT-ASV compared with non-automated ventilation strategies.

To date, VFD-28 was reported as the primary outcome in the ACTiVE trial [1] and as a secondary outcome in the EASiVENT study [11]. Both studies found no difference in VFD-28 between groups. Accordingly, the neutral prior will be normally distributed and centered on no effect (OR = 1; log[OR] = 0), with moderate strength such that 95% of the prior probability lies within the range 0.5 ≤ OR ≤ 2. Therefore, the neutral prior is defined as:

$$\log(OR_{VFD-28}) = Normal(0, 0.35^2).$$

Optimistic and pessimistic priors will be centered on a small benefit (OR = 2; log[OR] = 0.7) and a small harm (OR = 0.5; log[OR] = −0.7), respectively, with a standard deviation (σ) so that each prior assigns a 30% probability to the opposite effect direction. Accordingly, these priors will be considered weakly informative.

$$Optimistic: \log(OR_{VFD-28}) = Normal(0.7, 1.34^2),$$

$$Pessimistic: \log(OR_{VFD-28}) = Normal(-0.7, 1.34^2).$$

No studies evaluating INTELLiVENT-ASV have demonstrated either beneficial or harmful effects on mortality. Therefore, priors for the 28-day mortality outcome will be defined as follows.

The neutral prior will be normally distributed and centered on no effect (OR = 1; log[OR] = 0), with moderate strength such that 95% of the prior probability lies within the range 0.5 ≤ OR ≤ 2:

$$\log\left(OR_{MORT-28}\right) = Normal(0, 0.35^2);$$

Optimistic prior is normally distributed and centered at beneficial effect with weak strength and σ to retain a 30% probability of harm. The mean effect is informed based on the evidence of the trial by *Bialais et al.* (OR for mortality at day 28 = 0.44) [10]:

$$\log\left(OR_{MORT-28}\right) = Normal(-0.82, 1.56^2);$$

Pessimistic prior is normally distributed, centered at harmful effect and weak (σ to retain a 30% probability of benefit). The mean effect is informed based on the evidence of the trial by *Arnal et al.* (OR for mortality at day 28 = 1.44) [12]:

$$\log(OR_{MORT-28}) = Normal(0.36, 0.7^2).$$

For the ventilation duration (VD) outcome, we will account for the moderate evidence suggesting a reduction in duration with INTELLiVENT-ASV. The neutral prior will be normally distributed and centered on no effect (mean difference [MD] = 0), with weak strength such as 95% of the prior probability lies within the range −2 ≤ MD ≤ 2. Therefore, the neutral prior is defined as:

$$MD_{VD} = Normal(0, 1.02^2);$$

The optimistic prior is normally distributed and centered at a moderate reduction in ventilation duration. The mean difference is informed by *Bialais et al*. [10] with σ to retain moderate strength and a 15% probability of harm:

$$MD_{VD} = Normal(-2.5, 2.41^2).$$

The pessimistic prior is normally distributed and centered at a small increase ventilation duration in the INTELLiVENT-ASV group with weak strength to represent the current evidence. The mean effect is informed by *Arnal et al.* [12], and σ is selected to retain a 30% probability of benefit:

$$MD_{VD} = Normal(1, 1.91^2);$$

All priors are reported in **Figure 1** and **Table 2**.

2.8.2 Description of the ACTiVE survey

The final survey contained open and closed-ended questions and was designed for completion within 10 minutes. It comprised 43 items organized into 3 main sections: 1) Participants' General Information; 20) Effect on general intensive care unit (ICU) population; and 3) Effect on prespecified subgroups. It was administered to health-care professionals directly involved in the management of critically ill patients between 18-11-2025 and 09-12-2025 via the Castor CDMS Case Report Form. Participation was entirely voluntary. Prior to commencing the survey, invited participants were informed via an online presentation regarding the study procedures, objectives and data management practices. The purpose of the survey was to obtain opinions about the effect of INTELLiVENT-ASV on commonly used endpoints in clinical ventilation studies of intensive care patients. Questions refer to a mixed population of critically ill patients requiring mechanical ventilation for more than one day. Participants full name was used to compile the participants' list and immediately afterwards

removed from the database. The analysis was carried out in a deanonymized dataset without the participants' name. The final cohort included 59 participants (**Table 2**).

2.8.3 Derivation of the survey priors

Primary and secondary outcomes in the general ICU population

We assumed that our survey data reflect the prevailing opinion on the use of INTELLiVENT-ASV in mechanically ventilated ICU patients and can therefore be treated as consensus information to inform a prior distribution. Consistent with this assumption, the survey-derived prior should be centered on the aggregated effect estimate implied by participants' responses regarding the difference between INTELLiVENT-ASV and non-automated ventilator modes in the target population. In addition, the prior's strength should not be specified a priori; instead, it should be determined directly by the uncertainty in participants' opinions. For VFD-28, we specified a Normal survey prior:

$$\log(OR_{VFD\text{-}28}) \sim \text{Normal}(\mu, \sigma^2).$$

After checking variables distribution plots, we computed:

1- the median absolute difference (MedD) in VFD-28 between groups, calculated from the expected VFD-28 with INTELLiVENT-ASV and with conventional ventilation as reported by the survey participants:

$$MedD_{VFD_{28}} = median(VFD28_{INTELLiVENT-AS} - VFD28_{conventional\ ventilation});$$

2- the standard deviation of the absolute difference in VFD-28 between groups, back transforming the elicited upper (*U*) and lower (*L*) bounds of the 95%CI:

$$SD_{VFD_{28}} = \frac{mean(U - L)}{2 * 1.96};$$

3- the standard deviation of the VFD-28 distribution in the target population as the standard deviation of VFD-28 in the conventional ventilation group of the ACTiVE trial, $SD_{\text{VFD-28,target population}}$.

Applying the Cohen's D method, we computed:

1- the standardized mean difference (SMD) in VFD-28 between groups conditional to the dispersion of VFD-28 in the target population (i.e., $SD_{\text{VFD-28,target population}}$):

$$SMD_{VFD-} = \frac{MD_{VFD-28}}{\text{SD}_{VFD-28,target\ population}},$$

2- The standardized standard deviation of the VFD-28 difference between group conditional to the dispersion of VFD-28 in the target population (i.e., $SD_{\text{VFD-28,target population}}$):

$$StdSD_{VFD-28} = \frac{SD_{VFD-}}{\text{SD}_{VFD-\ \ ,target\ population}}.$$

We transformed our $SMD_{\text{VFD-28}}$ and $StdSD_{\text{VFD-28}}$ to the log-odds scale and compute μ and σ via the formula [13]:

$$log(OR) \approx \frac{\pi}{\sqrt{3}} * SMD.$$

Therefore:

$$\mu \approx 0.15\ ;$$

$$\sigma \approx 0.2.$$

Our survey prior for VFD-28 will be:

$$\log(OR_{\text{VFD-28}}) \sim \text{Normal}(0.15, 0.2^2),$$

corresponding to an OR of 1.16 with 95%CrI 0.79 to 1.72.

For the mortality at day 28 outcome, we specified a Normal survey prior:

$$\log(OR_{28\text{-day mortality}}) \sim \text{Normal}(\mu, \sigma^2).$$

To derive the prior μ on the log odds ratio (OR) scale, we defined it as:

$$\mu = \left(\frac{\frac{P_T}{1 - P_T}}{\frac{P_C}{1 - P_C}} \right),$$

where P_T and P_C represent mortality probabilities in the INTELLiVENT-ASV and conventional ventilation group elicited from participants in the ACTiVE survey.

From each of 59 participants (*i*), considered independent and equally weighted, we obtained:

- a point estimate of control mortality P_C;
- a point estimate of intervention mortality P_T;
- the estimated absolute risk difference (RD):

$$RD_i = P_{T,i} - P_{C,i};$$

For each participant *i*, we computed the log(OR) :

$$\log(OR)_i = logit\left(P_{T,i}\right) - logit\left(P_{c,i}\right),$$

and the prior μ was defined as the median across participants:

$$\mu = median(\log(OR)_i) = 0,$$

corresponding to an OR of 1.

To derive the prior standard deviation (σ), we used the 95%CrI expected upper (*L*) and lower bounds (*U*) provided by participants.

Subsequently, uncertainty elicited on the risks scale must be modelled on the log-odds scale. To do so, we applied a Monte Carlo simulation method, and we propagated within-expert uncertainty in RD. For each participant *i,* we assumed that RD followed a normal distribution, and we simulated:

$$RD_i \sim Normal(RD_{center,i}, \sigma^2_{RD,i}),$$

where

$$RD_{center,i} = \frac{U_i - L_i}{2},$$

and

$$\sigma_{RD,i} = \frac{U_i - L_i}{3.92}.$$

We then generated 1000 independent draws *m* and compute for each draw the mortality risk for treated patient conditional on each participant's elicited mortality risk in the conventional ventilation group:

$$P^m_{T,i} = P_{C,i} + RD^m_{center,i},$$

we simulated each participant mortality OR on the log-odds scale:

$$\log(OR)^m_i = logit(P^m_{T,i}) - logit(P^m_{C,i}).$$

Finally, we pooled all simulated $\log(OR)^m_i$ across participants distribution and computed the σ survey prior as:

$$\sigma = SD(\log(OR)^m) = 0.35 .$$

Therefore, we will center our survey prior distribution to an OR of 1 (log(OR) = 0) with a SD of 0.35:

$$\log(OR_{28\text{-day mortality}}) = \text{Normal}(0, 0.35^2),$$

corresponding to an OR of 1 with 95%CrI 0.5 to 2.

For the duration of ventilation outcome (VD), we specified a Normal survey prior for the mean difference (MD):

$$MD_{VD} \sim \text{Normal}(\mu, \sigma^2).$$

After checking variables distribution plots, we derived μ as the median of the provided absolute difference of VD between INTELLiVENT-ASV and conventional ventilation groups:

$$\mu = -1;$$

we derived σ as the value corresponding to the 95% of the mass of the normal distribution of spanning between the median lower (*L*) and upper (*U*) bounds of the 95% CI provided by participants:

$$\sigma = \frac{U - L}{2 * 1.96} = 0.77$$

Therefore, we will center our survey prior distribution to a MD of -1 with a SD of 0.92:

$$MD_{VD} = \text{Normal}(-1, 0.77^2).$$

Primary outcome in prespecified subgroups

Responses in this section were recorded on a 5-point Likert scale:

1. Strong decrease in VFDs (conventional ventilation is better);
2. Slight decrease in VFDs (conventional ventilation is a bit better);
3. No difference;

4. Slight increase in VFDs (INTELLiVENT-ASV is a bit better);
5. Strong decrease in VFDs (INTELLiVENT-ASV is better).

We analyzed the 5-point Likert scale as an ordinal variable (**Table 3, Figure 2**). Cumulative agreement with the question reported in each item was classified as follow: "conventional ventilation is better" if >50% of respondents selected "Strong decrease in VFDs (conventional ventilation is better)" or "Slight decrease in VFDs (conventional ventilation is a bit better)"; "INTELLiVENT-ASV is better" if >50% selected "Slight increase in VFDs (INTELLiVENT-ASV is a bit better)" or "Strong decrease in VFDs (INTELLiVENT-ASV is better"; "no difference" if >50% selected "No difference" or if neither "conventional ventilation is better" nor 'INTELLiVENT-ASV is better" exceeded 50%.

Subsequently, a neutral, optimistic or pessimistic survey prior was assigned to each subgroup based on the cumulative agreement elicited by survey's participants (**Table 4**). All survey priors were specified with weak strength [3].

2.8.4 Heterogeneity prior

Being the ACTiVE trial a multicentric trial conducted within two countries, we will expect a mild degree of heterogeneity between hospitals thus the random effect prior will be moderately informative and defined as:

$$\tau = \text{Half} - \text{Normal}(0, 0.5^2).$$ [14] (**Figure 3**).

2.9 Thresholds for superiority and Range of Practical Equivalence

The intervention will be considered superior if the posterior probability exceeds 95% for all of the following: an odds ratio (OR) > 1 for VFD-28, an OR < 1 for 28-day mortality, and a mean difference (MD) < 0 for duration of mechanical ventilation (**Table 2**).

A region of practical equivalence (ROPE) will be defined as ORs between 0.9 and 1.1 for both VFD-28 and 28-day mortality, representing effect sizes considered clinically negligible. No ROPE will be defined for the ventilation duration outcome given the current lack of clinically meaningful reference points on a continuous scale. The probability of clinically meaningful benefit will be reported as the posterior probability mass lying above the ROPE for VFD-28 and below the ROPE for 28-day mortality. The probability of clinically meaningful harm will be reported as the posterior probability mass lying below the ROPE for VFD-28 and above the ROPE for 28-day mortality.

2.10 Subgroup analyses

We will perform different subgroup analyses for the primary and secondary outcomes in the same subgroups of the original protocol of ACTiVE. This will be done fitting Bayesian logistic regressions models incorporating an interaction term between treatment and subgroups. We will adopt priors derived from the ACTiVE survey for VFD-28 and neutral, weak priors for the secondary outcomes (**Table 4, Table 5, Table 6**).

We will assess the following subgroups:

- Type of admission (medical vs surgical);
- Neurological reason for ICU admission (yes vs. no);
- Admission for cardiac arrest (yes vs. no);
- PaO_2/FiO_2 at enrolment (≤200 vs. >200);
- Body mass index (>30 vs. ≤30);
- Severity of illness (high vs low).

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371 **Tables and Figures**

Table 1. Summary of studies to inform literature-based priors			
	INTELLiVENT-ASV		
Study	*Bialais et al.*	*Arnal et al.*	*EASiVENT (unpublished)*
Year	2016	2018	2022
Setting	Belgium, medico-surgical ICU	France, mixed ICU	Portugal, mixed ICU
Methods	Single center RCT	Single center RCT	Single center RCT
Sample size	80 patients (42 intervention arm, 38 control arm)	60 patients (30 per arm)	62 patients (intervention arm, control arm)
Inclusion criteria	- age ≥18 years; - expected duration of MV ≥48 hours; - BMI <40 kg/m^2	- age ≥18 years; - less than 24 hours of invasive MV; - expected duration of MV ≥48 hours.	- age ≥21 years; - weight greater than 40 kg; - under invasive ventilation; - expected to be mechanically ventilated after enrollment for at least 24 hours; - agrees to not participate in other interventional research studies involving mechanical ventilation for the duration of study; - signature of the informed consent by the patient or his/her next-of-kin according to country or state regulation.
Exclusion criteria	- ventricular assistance with intra-aortic balloon; - presence of broncho-pleural fistula; - $EtCO_2$, $PaCO_2$ gradient >15 mmHg; - pregnancy; - adults under guardianship; - people deprived of freedom; - inclusion in another study.	- brain injury with GCS <6; - presence of broncho-pleural fistula; - chronic or acute dyshemoglobinemia; - ventilation drive disorders; - moribund patient; - “Do Not Resuscitate” order; - Chronic respiratory disease requiring home ventilation; - mechanical ventilation for planned surgery; - pregnancy; - lack of informed consent; - participation in another clinical trial.	- fulfilling weaning criteria according to the weaning procedure of the ICU; - Need for "rescue therapy" (e.g: ECMO); - brain death status; - respiratory drive disorder (Cheyne-Stokes breathing) - arterial hypoxia due to a non-pulmonary condition (right-to-left shunting due to congenital disease, hepato-pulmonary syndrome); - broncho-pleural fistula; - chronic or acute dyshemoglobinemia; - chronic respiratory failure requiring long term invasive ventilation; - moribund patient; - patient under guardianship, deprived of liberties; - any other condition, that in the opinion of the IoR/designee, would preclude informed consent (by the spouse/next of kin), make study participation unsafe, complicate interpretation of

			study outcome data, or otherwise interfere with achieving the study objectives; - low quality index on the SpO2 (Oxygen Saturation Measured by Pulse Oximetry) measurement; - patients already enrolled in the present study in a previous episode of acute respiratory failure; - high PaCO2 - ETCO2 gap (> 2.6 kPa or 19.5 mmHg) for > 3 hours; - patient tracheostomized at the time of inclusion; - patient ventilated with helium.
Intervention	INTELLiVENT-ASV	INTELLiVENT-ASV + QUICK WEAN	INTELLiVENT-ASV
Control	Conventional ventilation with PAC or PSV mode.	Conventional ventilation with VAC or PSV mode.	Conventional ventilation with non-automated modes.
Primary outcome	Time spent in non-optimal ventilation zones by study group	Total number of manual ventilation setting changes per subject by study group.	- Percentage of time spent in optimal ventilation range; - Percentage of time spent in sub-optimal range
Relevant outcomes for priors:			
Duration of Ventilation	Median days (IQR): - INTELLiVENT-ASV: 5.5 (11); - control: 8 (10); - p-value: 0.55.	Median days (Q1, Q3): - INTELLiVENT-ASV: 6 (3, 8); - control: 5 (3.5, 10) - p-value: 0.7.	Median days (Q1, Q3): - INTELLiVENT-ASV: 4.7 (3, 8.9); - control: 5.3 (3.9, 9.9); - p-value: >0.05.
Mortality	Total mortality, N(%): - INTELLiVENT-ASV: 10 (24%); - control: 16 (42%); - p-value: 0.08.	At day 28, N(%): - INTELLiVENT-ASV: 9 (23%); - control: 7 (35%); - p-value: 0.75.	At day 28, N(%): - INTELLiVENT-ASV: 7 (22.6%); - control: 11 (35.5%); - p-value: >0.05.
Ventilator-free days	Not reported.	Not reported.	At day 28, Median days (Q1, Q3): - INTELLiVENT-ASV: 18.5 (0, 24); - control: 18.5 (0-21); - p-value: 0.91.
Notes	Study sponsored by Hamilton Medical.	Study sponsored by Hamilton Medical..	Study sponsored by Hamilton Medical. Study terminated prematurely for business reasons.

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Table 2. Priors, superiority threshold and ROPE			
Variable	**VFD-28**	**28-day mortality**	**Ventilation duration**
Neutral prior	*Normal(0, 0.35^2)*	*Normal(0, 0.35^2)*	*Normal(0, 1.02^2)*
Optimistic prior	*Normal(0.7, 1.34^2)*	*Normal(-0.82, 1.56^2)*	*Normal(-2.5, 2.41^2)*
Pessimistic prior	*Normal(-0.7, 1.34^2)*	*Normal(0.36, 0.7^2)*	*Normal(1, 1.91^2)*
Survey prior	*Normal(0.15, 0.2^2)*	*Normal(0, 0.35^2)*	*Normal(-1, 0.77^1)*
Superiority threshold	*OR >1,* *Posterior probability ≥95%*	*OR <1,* *Posterior probability ≥95%*	*MD <0,* *Posterior probability ≥95%*
ROPE	*OR >9 & <1.1*	*OR >0.9 & ,1.1*	*Not defined*

Abbreviations: VFD-28, ventilator-free days at day 28; ROPE, region of practical equivalence; OR, Odds Ratio; MD, mean difference.

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Table 3. Summary table of the ACTiVE survey	
	Summary N = 59*
General information	
Professional role	
Intensivist	40 (69%)
Ventilation Practitioner	8 (14%)
Intensive Care Nurse	5 (8.6%)
Other	5 (8.6%)
Years of experience	12 (6, 20)
Hospital type	
University hospital	28 (48%)
Teaching hospital	17 (29%)
Peripheral hospital	13 (22%)
Hospital location	
the Netherlands	39 (66%)
Europe	20 (34%)
ICU beds	15 (12, 28)
Use of Hamilton ventilator	47 (80%)
Use of INTELLiVENT-ASV	37 (79%)
Years of experience with INTELLiVENT-ASV	2 (1, 5)
Percentage of patients ventilated with INTELLiVENT-ASV on average	25 (10, 65)
Effect on general ICU population	
Estimated VFDs in the INTELLiVENT-ASV group, days	21 (20, 23)
Estimated VFDs in the conventional ventilation group, days	21 (20, 21)
Estimated absolute difference in VFDs between groups, days	1 (0, 2)
Estimated 95% CI lower bond of VFDs difference, days	0 (-2, 1)
Estimated 95% CI upper bond of VFDs difference, days	4 (2, 5)
Estimated mortality rate in the INTELLiVENT-ASV group, %	30 (20, 31)
Estimated mortality rate in the conventional ventilation group, %	30 (20, 31)
Estimated risk difference in mortality between groups, %	0 (-2, 0)
Estimated 95% CI lower bond of mortality difference, %	0 (-3, 1)
Estimated 95% CI upper bond of mortality difference, %	5 (2, 8)
Estimated duration of ventilation in the INTELLiVENT-ASV group, days	4 (3, 7)
Estimated duration of ventilation in the conventional ventilation group, days	5 (4, 7)
Estimated absolute difference in duration of ventilation between groups, days	-1 (-2, 0)
Estimated 95% CI lower bond of ventilation duration difference, days	0 (-1, 1)
Estimated 95% CI upper bond of mortality difference, days	3 (2, 5)
Effect on subgroups	
Expected effect on VFDs of INTELLiVENT-ASV in medical ICU patients	
Strong increase in VFDs (INTELLiVENT-ASV is better)	4 (6.8%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	36 (61%)
No difference	18 (31%)
Slight decrease in VFDs (conventional ventilation is a bit better)	1 (1.7%)
Strong decrease in VFDs (conventional ventilation is better)	0 (0%)
Expected effect on VFDs of INTELLiVENT-ASV in surgical ICU patients	
Strong increase in VFDs (INTELLiVENT-ASV is better)	8 (14%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	32 (54%)
No difference	17 (29%)
Slight decrease in VFDs (conventional ventilation is a bit better)	2 (3.4%)
Strong decrease in VFDs (conventional ventilation is better)	0 (0%)
Expected effect on VFDs of INTELLiVENT-ASV in neurocritical patients	
Strong increase in VFDs (INTELLiVENT-ASV is better)	3 (5.1%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	20 (34%)
No difference	31 (53%)

Table 3. Summary table of the ACTiVE survey	
	Summary N = 59*
Slight decrease in VFDs (conventional ventilation is a bit better)	3 (5.1%)
Strong decrease in VFDs (conventional ventilation is better)	2 (3.4%)
Expected effect on VFDs of INTELLiVENT-ASV in patients with cardiac arrest	
Strong increase in VFDs (INTELLiVENT-ASV is better)	1 (1.7%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	25 (42%)
No difference	33 (56%)
Slight decrease in VFDs (conventional ventilation is a bit better)	0 (0%)
Strong decrease in VFDs (conventional ventilation is better)	0 (0%)
Expected effect on VFDs of INTELLiVENT-ASV in hypoxemic respiratory failure patients	
Strong increase in VFDs (INTELLiVENT-ASV is better)	9 (15%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	28 (47%)
No difference	12 (20%)
Slight decrease in VFDs (conventional ventilation is a bit better)	8 (14%)
Strong decrease in VFDs (conventional ventilation is better)	2 (3.4%)
Expected effect on VFDs of INTELLiVENT-ASV in patients with BMI > 30 kg/m2	
Strong increase in VFDs (INTELLiVENT-ASV is better)	6 (10%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	27 (46%)
No difference	21 (36%)
Slight decrease in VFDs (conventional ventilation is a bit better)	3 (5.1%)
Strong decrease in VFDs (conventional ventilation is better)	2 (3.4%)
Expected effect on VFDs of INTELLiVENT-ASV in patients with high severity of illness	
Strong increase in VFDs (INTELLiVENT-ASV is better)	6 (10%)
Slight increase in VFDs (INTELLiVENT-ASV is a bit better)	17 (29%)
No difference	23 (39%)
Slight decrease in VFDs (conventional ventilation is a bit better)	12 (20%)
Strong decrease in VFDs (conventional ventilation is better)	1 (1.7%)

**Continuous variables are presented as median (Q1, Q3), categorical variables as n(%).*
Abbreviations: ICU, Intensive Care Unit; ASV, Adaptive Support Ventilation; VFDs, Ventilator-Free Days; 95% CI, 95% Confidence Interval.

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Table 4. Survey priors for the VFD-28 subgroup analysis			
Subgroup	**Prior**	**Belief**	**Notes**
Type of admission	$log(\beta_{interaction}) \sim Normal(0.7, 1.34^2)$	Optimistic, weak	Retaining 30% harm
Neurocritical	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
Cardiac arrest	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
H-ARF	$log(\beta_{interaction}) \sim Normal(0.7, 1.34^2)$	Optimistic, weak	Retaining 30% harm
BMI >30 kg/m^2	$log(\beta_{interaction}) \sim Normal(0.7, 1.34^2)$	Optimistic, weak	Retaining 30% harm
High severity of illness	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)

Abbreviations: $\beta_{interaction}$, coefficient for interaction between treatment and subgroup; OR, Odds Ratio; H-ARF, hypoxemic acute respiratory failure; BMI, body mass index; 95%CI, 95% confidence interval.

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Table 5. Priors for the mortality at day 28 subgroup analysis			
Subgroup	**Prior**	**Belief**	**Notes**
Type of admission	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
Neurocritical	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
Cardiac arrest	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
H-ARF	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
BMI >30 kg/m^2	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)
High severity of illness	$log(\beta_{interaction}) \sim Normal(0, 1.4^2)$	Neutral, weak	Corresponding to OR 1 (95% CrI 0.25 to 4)

Abbreviations: $\beta_{interaction}$, coefficient for interaction between treatment and subgroup; OR, Odds Ratio; H-ARF, hypoxemic acute respiratory failure; BMI, body mass index; 95%CI, 95% confidence interval.

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Table 6. Priors for the duration of ventilation subgroup analysis			
Subgroup	**Prior**	**Belief**	**Notes**
Type of admission	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)
Neurocritical	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)
Cardiac arrest	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)
H-ARF	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)
BMI >30 kg/m^2	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)
High severity of illness	$\beta_{interaction} \sim Normal(0, 1.02^2)$	Neutral, weak	Corresponding to MD 0 (95%CrI -2 to 2)

Abbreviations: $\beta_{interaction}$, coefficient for interaction between treatment and subgroup; MD, Mean Difference; H-ARF, hypoxemic acute respiratory failure; BMI, body mass index; 95%CI, 95% confidence interval.

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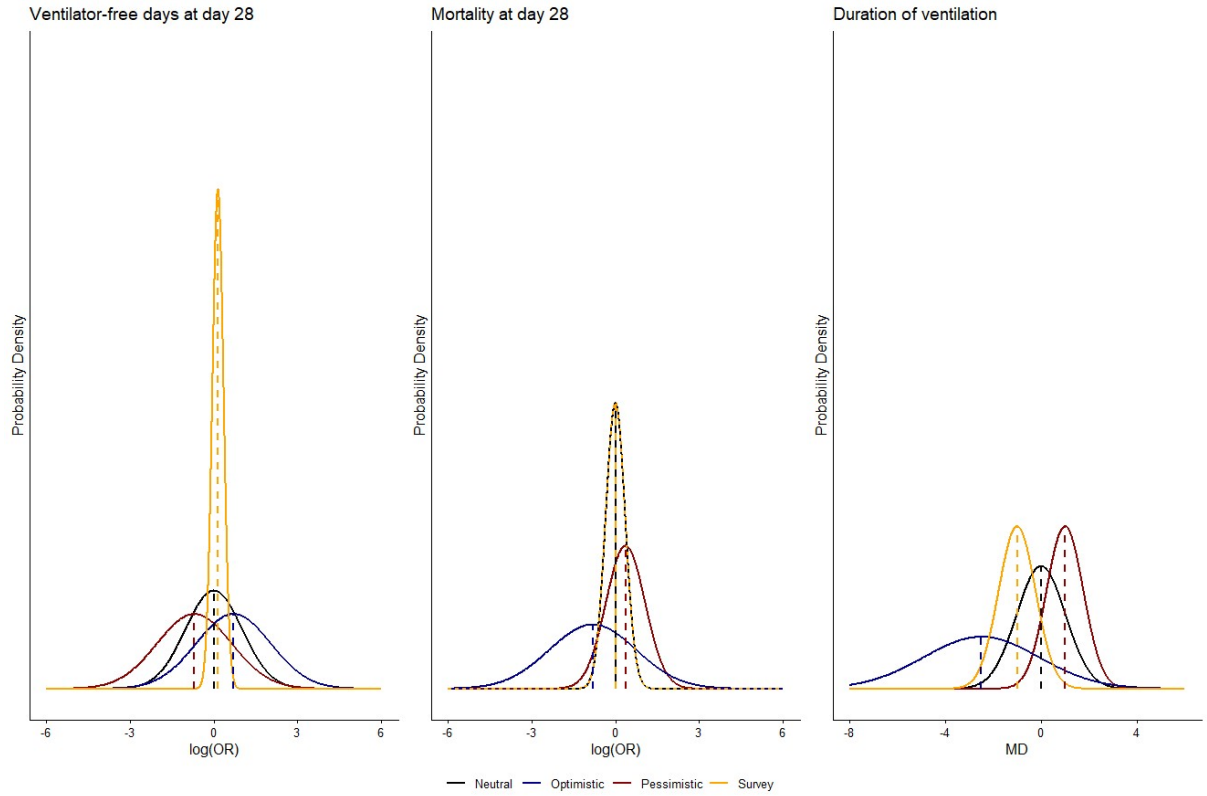
Figure 1. Priors' distribution



Abbreviations: OR, odds ratio; MD, mean difference.

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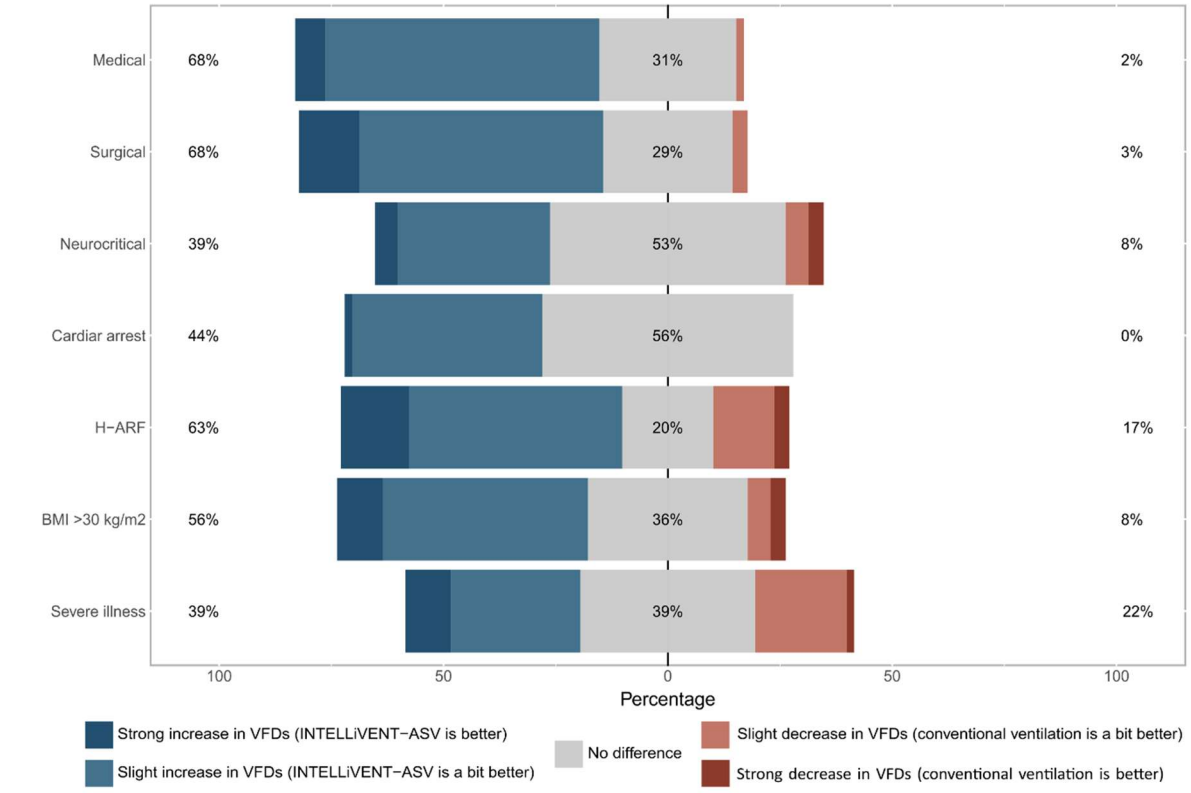
Figure 2. Distribution of Likert-scale responses per prespecified subgroup



Abbreviations: VFDs, ventilator-free days; ASV, Adaptive Support Ventilation; H-ARF, hypoxemic respiratory failure, BMI, body mass index.

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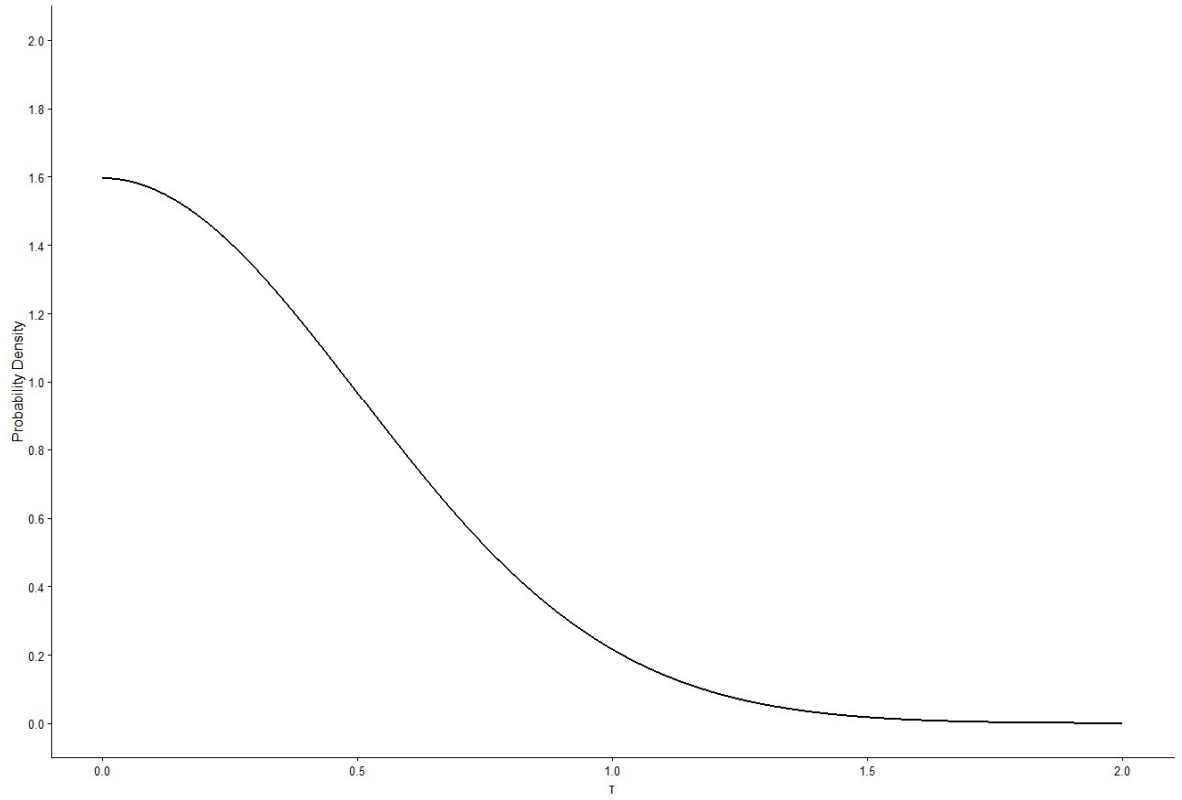
Figure 3. Heterogeneity prior



Abbreviations: τ, heterogeneity.

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