Effect of Automated Closed–loop Ventilation versus Conventional Ventilation on Duration and Quality of Ventilation (‘ACTiVE’) – protocol for a randomized clinical trial in intensive care unit patients

The ACTiVE* investigators for the PROVE network**

*‘Automated Closed–loop versus convenTional VEntilation on duration and quality of ventilation study’

**‘Protective Ventilation Network’ (www.provenet.eu)

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<thead>
<tr>
<th>Protocol ID</th>
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<tr>
<td>Short title</td>
<td>Automated versus conventional ventilation</td>
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<td>Version</td>
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<td>Head of Departments:</td>
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<td><em>Prof. dr. M.B. Vroom, Professor of Intensive Care</em></td>
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<td>Coordinating Investigator/Project leader and Principal Investigator:</td>
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<td><em>dr. J. Horn</em></td>
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## SIGNATURE SHEET OF STEERING COMMITTEE MEMBERS

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<th>Core Steering Committee Members</th>
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<td>Prof. dr. M.J. Schultz, MD PhD, Amsterdam University Medical Centers, location ‘AMC’; University of Amsterdam</td>
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<td>Prof. dr. A. Serpa Neto, MD MSc, Hospital Israelita Albert Einstein</td>
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<td>Prof. P. Pelosi, MD, IRCCS San Martino IST, University of Genoa</td>
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</tbody>
</table>
# TABLE OF CONTENTS

1. **INTRODUCTION AND RATIONALE** ................................................................. 11  
   1.1 Mechanical ventilation–associated lung and respiratory muscle injury  ... 11  
   1.2 Fully automated closed–loop ventilation ............................................. 11  
   1.3 Need for a randomized clinical trial .................................................. 11  
   1.4 The ACTiVE trial .............................................................................. 12  

2. **OBJECTIVES AND HYPOTHESIS** .................................................................. 13  
   2.1 Objectives ......................................................................................... 13  
      2.1.1 Primary objective ........................................................................ 13  
      2.1.2. Secondary objectives ............................................................... 13  
   2.2 Hypothesis ......................................................................................... 13  
      2.2.1 Primary hypothesis .................................................................... 13  
      2.2.2. Secondary hypotheses ............................................................. 13  

3. **STUDY DESIGN** ........................................................................................ 14  

4. **STUDY POPULATION** .................................................................................. 15  
   4.1 Population ........................................................................................ 15  
   4.2 Inclusion criteria ................................................................................ 15  
   4.3 Exclusion criteria ............................................................................... 15  
   4.4 Sample size ....................................................................................... 16  

5. **INTERVENTIONAL TREATMENT OF SUBJECTS** .................................. 17  
   5.1 Randomization .................................................................................. 17  
   5.2 INTELLiVENT–ASV .......................................................................... 17  
   5.3 Conventional ventilation .................................................................... 17  

6. **STANDARD TREATMENT OF SUBJECTS** ............................................. 19  
   6.1 Tracheostomy .................................................................................... 19  
   6.2 Sedation protocol .............................................................................. 19  
   6.3 Non–ventilatory management .............................................................. 20  
      6.3.1 Selective oropharyngeal– or digestive tract decontamination ....... 20  
      6.3.2 Thrombosis prophylaxis ............................................................... 20  
      6.3.3 Fluid regimens .......................................................................... 20  
      6.3.4 Nutrition ................................................................................... 20  

7. **METHODS** .................................................................................................. 21  
   7.1 Study parameters/endpoints ............................................................... 21  
      7.1.1 Main study parameter .................................................................. 21  
      7.1.2 Secondary study parameters ....................................................... 21  
   7.2 Study procedures ............................................................................... 22  
   7.3 Data collection .................................................................................... 22  
      7.4.1. Other data to be collected .......................................................... 23  
   7.5 Withdrawal of individual subject ........................................................ 24  
   7.6 Follow up of subject withdrawn from the study .................................. 24  
   7.7 Replacement of individual subjects when deferred consent could not be obtained .............................................................. 24  

8. **SAFETY REPORTING** ................................................................................. 25  
   8.1 Temporary halt for reasons of subject safety ...................................... 25  
   8.2 Secondary endpoints for safety ............................................................ 25  
   8.3 Data Safety Monitoring Board (DSMB) ............................................... 25
9. STATISTICAL ANALYSIS ........................................................................................................... 27
  9.1 General considerations ........................................................................................................ 27
  9.2 Primary study parameter ................................................................................................... 27
  9.3 Secondary study parameter(s) .......................................................................................... 28
  10.1 Regulation statement ....................................................................................................... 29
  10.2 Recruitment and consent ................................................................................................. 29
    10.2.1 Deferred consent ..................................................................................................... 29
    10.2.2 No deferred consent in patients who die before obtaining informed consent .......... 31
    10.2.3 Conclusion deferred consent .................................................................................. 31
    10.2.4 Ethical aspects ....................................................................................................... 31
  10.3 Benefits and risks assessment, group relatedness ............................................................ 32
    10.4 Compensation of injury ............................................................................................... 32
11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION .................. 33
    11.1 Handling and storage of data and documents .............................................................. 33
    11.2 Monitoring and Quality Assurance ............................................................................. 33
    11.3 Amendments .............................................................................................................. 33
    11.4 Annual progress report ................................................................................................ 33
    11.5 End of study report ...................................................................................................... 33
    11.6 Public disclosure and publication policy ......................................................................... 34
## ABBREVIATIONS AND DEFINITIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMC</td>
<td>Academic Medical Center</td>
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<tr>
<td>APACHE</td>
<td>Acute Physiology and Chronic Health Evaluation</td>
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<td>ARDS</td>
<td>Acute Respiratory Distress Syndrome</td>
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<tr>
<td>ASV</td>
<td>Adaptive Support Ventilation</td>
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<tr>
<td>AVG</td>
<td>General Data Protection Regulation (GDPR) in Dutch: Algemene verordening gegevensbescherming</td>
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<tr>
<td>BPS</td>
<td>Behavioral Pain Scale</td>
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<td>CCPOT</td>
<td>Critical Care Pain Observation Tool</td>
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<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
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<tr>
<td>ECMO</td>
<td>Extracorporeal Membrane Oxygenation</td>
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<tr>
<td>ETCO₂</td>
<td>End-Tidal Carbon Dioxide</td>
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<tr>
<td>FiO₂</td>
<td>Fraction of inspired Oxygen</td>
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<tr>
<td>GAMLSS</td>
<td>Generalized additive model for location scale and shape</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<tr>
<td>IQR</td>
<td>Interquartile ranges</td>
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<td>ISPOR</td>
<td>International Society for Pharmaco-economics and Outcomes Research</td>
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<tr>
<td>LOS</td>
<td>Length of Stay</td>
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<tr>
<td>MIP</td>
<td>Maximal Inspiratory Pressure</td>
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<td>METC</td>
<td>Medical Research Ethical Committee (MREC) in Dutch: Medische Ethische Toetsings Commissie</td>
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<tr>
<td>MV</td>
<td>Minute Ventilation</td>
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<tr>
<td>NICE</td>
<td>National Intensive Care Evaluation</td>
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<tr>
<td>NRS</td>
<td>Numeric Rating Scale</td>
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<td>PBW</td>
<td>Predicted Body Weight</td>
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<td>PEEP</td>
<td>Positive End–Expiratory Pressure</td>
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<tr>
<td>PCV</td>
<td>Pressure controlled ventilation</td>
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<td>PSV</td>
<td>Pressure support ventilation</td>
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<tr>
<td>P&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Maximum airway pressure</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>$P_{\text{peak}}$</td>
<td>Peak pressure</td>
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<tr>
<td>$P_{\text{plateau}}$</td>
<td>Plateau pressure</td>
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<tr>
<td>RCT</td>
<td>Randomized Clinical Trial</td>
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<tr>
<td>RR</td>
<td>Respiratory Rate</td>
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<td>SAEs</td>
<td>Serious Adverse Events</td>
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<td>SAPS</td>
<td>Simplified Acute Physiology Score</td>
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<tr>
<td>SBT</td>
<td>Spontaneous Breathing Trial</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SDD</td>
<td>Selective decontamination of the digestive tract</td>
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<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment score</td>
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<tr>
<td>SpO$_2$</td>
<td>Saturation of peripheral Oxygen</td>
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<td>Sponsor</td>
<td>The party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator; a party that provides funding for a study bus does not commission is not regarded as the sponsor, but referred to as a subsidizing party</td>
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<tr>
<td>VAP</td>
<td>Ventilator Associated Pneumonia</td>
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<td>VAS</td>
<td>Visual Analogue Scale</td>
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<td>VFD–28</td>
<td>Ventilator–free days and alive at day 28</td>
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<tr>
<td>VILI</td>
<td>Ventilation–induced Lung Injury</td>
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<tr>
<td>$V_T$</td>
<td>Tidal volume</td>
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<td>WGBO</td>
<td>Medical Treatment Agreement Act in Dutch: Medical Treatment Agreement Act: <em>Wet op de Geneeskundige Behandelovereenkomst</em></td>
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<tr>
<td>WMO</td>
<td>Medical Research Involving Human Subjects Act in Dutch: <em>Wet medisch-wetenschappelijk onderzoek met mensen</em></td>
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SUMMARY

Rationale
INTELLiVENT–adaptive support ventilation (ASV) is a fully automated closed–loop mode of ventilation available on commercial ventilators. Evidence for benefit of INTELLiVENT–ASV in comparison to non–automated ventilation is lacking.

Objective
To compare INTELLiVENT–ASV to non–automated ventilation in critically ill patients.

Hypothesis
INTELLiVENT–ASV shortens ventilation duration and improves quality of breathing.

Study design
International multicenter randomized clinical trial.

Study population
Consecutively intubated and ventilated adult ICU patients with an anticipated duration of ventilation of at least 24 hours.

Procedure
Patients are randomly assigned in a 1:1 ratio to INTELLiVENT–ASV or non–automated ventilation.

Study endpoints
The number of ventilator–free days and alive at day 28 (primary), breath–by–breath analysis of ventilation parameters and variables, duration of ventilation in survivors, ICU and hospital length of stay, ICU– and hospital mortality, 28– and 90–day mortality, proportion of patients developing pulmonary complications, and proportion of patients developing respiratory muscle weakness.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness
Differences in burden and risks of the two compared ventilation strategies are not expected. Both modes are currently variably used as part of standard care in the participating centers. No other interventions are performed. Collection of demographic data, ventilation data and outcome data causes no harm to patients.
1. INTRODUCTION AND RATIONALE

1.1 Mechanical ventilation–associated lung and respiratory muscle injury

Critically ill patients who are admitted to the intensive care unit (ICU) often need invasive ventilation. Invasive ventilation can be lifesaving, but also has the potential to harm lung tissue\(^1,2\) and injure respiratory muscles\(^3,4\). The risk of ventilator–induced lung injury (VILI) is reduced by tidal volume (VT) limitation\(^5,6\), appropriate setting of positive end–expiratory pressure (PEEP)\(^7,8\) and a low driving pressure (ΔP)\(^9,10\). Early use of supported modes of ventilation combined with spontaneous breathing trials (SBTs) for timely recognition of extubation readiness, decreases the risk of respiratory muscle injury\(^3,4\).

Due to rapidly changing conditions in individual critically ill patients, proper evaluation and adjustment of ventilator settings is an extremely challenging and time-consuming task for healthcare professionals. Consequently, ventilator settings are often suboptimal\(^11-15\), increasing the risk of VILI and respiratory muscle injury. This may result in a longer duration of invasive ventilation, and therefore stay in the ICU\(^16\).

1.2 Fully automated closed–loop ventilation

Ventilator manufacturers have developed diverse types of fully automated closed–loop modes of ventilation. Such modes continuously monitor patients’ status and adapt to their needs, using algorithms to automatically adjust ventilator settings and switch to spontaneous breathing. INTELLiVENT–adaptive support ventilation (ASV) is one of the most sophisticated forms of a fully automated closed–loop ventilation and acts in both active and passive patients, thus covering ventilation from intubation and start of ventilation to extubation. This mode is available on ventilators produced by Hamilton (Hamilton Medical, Bonaduz, Switzerland), which are broadly used worldwide.

1.3 Need for a randomized clinical trial

Small–sized clinical trials have shown INTELLiVENT–ASV to be a safe and feasible ventilation mode in diverse groups of critically ill patients\(^17-21\). However, so far clinical trials have been underpowered to demonstrate the superiority of INTELLiVENT–ASV with respect to patient–centered outcomes. In addition, INTELLiVENT–ASV has only been compared to non–automated ventilation in patients that are generally seen as ‘easy to ventilate and wean from invasive ventilation’. Robust evidence for clinical benefit of fully automated closed–loop ventilation in critically ill ICU patients is actually
missing. Sufficiently–sized, randomized clinical trials using patient–centered outcomes, like duration of ventilation, are explicitly awaited by the ICU community.

1.4 The ACTiVE trial

The ‘Effect of Automated closed–loop ventilation versus Conventional VEntilation on duration and quality of ventilation’ (‘ACTiVE’) study is an international multicenter randomized clinical trial. This study will be among the first to test the hypothesis that fully automated closed–loop ventilation is superior to non–automated ventilation with respect to ventilation duration and quality of breathing in critically ill ICU patients.
2. OBJECTIVES AND HYPOTHESIS

2.1 Objectives

2.1.1 Primary objective
The primary objective of this trial is to compare INTELLiVENT–ASV with non-automated ventilation in critically ill intensive care unit (ICU) patients with respect to ventilation duration and quality of breathing.

2.1.2. Secondary objectives
Secondary objectives are to compare INTELLiVENT–ASV with non-automated ventilation with respect to ventilation duration in survivors, length of stay in ICU and hospital, ICU and hospital mortality, 28– and 90–day mortality, development of pulmonary complications, and development of respiratory muscle weakness.

2.2 Hypothesis

2.2.1 Primary hypothesis
INTELLiVENT–ASV shortens ventilation duration and improves quality of breathing.

2.2.2. Secondary hypotheses
INTELLiVENT–ASV shortens ventilation duration in survivors, shortens length of stay in ICU and hospital, reduces mortality, and decreases the risk of developing pulmonary and respiratory muscle complications.
3. STUDY DESIGN
The ACTiVE study is an international, multicenter, superiority randomized clinical trial in critically ill, intubated and ventilated adult ICU patients with an anticipated duration of ventilation of at least 24 hours.
4. STUDY POPULATION

4.1 Population
The ACTiVE study will recruit 1,200 intensive care unit (ICU) patients with an anticipated duration of ventilation of at least 24 hours. Patients are recruited in the ICUs of hospitals in the Netherlands (~900 patients) and Italy (~300 patients). The list of participating centers is enclosed in APPENDIX III.
Patients are screened for eligibility and randomized within one hour after start of invasive ventilation in the ICU.

4.2 Inclusion criteria
In order to be eligible to participate in this study, patients must meet all of the following criteria:
- admission to one of the participating ICUs;
- intubated and receiving invasive ventilation; and
- anticipated duration of ventilation of at least 24 hours

4.3 Exclusion criteria
Patients who meet any of the following criteria are excluded from participation:
- age below 18 years;
- patients with suspected or confirmed pregnancy;
- invasive ventilation > 1 hour in the ICU;
- invasive ventilation > 6 hours in the operating room or emergency department directly preceding the current ICU admission;
- participation in another interventional trial using similar endpoints;
- after recent pneumectomy or lobectomy;
- morbid obesity (body mass index > 40 kg/m²);
- premorbid restrictive pulmonary disease (evidence of chronic interstitial infiltration on chest radiographs);
- unreliable pulse oximetry, e.g., patients with carbon monoxide poisoning;
- any neurologic diagnosis that can prolong duration of mechanical ventilation, e.g., Guillain–Barré syndrome, high spinal cord lesion or amyotrophic lateral sclerosis, multiple sclerosis, or myasthenia gravis;
- patients receiving or planned to receive veno–venous, veno–arterial or arterio–venous extracorporeal membrane oxygenation (ECMO);
- previous randomized in this study; or
• no informed consent

4.4 Sample size
The sample size is based on the hypothesis that INTELLiVENT–ASV will shorten ventilation duration by 1.5 days with no changes in mortality rate. Based on previously performed studies in which the mean number of ventilator–free days and alive at day 28 (VFD–28) was 20 (±9) days,22,23 a sample of 1,200 patients (600 in each treatment group) is needed to have beta of 80% power and a two–tailed alpha of 0.05, to detect a mean between–group difference of 1.5 VFD–28, allowing a dropout rate of 5%. By including 1,200 patients, this study will be sufficiently powered to detect differences in the co–primary endpoint, which is quality of breathing.
5. INTERVENTIONAL TREATMENT OF SUBJECTS

5.1 Randomization
Within one hour of start of ventilation in the ICU, patients are randomly assigned in a 1:1 ratio to INTELLiVENT–ASV or non–automated ventilation (henceforth called ‘conventional ventilation’). Randomization will be stratified by center. As soon as possible after randomization, but within a maximum of 72 hours, deferred consent is obtained from the legal representative of the patient.

5.2 INTELLiVENT–ASV
In patients who are randomized to INTELLiVENT–ASV, the ventilator is switched to this fully automated mode as soon possible, which is directly after the results of the first arterial blood gas analysis have become available (usually within the hour after start of ventilation in the ICU). The sensors for end–tidal carbon dioxide (ETCO2) and pulse oximetry (SpO2) are connected and activated in the ventilator. Patient’s gender and height are set on the ventilator and patient condition is chosen if applicable (i.e., ‘acute respiratory distress syndrome (ARDS)’, ‘chronic hypercapnia’ and ‘traumatic brain injury’). If needed, the targets zones for ETCO2 and SpO2 are adjusted. The default alarm limits are accepted.

It is advised to enable QuickWean, a function designated to automate and standardize the weaning process, in all patients. The use of the automated Spontaneous Breathing Trial (SBT) function is left to the discretion of the clinician. Each SBT result will be used to check for extubation readiness.

Patients are extubated if standard extubation criteria are fulfilled, i.e., normal body temperature, patient awake and responsive/cooperative, adequate cough reflex, adequate oxygenation and hemodynamically stable.

5.3 Conventional ventilation
Patients who are randomized to conventional ventilation, will be ventilated with a mode that is not fully automated. Thus, conventional ventilation consists of standard volume controlled (VCV) or pressure controlled ventilation (PCV), and pressure support ventilation (PSV), depending on patient’s activity. None of the following semi or fully automated modes of ventilation is allowed at any time: Neurally Adjusted Ventilatory Assist (NAVA) (Maquet, Getinge Group, Rastatt, Germany), SmartCare/PS (Dräger, Lubeck, Germany) or Proportional Assist Ventilation (PAV) (Maquet, Getinge Group, Rastatt, Germany).
In all patients who receive assist ventilation (i.e., VCV or PCV), three times a day it should be checked whether the patient can accept supported ventilation (i.e., PSV); this should also be tried when the patient shows respiratory muscle activity during assist ventilation, or in case of patient–ventilator asynchrony.

Patients can be subjected to SBTs using either a T–piece or ventilation with minimal support (pressure support level < 10 cm H2O). An SBT is deemed successful when the following criteria are met for at least 30 minutes, i.e., respiratory rate < 35/min, peripheral oxygen saturation > 90%, increase < 20% of heart rate and blood pressure, and no signs of anxiety and diaphoresis. Each SBT result will be used to check for extubation readiness.

Patients are extubated if standard extubation criteria are fulfilled, i.e., normal body temperature, patient awake and responsive/cooperative, adequate cough reflex, adequate oxygenation and hemodynamically stable.
6. STANDARD TREATMENT OF SUBJECTS

6.1 Tracheostomy

Early tracheostomy has no advantage over late tracheostomy\textsuperscript{24}. Therefore, tracheostomy is only to be performed on strict indications and preferably not earlier than 10 days after intubation. Tracheostomy can be considered in case of:

- expected duration of ventilation > 14 days;
- prolonged or unsuccessful weaning;
- airway protection, i.e., Glasgow Coma Scale < 7 with inadequate swallow or cough reflex and retention of sputum;
- severe ICU–acquired weakness, based on clinical judgement;
- repeatedly failed extubations; or
- pre–existent diminished pulmonary reserves

Weaning with a tracheostomy follows recommendations follows the local guideline; a suggested scheme for unassisted breathing with a tracheostomy is described in APPENDIX I.

6.2 Sedation protocol

Sedation strategies also follow local guidelines. Use of analgo–sedation over hypno–sedation is favored, as is use of bolus over continuous infusion of sedating agents, and the use of sedation scores.

Nurses should determine the level of sedation at least three times per day. The adequacy of sedation in each patient is evaluated using a Richmond Agitation Sedation Scale (RASS)\textsuperscript{25,26}. The goals of sedation are to minimize agitation, stress and fear; to reduce oxygen consumption (heart rate, blood pressure and minute volume are measured continuously); and to reduce physical resistance to and fear of daily care and medical examination. Patient comfort, and not sedation, is the primary goal.

Level of pain is determined using scales such as Numeric Rating Scale (NRS), Visual Analogue Scale (VAS), Critical Care Pain Observation Tool (CCPOT) or Behavioral Pain Scale (BPS).
6.3 Non–ventilatory support

6.3.1 Selective digestive tract decontamination
If consistent with national protocol, selective decontamination of the digestive tract (SDD) should be applied in all patients who are expected to need ventilation for longer than 48 hours, and/or are expected to stay in ICU for longer than 72 hours27.

6.3.2 Thrombosis prophylaxis
Thrombosis prophylaxis is indicated for all patients who are not treated with anticoagulants, e.g., for therapeutic reasons or systemic prophylaxis because of an implanted device or extra–corporal circulation like for renal replacement therapy. Thrombosis prophylaxis will be given according to local guidelines.

6.3.3 Fluid regimens
A fluid balance targeted at normovolemia and a diuresis of ≥ 0.5 ml/kg/hour should be maintained. Crystalloid infusions are preferred over infusions of other fluids.

6.3.4 Nutrition
A hypo–caloric, protein–rich diet (1.2–1.7 gr/kg bodyweight /24 hours) should be started as soon as possible after ICU admission. Enteral nutrition with a feeding gastric tube is preferred over intravenous feeding. If stomach retention occurs, a duodenal tube can be used if administration of prokinetic drugs is not sufficient, according to local guidelines. When optimal protein intake cannot be reached within 4 days, additional parenteral nutrition can be started.
7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter

The primary endpoint is the number of ventilator–free days and alive at day 28 (VFD–28), defined as the number of days from day 1 to day 28 the patient is alive and breathes without assistance of the mechanical ventilator, if the period of unassisted breathing lasted at least 24 consecutive hours (APPENDIX I).

The co–primary endpoint is quality of breathing, defined as time spent within predefined zones of optimal ventilation. These zones will be determined by cut–off values of ventilation variables based on assumptions found in literature. Different zones will be specified for certain patient categories (e.g., patients with Acute Respiratory Distress Syndrome (ARDS), or patients with chronic obstructive pulmonary disease). The ventilation variables will be measured breath–by–breath directly after randomization. This analysis will only be performed in patients of whom we can safely and correctly collect this dense data, depending on whether there are a sufficient number of serial ports to connect a data recorder.

7.1.2 Secondary study parameters

Secondary study parameters include:

- duration of ventilation in survivors;
- intensive care unit (ICU) length of stay (LOS);
- hospital LOS;
- ICU mortality;
- hospital mortality;
- 28–day mortality;
- 90–day mortality;
- incidence of development of ARDS (APPENDIX I);
- incidence of severe hypoxemia (APPENDIX I);
- incidence of severe hypercapnia (APPENDIX I);
- incidence of severe atelectasis, if a chest radiograph is obtained (APPENDIX I);
- incidence of pneumothorax, if a chest radiograph or other kind of imaging suitable for diagnosing pneumothorax is obtained (e.g., electric impedance tomography, chest computer tomography, chest radiography or lung ultrasound) (APPENDIX I);
- incidence of pneumonia (APPENDIX I);
• incidence of use of rescue therapies for severe hypoxemia or severe atelectasis:
  o recruitment maneuver (APPENDIX II)
  o prone positioning
  o bronchoscopy for opening atelectasis
• incidence of extubation failure (reintubation within 24 hours); and
• maximal inspiratory pressure (MIP) within 24 hours after extubation
• quality of life at day 28 (APPENDIX IV);

7.2 Study procedures
Patients in participating ICUs are screened and randomized within 1 hour after start of ventilation in the ICU. Demographic data of all screened patients, regardless of meeting the enrolment criteria, will be recorded (age, gender, expected duration of ventilation > or < than 24 hours). The appropriate ventilation mode is turned on based on randomization.

    Every day, at fixed time points (see 7.3), data will be collected, and if a serial port is available, breath–by–breath ventilation data are captured from the ventilator.

7.3 Data collection
• On admission and within the first 24 hours:
  o gender and age (male + years);
  o height and weight (cm + kg);
  o reason for ICU admission;
  o reason for ventilation support;
  o cause of respiratory failure; and
  o the APACHE II or IV score and/or the SAPS II
• On admission, and every day at a fixed time point until day 28:
  o intubation status (if extubated: time of extubation);
  o tracheostomy status (if tracheostomized: time of tracheostomy); and
  o invasiveness of ventilation (invasive, non–invasive, high–flow or intermittent ventilation via tracheostomy)
• Every day at a fixed time point until day 28, and at day 90:
  o location (in ICU, hospital, other facility, or home); and
  o life status (alive or deceased)
• Every day at a fixed time point until day 28 or discharge from ICU, whatever comes first:
o pulmonary complications
  ▪ ARDS (yes or no) (APPENDIX II);
  ▪ severe hypoxemia (yes or no) (APPENDIX II);
  ▪ severe hypercapnia (yes or no) (APPENDIX II);
  ▪ pneumonia (yes or no) (APPENDIX II);
  ▪ severe atelectasis (yes or no) (APPENDIX II);
  ▪ pneumothorax (yes or no) (APPENDIX II);
  ▪ rescue therapies for severe hypoxemia or severe atelectasis (yes or no);
    • recruitment maneuver (APPENDIX II)
    • prone positioning
    • bronchoscopy for opening atelectasis
  o ICU–acquired weakness (yes or no) (APPENDIX II); and
  o ICU–delirium (yes or no) (APPENDIX II)
• Within 24 hours after extubation
  o extubation failure; and
  o maximal inspiratory pressure (MIP)
• At day 28
  o quality of life (APPENDIX IV)

7.4.1. Other data to be collected
• Continuously for the first 24 hours:
  o breath–by–breath ventilation parameters and variables, including:
    ▪ saturation of peripheral oxygen levels (SpO₂) (%);
    ▪ end–tidal carbon dioxide levels (ETCO₂) (kPa);
    ▪ tidal volume (VT) (ml); and
    ▪ airway pressures (cm H₂O)
• Directly before and 1 hour after randomization and every day at a fixed time point
  around 08:00, major ventilation and clinical data until day 5 and basic ventilation
  and clinical data until day 28, including:
  o Ventilation data
    ▪ mode of ventilation
    ▪ VT
    ▪ positive end–expiratory pressure (PEEP) (cm H₂O);
- maximum airway pressure (Pmax) or plateau pressure (Pplateau) or peak pressure (Ppeak) (cm H₂O);
- level of pressure support (PS) above PEEP (cm H₂O);
- inspired fraction of oxygen (FiO₂) (%);
- set and measured respiratory rate (RR) (min⁻¹);
- percentage of minute ventilation (%MinVol);
- arterial pH;
- arterial partial pressure of oxygen (PaO₂) (kPa or mmHg);
- arterial partial pressure of carbon dioxide (PaCO₂) (kPa or mmHg);
- arterial bicarbonate (HCO₃⁻) (mmol/L);
- arterial saturation of oxygen (SaO₂) (%); and
- arterial lactate levels (mmol/L);

- Clinical data
  - Sequential Organ Failure Assessment score (SOFA) score;
  - daily cumulative fluid balance (ml);
  - transfusion of blood products (type and ml); and
  - cumulative dose of sedatives (mg)

- Every day at fixed time point until liberation from the ventilator:
  - extra–pulmonary infection, sepsis, re–operation, cardiac arrest;
  - duration of ventilation according to randomization (hours); and
  - if mode according to randomization is changed, rationale for adjustment

7.5 Withdrawal of individual subject

Subjects can leave the study at any time for any reason, if they wish to do so and without any consequences.

7.6 Follow up of subject withdrawn from the study

Patients withdrawn from the trial will not be subjected to follow up.

7.7 Replacement of individual subjects when deferred consent could not be obtained

A randomized subject will be replaced if deferred consent is not obtained after randomization and provisional inclusion of a patient. In the randomization log, these cases will be recorded without patient–specific data. The randomization subjects will be replaced in order to retain properly distributed randomization groups. In the sample size calculation, a dropout rate of 5 % has been considered.
8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the Medical Research Involving Human Subjects Act (WMO), the sponsor will suspend the trial if there is sufficient ground that continuation of the trial will jeopardize subject health or safety. The sponsor will notify the accredited Medical Research Ethical Committee (METC) without undue delay of a temporary halt including the reason for such an action. The trial will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 Serious Adverse Events and secondary endpoints for safety

In this study we compare two ventilation strategies that are currently widely used in standard care. For this reason, we are not expecting Serious Adverse Events (SAEs) related to the study. Furthermore, the study population consists of critically ill patients, with a high incidence of death or life–threatening events due to the severity of their illness (the hospital mortality in ventilated intensive care unit (ICU) patients is 21%\(^{12}\)). Therefore, we propose to report the secondary endpoints of this trial, which incorporate ventilation specific complications, in a line listing two times per year to the METC to monitor safety of both treatment strategies. The METC will receive a line listing of the secondary endpoints incorporating ventilation specific complications (see below). These endpoints will be specified per study arm in the line listing without disclosing the specific arms.

Those ventilation specific complications include:

- ICU mortality;
- incidence of Acute Respiratory Distress Syndrome (ARDS) (APPENDIX II);
- incidence of severe atelectasis (APPENDIX II);
- incidence of pneumothorax (APPENDIX II);
- incidence of pneumonia (APPENDIX II);
- incidence of severe hypoxemia (APPENDIX II); and
- incidence of severe hypercapnia (APPENDIX II);

8.3 Data Safety Monitoring Board (DSMB)

A DSMB will be installed to monitor safety and the overall conduct of the trial. The DSMB will compose of 4 individuals who will be invited, one of which will assigned as the chair.
• The DSMB will first meet after inclusion of the first 150 patients, approximately 6 months after the first patient is enrolled.
• Subsequent to this meeting, the DSMB will meet virtually every 6 months.
• The DSMB will review the overall status of the program, number of patients enrolled overall and, in each center, adherence to the protocol overall and by each center.
• The DSMB will monitor safety of both ventilation strategies by monitoring the secondary endpoints of ventilation specific complications.
• DSMB are still to be invited, this will be done as soon as the study protocol is approved by the IRB.

The report and/or advice of the DSMB will only be sent to the sponsor of the study, the Amsterdam University Medical Center (UMC), location ‘Academic Medical Center’ (‘AMC’). Should the sponsor decide not to fully implement the advice of the DSMB, the sponsor will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.
9. STATISTICAL ANALYSIS

9.1 General considerations
This is an international multicenter superiority randomized clinical trial comparing a fully automated closed-loop mode of ventilation to conventional ventilation in intensive care unit (ICU) patients expected to receive invasive ventilation for more than 24 hours.

The statistical analysis will be based on the intention-to-treat principle, with patients analyzed according to their assigned treatment arms, except for cases lost to follow-up, or patients who are withdrawn due to lack of deferred informed consent. In addition, we will conduct per-protocol analyses, which only considers those patients who completed the treatment according to the originally allocated protocol.

When appropriate, statistical uncertainty will be expressed by the 95% confidence levels. P-values of 0.05 will be used for statistical significance. Continuous distribution of the data will be assessed by visual inspection of histograms and normality tests. For the experimental and control arms, continuous normally distributed variables will be expressed by their mean and standard deviation or, when not normally distributed, as medians and their interquartile ranges. Categorical variables will be expressed as frequencies and percentages.

All statistical analyses will be described in full detail in a statistical analysis plan, which will be published before the database is locked and analysis starts. Analysis will be performed with the R version 3.3.2.

9.2 Primary study parameter
The primary outcome is the number of ventilator–free days and alive at day 28 (VFD–28) after ICU admission, which is a composite outcome measure that combines survival and duration of ventilation. The number of VFD–28 data will be presented as a median difference and a two-sided 95% confidence interval.

Since ventilator–free days is a highly skewed variable with a peak in 0 due to 28–day mortality, the mean ratio will be estimated using a generalized additive model for location scale and shape (GAMLSS) considering a zero–inflated beta distribution and using the delta method to estimate the confidence interval.

Additionally, Kaplan–Meier curves will be used to report time to freedom from mechanical ventilation; differences between groups will be compared with the log–rank tests. A subgroup analysis will be performed in order to assess whether there is a
differential effect on the primary outcome in elderly ICU patients and in patients with Acute Respiratory Distress Syndrome (ARDS).

9.3 Secondary study parameter(s)
Variables will be expressed as frequencies and percentages, means and standard deviations (SD), or medians and interquartile ranges (IQR) whenever appropriate (see paragraph 9.1).

Differences between groups in continuous variables will be analyzed with Student’s t-test or, if continuous data is not normally distributed, the Mann–Whitney U test will be used. Categorical variables will be compared with the Chi–squared test or Fisher’s exact test, as appropriate. Mortality rates and length of ICU and hospital stay will be compared using Kaplan–Meier mortality curves.

Quality of breathing will be analyzed as in a previous study by our group, in which INTELLiVENT–ASV was compared to conventional ventilation in the ICU following cardiac surgery28.
10. ETHICAL CONSIDERATIONS

10.1 Regulation statement
This trial will be conducted according to the principles of the Declaration of Helsinki as stated in the current version of Fortaleza, Brazil, 2013 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

10.2.1 Deferred consent
For this study we ask for deferred consent and we appeal to the emergency procedure for consent in medical research as stated in article 6, paragraph 4 of the WMO, as in two previously performed trials of ventilation in a similar patient cohort (PRotective VENTilation in Patients without ARDS at Start of Ventilation – PReVENT, a Randomized Controlled Trial’ (METC 2014_075) and ‘REstricted versus Liberal positive end–expiratory pressure in patients without Acute respiratory distress syndrome (RELAx) – a multicenter randomized controlled trial (METC 2017_074)), for reasons as explained below.

In patients admitted for ventilatory support to an intensive care unit (ICU), invasive ventilation is needed urgently in almost all cases. Consequently, ventilation starts right at ICU admission, or within the hour after admission. However, ventilator–related side–effects are seen after relatively short periods of ventilation, e.g., after ventilation during general anesthesia for surgery. For this reason, we consider it of utmost importance to set the ventilator according to the mode investigated in this study as soon as possible (i.e., within 1 hour after start of ventilation in the ICU). Any other strategy would largely reduce the validity of the results of this study.

Patients admitted for ventilatory support to the ICU are, without exception, not able to give informed consent. Persons who may take the role of legal representative in accordance with the Medical Treatment Agreement Act (WGBO) are: a predefined representative, husband or wife, registered partner or other life partner, a parent or child, brother or sister, and incidentally a curator appointed by a judge. However, the legal representatives are frequently absent at the moment their beloved ones are admitted to or when ventilation starts in the ICU. Obtaining informed consent from a legal representative usually takes time, even by an experienced research team, as consent requires sufficient time to read and consider the provided written information. Last but not least, shortly after admission to or start of ventilation in the ICU, the legal
representatives are far more concerned about the wellbeing of the patient than participation in a trial\textsuperscript{31,32}.

Finally, the experience of ICU patients enrolled under deferred consent is mainly positive. For example, an investigation of the contentment of participants that were included using deferred consent in the ‘Normoglycemia in Intensive Care-Survival Using Glucose algorithm Regulation’ (‘NICE-SUGAR’) trial, showed that a majority of the patients were happy with the decision made by the representative (93%) and would have granted consent if asked (96%)\textsuperscript{33}. This is in line with our personal experiences conducting research using deferred consent (see Textbox 1 – Personal experiences with deferred consent in critically ill patients).

For these reasons, we opt for using deferred consent, where informed consent from a legal representative must be obtained as soon as possible, but always within 72 hours after randomization (see Textbox 1 – Personal experiences with deferred consent in critically ill patients). If informed consent is not obtained, or if a legal representative denies participation within the time window of 72 hours, the patient is excluded and data will no longer be used. Thenceforth the patient is ventilated according to the policy of the attending physician.

\begin{boxed_text}
\textbf{Textbox 1 – Personal experiences with deferred consent in critically ill patients}

Deferred consent was used in two recent ventilation studies, the PReVENT (METC 2014_075) and RELAx (METC 2017_074) studies.

From the PReVENT study, we learned that it is possible to inform legal representatives about the trial within 24 hours, but due to longer travelling distances for some of the legal representatives, obtaining written informed consent was sometimes not possible within that timeframe: in as many as 19 out of 174 patients (11%) randomized in the AMC, this was the reason for exclusion. Informed consent may have been obtainable within 48 hours in all these cases.

In the RELAx study, that was recently finished, researchers had to inform legal representatives about the trial within 48 hours. We learned that the timeframe of 48 hours was still too short, mainly because legal representatives lived far from the hospital and could not always come to the hospital to sign the requested documents.

Therefore, we opt to delay the deadline for obtainment of deferred consent to 72 hours after inclusion. If granted, we would like to stress that this is an absolute deadline. In practice, we will seek to obtain deferred consent as soon as possible in all cases.
\end{boxed_text}
10.2.2 No deferred consent in patients who die before obtaining informed consent

In case a patient dies before informed consent could be obtained from the legal representative, we propose to use the data and inform the legal representative about the research without obtaining informed consent. This is in line with the advice from Jansen and colleagues regarding ethical validity and practical feasibility of deferred proxy consent in emergency critical care research and in line with the advice of the Central Committee on Research Involving Humans (CCMO, the Dutch national Ethics Committee) in these circumstances in the early lactate-directed therapy in the ICU. The CCMO judged that the situation in which a patient dies before consent could be obtained is comparable to the situation in which the research project has already finished at the time deferred consent can be obtained. They concluded that the legal representative should be notified about the study, but that seeking consent was not useful anymore due to the lack of consequences. The representation of the patient by a legal representative ends when the patient dies. In the Dutch law, the consent of the patient or his/her relative primarily relates to the participation in the study and not to using the data collected in the study.

10.2.3 Conclusion deferred consent

Critically ill patients in need of ventilation are, without exception, incapable of giving informed consent at the moment of ICU admission. Obtaining informed consent from a legal representative takes too much time to allow timely start of the ventilation strategies to be compared in this trial. Timely start is essential due to the risk of the injurious effects on the lungs even after a short period of ventilation not following protocol and thereby reducing the validity of the trial. Both ventilation strategies to be compared in this trial are currently used as standard care.

10.3 Ethical aspects

We can underpin the idea of ‘clinical equipoise’ both fully automated closed-loop ventilation as well as conventional modes of ventilation are used in ICUs throughout the Netherlands and Europe. Whether fully automated closed-loop ventilation performs better than conventional ventilation remains uncertain.
10.4 Benefits and risks assessment, group relatedness
Invasive ventilation using lung–protective settings has been shown to reduce ventilator–induced lung injury. It is therefore plausible that patients will gain clinical benefit from ventilation settings being optimized breath–by–breath, as opposed to being intermittently changed by clinicians. Both ventilation strategies are currently in use, but it has not yet been proven that one strategy is superior to the other. Therefore, burden and risks of the ventilation strategies are uncertain, yet there is no additional risk to be expected for patients enrolled in this study.

We specifically chose not to exclude incompetent patients for two reasons. First, critically ill patients needing ventilation should be considered incompetent due to their needs for continuous sedation within the first days. Second, the strategies to be compared in this study are to be used in critically ill, intubated and ventilated patients. These conditions are not present in patients who are not suffering from a critical illness. We therefore consider it impossible not to include these patients in a study comparing strategies for mechanical ventilation.

10.5 Compensation of injury
The sponsor/investigator has a liability insurance, which is in accordance with article 7 subsection 6 of the WMO. As this study compares two ventilation strategies used for standard care, an exception from the requirement for insurance to cover for damage to research subjects through injury or death caused by the study is applicable.
11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents
All patients will be addressed to the interventions with a random patient identification code. The codebook will be stored digitally and in paper. The paper version will be stored behind a lock and the digital form will be encrypted with a double password. All data will be stored for the length of the study and for 15 years afterwards. All handling of personal date will comply with the General Data Protection Regulation (AVG).

11.2 Monitoring and Quality Assurance
Queries on the database will be done by a statistician and analyzed by the monitor to signalize early aberrant patterns, trends, issues with consistency of credibility and other anomalies.

On site monitoring will compromise controlling presence and completeness of the research dossier and the informed consent forms and the performance of source data checks, as described in the monitoring plan. Every participating center will be visited after the inclusion of the first ten patients, and thereafter at least once every year. A monitoring plan is being developed.

11.3 Amendments
Amendments are changes made to the research after a favorable opinion by the accredited Medical Research Ethical Committee (METC, Dutch Medical Ethics Committee) has been given. The METC and the competent authority will be notified of all substantial amendments. Non–substantial amendments (typing errors and administrative changes) will not be notified to accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.4 Annual progress report
The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, unexpected problems and amendments.

11.5 End of study report
The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the 90<sup>th</sup> day after the last patient inclusion in the study. In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature
termination. Within one year after the end of the study, the investigator/spONSOR will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.6 Public disclosure and publication policy
The study protocol will be registered before inclusion of the first patient on Clinicaltrials.gov. The results of the study will find their way into (inter–)national scientific journals and guidelines. We will submit analyses to scientific journals in the field of intensive care medicine as well as anesthesiology, since both ICU physicians and anesthesiologists apply ventilation in the ICU setting.
12. REFERENCES


APPENDIX I

SCHEME FOR UNASSISTED VENTILATION WITH TRACHEOSTOMY

The following suggested scheme can be used for unassisted ventilation with a tracheostomy, but should be individualized in every patient:

1. Unassisted ventilation for 30 minutes, three times per day
2. Unassisted ventilation for 1 hour, three times per day
3. Unassisted ventilation for 2 hours, three times per day
4. Unassisted ventilation for 4 hours, three times per day
5. Unassisted ventilation for 6 hours, two times per day
6. Unassisted ventilation for 18 hours
7. Unassisted ventilation for 24 hours
APPENDIX II

DEFINITIONS

- Ventilator–free days and alive at day 28 (VFD–28):
  - $\text{VFD–28} = 0$ if subject dies within 28 days of mechanical ventilation
  - $\text{VFD–28} = 28 - x$ if successfully liberated from ventilation $x$ days after initiation
  - $\text{VFD–28} = 0$ if the subject is mechanically ventilated for $\geq 28$ days

- **APACHE (Acute Physiology and Chronic Health Evaluation):** severity-of-disease classification system for ICU patients, collecting general health data and the worst physiologic values measured within 24 hours of admission to the ICU to determine the chance of hospital survival. APACHE II point scores range from 0-71, and from 0-286 in APACHE IV, respectively. Higher scores correspond to more severe disease and higher risk of death. **Delirium:** disturbance of consciousness and cognition that develops over a short period of time (hours to days) and fluctuates over time

- **ICU-acquired weakness:** clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness

- **Pneumonia:** new or progressive radiographic infiltrate plus at least two of the following: fever (typanic temperature $> 38.5 \, ^\circ \text{C}$), leukocytosis or leucopenia and/or purulent secretions

- **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 severe atelectasis

- **Recruitment maneuver:** increase of inspiratory pressure or the level of PEEP for at least 40 seconds

- **Respiratory muscle weakness:** ICU-acquired weakness of (expiratory) respiratory muscles, assessed by extubation failure and maximal inspiratory pressure (MIP) within 24 hours after extubation

- **SAPS (Simplified Acute Physiology Score) II:** point score ranging from 0–163, as APACHE

- **Severe atelectasis:** at least complete lobar atelectasis of a lung on chest radiograph or other kind of imaging suitable for diagnosis severe atelectasis
• **Severe hypoxemia:** \( \text{SpO}_2 < 88\% \) or \( \text{PaO}_2 < 7.3 \text{ kPa} \) more than 5 minutes or a rise of the oxygen fraction > 60% for more than 5 minutes related to a hypoxemic event

• **Severe hypercapnia:** \( \text{EtCO}_2 \geq 51 \text{ mmHg} \) or \( \text{PaCO}_2 > 7.33 \text{ kPa} \) more than 5 minutes
APPENDIX III

LIST OF PARTICIPATING CENTERS

<table>
<thead>
<tr>
<th>Hospital</th>
<th>City</th>
<th>Principal Investigator</th>
</tr>
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<tr>
<td>Amsterdam UMC location AMC</td>
<td>Amsterdam</td>
<td>Prof. Dr. M.J. Schultz</td>
</tr>
<tr>
<td>Canisius Wilhelmina Ziekenhuis</td>
<td>Nijmegen</td>
<td>Dr. O. Hoiting</td>
</tr>
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<td>Catharina Ziekenhuis</td>
<td>Eindhoven</td>
<td>Dr. A.J.G.H. Bindels</td>
</tr>
<tr>
<td>Flevoziekenhuis</td>
<td>Almere</td>
<td>Dr. M.E. Sleeswijk</td>
</tr>
<tr>
<td>Fondazione I.R.C.C.S. Policlinico San Matteo</td>
<td>Pavia, Italy</td>
<td>Prof. Dr. F. Mojoli</td>
</tr>
<tr>
<td>Leids UMC</td>
<td>Leiden</td>
<td>Prof. Dr. E. de Jonge</td>
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<td>Eindhoven</td>
<td>Dr. J. van Akkeren</td>
</tr>
<tr>
<td>Onze Lieve Vrouwe Gasthuis</td>
<td>Amsterdam</td>
<td>Dr. R.M. Determann</td>
</tr>
<tr>
<td>Ospedale Policlinico San Martino</td>
<td>Genova, Italy</td>
<td>Prof. Dr. P. Pelosi</td>
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<td>Reinier de Graaf Gasthuis</td>
<td>Delft</td>
<td>Dr. P.L. Tangkau</td>
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<td>M. van den Brink</td>
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<td>Diakonessenhuis</td>
<td>Utrecht</td>
<td>Dr. L.E.M. van Lelyveld-Haas</td>
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APPENDIX IV

EQ-5D-5L Quality of Life Questionnaire

### MOBILITY

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<td>I have slight problems in walking about</td>
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<tr>
<td>I have moderate problems in walking about</td>
<td>☐</td>
</tr>
<tr>
<td>I have severe problems in walking about</td>
<td>☐</td>
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<tr>
<td>I am unable to walk about</td>
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### SELF-CARE

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</tr>
<tr>
<td>I have slight problems washing or dressing myself</td>
<td>☐</td>
</tr>
<tr>
<td>I have moderate problems washing or dressing myself</td>
<td>☐</td>
</tr>
<tr>
<td>I have severe problems washing or dressing myself</td>
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<tr>
<td>I am unable to wash or dress myself</td>
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### USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

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<td>I have moderate problems doing my usual activities</td>
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<tr>
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### PAIN / DISCOMFORT

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<tr>
<td>I have slight pain or discomfort</td>
<td>☐</td>
</tr>
<tr>
<td>I have moderate pain or discomfort</td>
<td>☐</td>
</tr>
<tr>
<td>I have severe pain or discomfort</td>
<td>☐</td>
</tr>
<tr>
<td>I have extreme pain or discomfort</td>
<td>☐</td>
</tr>
</tbody>
</table>

### ANXIETY / DEPRESSION

<table>
<thead>
<tr>
<th>Description</th>
<th>Box</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am not anxious or depressed</td>
<td>☐</td>
</tr>
<tr>
<td>I am slightly anxious or depressed</td>
<td>☐</td>
</tr>
<tr>
<td>I am moderately anxious or depressed</td>
<td>☐</td>
</tr>
<tr>
<td>I am severely anxious or depressed</td>
<td>☐</td>
</tr>
<tr>
<td>I am extremely anxious or depressed</td>
<td>☐</td>
</tr>
</tbody>
</table>

We would like to know how good or bad your health is TODAY. This scale is numbered from 0 to 100. 100 means the best health you can imagine. 0 means the worst health you can imagine. Mark an X on the scale to indicate how your health is TODAY. Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = [ ]