Universitätsklinikum Hamburg-Eppendorf

# STUDY PROTOCOL

| Awake Prone Positioning in Patients with Acute Hypoxemic Respiratory Failure in Germany – A Randomized Controlled Study | |
|---|---|
| Clinical trials No. | N/A |
| Version/Date | 1.0 / 28.12.2024 |
| Sponsor | University Medical Center Hamburg<br>Martinistrasse 52<br>20246 Hamburg<br>Germany |
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## SIGNATURES

**Coordinating Principal Investigator**

I hereby confirm that I have acknowledged the protocol and agree to conduct the study in compliance with the protocol.

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|---|---|
| Coordinating Principal Investigator Signature | Date |
| Coordinating Principal Investigator Name | |

**Deputy & Coordinator**

I hereby confirm that I have acknowledged the protocol and agree to conduct the study in compliance with the protocol.

| | |
|---|---|
| Deputy-Principal Investigator Signature | Date |
| Deputy-PI/ Coordinator Name | |

**Deputy Coordinator**

I hereby confirm that I have acknowledged the protocol and agree to conduct the study in compliance with the protocol.

| | |
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| Deputy study coordination Signature | Date |
| Deputy study coordinator Name | |

**Statistician Signature**

Statistician Signature

Date

Statistician Name

## 2 SYNOPSIS

| | |
|---|---|
| **Title of study** | Awake **PRO**ne Positioning in Patient**S** with **A**cute Hypoxemic Respiratory Failure in Germany – A Randomized Controlled Study<br><br>Acronym: **PROSA** |
| **Coordinating Principal Investigator** | Stefan Kluge, MD |
| **Deputy-PI<br>Study coordinator** | Kevin Roedl, MD, MBA |
| **Deputy study coordinator** | Dominik Jarczak, MD |
| **Trial manager** | Mahir Karakas, MD, PhD, MBA |
| **Study centre** | University Medical Center Hamburg-Eppendorf<br>Department of Intensive Care Medicine<br>Martinistrasse 52<br>20246 Hamburg, Germany |
| **Clinical Trials-No.** | N/A |
| **Study Period** | First patient in to last patient out (months): 18.0<br>Duration of the entire trial (months): 30.0 (6 months preparation, 18 months trial conduction, 6 months reporting)<br>Recruitment period (months): 18<br>FPFV: Q2/2025<br>LPLV: Q4/2026 |
| **Phase of development** | Phase 4 |
| **Medical condition** | Acute Hypoxemic Respiratory Failure due to Pneumonia |
| **Objective(s)** | i. To evaluate if the application of standard awake prone positioning in spontaneous breathing patients (defined as patients without invasive mechanical ventilation or extracorporeal respiratory support) with acute hypoxic respiratory failure due to pneumonia at the intensive care unit (ICU) is superior to standard supine/semi-recumbent position in reduction of the rate of tracheal intubation and/or all-cause death within 28 days after randomization.<br>ii. To assess safety and tolerability of awake prone positioning in patients with acute hypoxic respiratory failure due to pneumonia on the ICU. |
| **Hypothesis** | Prone positioning has shown beneficial effects in intubated patients with severe respiratory failure and positive effects in awake patients with COVID-19 pneumonia. Since the pandemic the rate of awake prone positioning has increased and became a standard medical therapy in ICUs worldwide. Conclusive evidence for patients with AHRF without COVID-19 is still missing. We hypothesis that awake prone position in patients with AHRF is beneficial in terms of reducing the rate of tracheal intubation and/or all-cause death. |
| **Intervention** | **Intervention:**<br>- Standard Awake Prone Positioning as defined by the study manual for a length of at least 72 hours |

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| | **Control:**<br>- Standard positioning (supine/semi-recumbent) (alone) of patients with acute hypoxemic respiratory failure according to the usual practice of each participating centre<br><br>**Follow-up per patient:**<br>Follow-up for all patients will be 28 days. |
| **Key inclusion and exclusion criteria** | **Key inclusion criteria:**<br>• Patients in the intensive care unit<br>• High possibility of Pneumonia (community-acquired pneumonia or hospital-acquired pneumonia) either diagnosed by chest x-ray or computed tomography or clinically diagnosed at least with one of the following signs<br>  ○ Appearance of purulent secretions or changes in characteristics (color, odor, quantity, consistency)<br>  ○ Cough or dyspnea or tachypnea<br>  ○ Evocative auscultation<br>• Presence of acute hypoxemic respiratory failure (PaO2/FIO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 315)<br>  ○ with need for supplementary oxygen via HFNO, NIV or CPAP with at least 40% $FiO_2$<br><br>**Key exclusion criteria:**<br>• Age below 18<br>• Pregnant woman<br>• Patient is unlikely/unable to awake prone positioning, or to be compliant as indicated by the treating team<br>• Prolonged need (≥ 4 days) for HFNO, NIV or CPAP before study inclusion<br>• Urgent need for endotracheal intubation<br>• Invasive Mechanical Ventilation<br>• Shock<br>  ○ Defined as need for vasopressor ≥ 0.4 mcg/kg/min to maintain a mean blood pressure ≥ 65 mmHg or a systolic blood pressure ≥ 90 mmHg<br>• Participation in another clinical interventional trial in the last 3 months<br>• Previous Participation in the PROSA Trial<br>• Long-term oxygenation therapy (LTOT) or continuous positive airway pressure (CPAP) therapy before hospital admission<br>• Treatment with intention of palliative care and/or Do not intubate order (DNI) at time of randomization |
| **Primary and Secondary Outcome(s)** | **Primary endpoint:**<br>• The primary endpoint will be:<br>  ○ Tracheal intubation and/or all-cause death within 28-days<br><br>**Secondary endpoints:**<br>• The secondary objectives are to compare the intervention and the control groups with respect to:<br>  ○ All-cause mortality within 28-days<br>  ○ Tracheal intubation within 28-days<br>  ○ Duration of achieved awake prone position (per day and total) |

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| | ○ days free from invasive mechanical ventilation or non-invasive ventilation at 28 days (defined as days alive without invasive/non-invasive ventilation)<br>○ days free from cardiovascular organ support (including vasopressors, catecholamines and mechanical circulatory support)<br>○ Differences in AHRF presumed origin<br>▪ COVID-19<br>▪ Influenza<br>▪ Hospital acquired pneumonia<br>▪ Community acquired pneumonia<br>▪ Pneumonia in immunosuppressed individuals<br>○ Differences of Devices used<br>▪ HFNO<br>▪ NIV<br>▪ CPAP<br>▪ Combination of the above<br>○ Effect on Oxygenation after awake prone positioning<br>▪ Improvement of spO2<br>▪ Improvement in Horowitz Index<br>▪ Respiratory Rate<br>○ days alive and outside the intensive care unit at 28-days<br>○ days alive and outside the hospital at 28-days<br>○ hospital and intensive care unit length of stay<br>○ Organ support<br>▪ Rate and length of RRT<br>▪ Need for vv-ECMO<br>▪ Need for va-ECMO<br>○ APP Related events |
| **Trial Design** | Investigator-initiated, prospective, randomized, open, blinded endpoint assessment (PROBE) interventional multi-center, phase 4 trial. Adaptive design with an interim analysis and re-calculation of the sample size after follow-up of 50% of the planned sample size.<br>Eligible patients will be randomized (1:1) to standard awake prone positioning or standard supine/semi-recumbent positioning alone. Randomization will be stratified by centre, mode of ventilation at randomization, as well as age (below versus equal/ above 70 years) using block randomization with varying block sizes. |
| **Statistical analysis** | <u>Efficacy:</u><br>The objective of the trial is to prove superiority of the intervention arm versus the control arm. The primary analysis follows from the chosen adaptive design with one unblinded interim analysis after follow-up of 50% of the patients.<br><br><u>Description of the primary efficacy analysis and population:</u><br>The primary analysis will follow the intention to treat (ITT) principle in the FAS (Full Analysis Set); that includes all randomised patients, as belonging to their randomisation arm, regardless of whether awake prone positioning could be applied as intended, or whether other protocol deviations are known. All details on the analyses will be detailed in a statistical analysis plan, which will be finalised prior to inclusion of the first patient. The adaptive analysis strategy for the primary endpoint follows the Inverse Normal method to independent test statistics derived from models on per-stage data. Each analysis (interim and final) will consist of a mixed logistic regression model comparing the primary outcome ”tracheal intubation or all-cause death” between random groups with age and mode of respiratory support at inclusion as fixed effects and centre as random effect in order to map the stratified randomisation scheme. One-sided significance bounds for the two analyses are 0.0026 and 0.024. Overall, an alpha of 0.025 one-sided will be spent on the primary outcome. |

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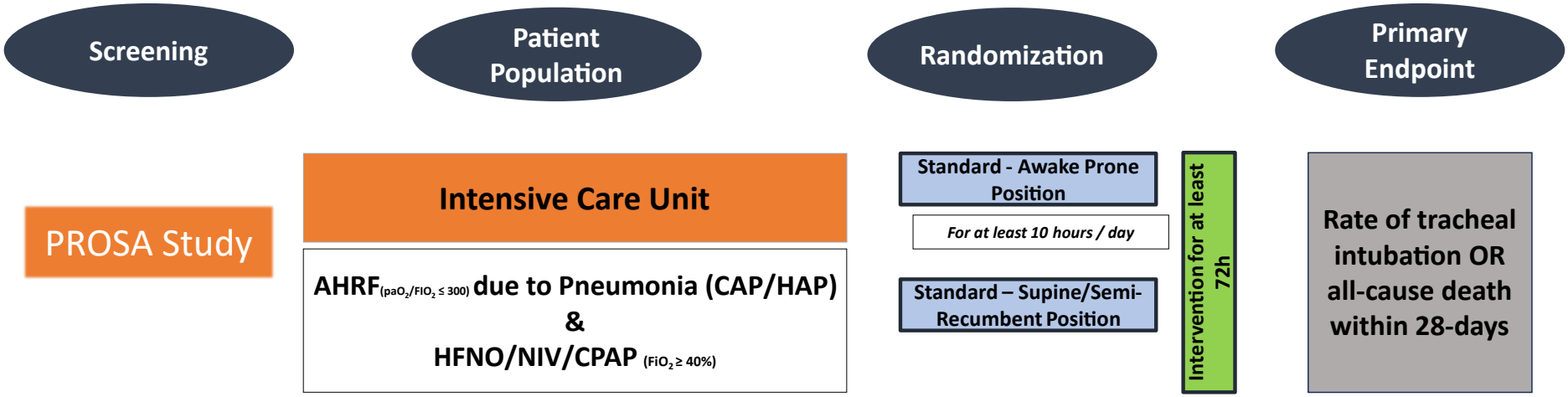
| | Effect size assumed for power calculation:<br>The sample size and power calculation are based on previous knowledge, assuming a 28-day event rate of the combined endpoint in the control group of 50%, and a reduction to 35% in patients with the experimental intervention. To account for possible imprecision regarding the assumptions, an adaptive design was chosen with one interim analysis after follow-up of 50% of the planned number of patients, in order to allow stopping early for futility or efficacy and to re-estimate the sample size. Based on these assumptions and for an overall one-sided type-one error of 2.5% and statistical power of 80%, 171 patients per group (342 overall) are planned to be enrolled to prove superiority. The maximum sample size will be restricted to 513 patients.<br><br>Safety:<br>Rates of adverse events and serious adverse events will be tabulated by treatment group, according to type of event and system organ class. Safety endpoints for the APP group will be analysed descriptively (event rates with two-sided 95% confidence intervals).<br><br>Secondary endpoint(s):<br>Treatment effects will be calculated with two-sided 95% confidence intervals and are of descriptive nature only. Secondary outcomes will be analysed depending on the scale type, corresponding to the primary analysis. |
| **Safety:** | Percentage of patients meeting key safety endpoints, as well as assessment of adverse events. |
| **Number of Patients** | To be randomized into the trial: n = 342<br>To be analysed: n = 342 – intention to treat analysis<br>Adaptive sample size: n = 342 - 513<br><br>Note: adaptive sample size (see below for details)<br>Note: recruitment will be competitively among sites (currently 20 sites planned) |

## Table 1. STUDY SCHEDULES

| Phase of study | Screening & Randomisation | Visit 2 | Visit 3 |
|---|---|---|---|
| **Point in time** | **Day 1** | **Day 1-3** | **Day 28 (±3 days)** |
| Informed Consent | ✓ | | |
| I/E Criteria | ✓ | | |
| Medical History & Demographics | ✓ | | |
| Vital Signs | ✓ | ✓ | |
| Routine laboratory values (blood count) | ✓ | ✓ | |
| Routine blood gas values | ✓ | ✓ | |
| Parameters of oxygenation and oxygenation therapy (HFNO, NIV, CPAP) | ✓ | ✓ | |
| Start of Intervention (Prone Positoning) therapy | ✓ | ✓ | |
| Endpoints | ✓ | ✓ | ✓ |

**Figure 1. Trial Flow**



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# 4 LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| AHRF | Acute Hypoxemic Respiratory Failure |
| APP | Awake Prone Positioning |
| ARDS | Acute Respiratory Distress Syndrome |
| BDRM | Blinded Data Review Meeting |
| CRF | Case Report Form |
| CSR | Clinical Study Report |
| DSMB | Data Safety Monitoring Board |
| FPFV | First Patient First Visit |
| FU | Follow-Up |
| GCP | Good Clinical Practice |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| ICU | Intensive Care Unit |
| ISF | Investigator Site File |
| LPLV | Last Patient Last Visit |
| MD | Medical Doctor |
| PI | Principal Investigator |
| PP | Prone Positioning |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SOP | Standard Operating Procedure |

# 5 ETHICS

## 5.1 Ethics Committee or Institutional Review Board

This study will be planned and performed in accordance with

- The Declaration of Helsinki in its version of Helsinki, 2024;
- The EU Clinical Trial Directive 2001/20/EC;
- The EU Clinical Trial Directive 2001/83/EC
- The "Note for Guidance on Good Clinical Practice" (CPMP/ICH/135/95), and other applicable laws.

## 5.2 Ethical Conduct of the Study

The Sponsor will submit, among other documents, the study protocol, the patient information and the informed consent form to all involved Ethics Committees and request for approval (favourable opinion). Further the sponsor will provide the clinical trial application. The approval of the Ethics Committee must be obtained prior to the start of any study related intervention.

## 5.3 Patient Information and Informed Consent

An Investigator will explain to the patients (or legal representative) the nature, significance and implications of the study. He will explain all methods, rules of conduct and any restrictions which may apply. Possible effects and side effects will be discussed. Patients (or legal representatives) will be informed that they are free to withdraw from the study at any time, without giving any reason for doing so. They must be able to understand the full implications of their decision. Study participation will be in consent with the patient or legal representative.

All participants (or legal representatives) will sign an informed consent form as evidence of consent. The patient information sheet and the informed consent form of each participant will be filed in the Investigator Site File (ISF). A second original of the signed consent form and a copy of the information sheet will be handed to the patients after signature and before enrolment.

If a patient is unconscious and not able to be informed/ to provide informed consent and a legal representation status is not established/ available, the inclusion is at the discretion of the local investigator and can be performed under an emergency enrolment strategy. In this case the informed consent process has to be repeated as soon as the patient is awake or a legal representation has been established as deferred consent strategy.

## 5.4 Confidentiality

The Principal Investigator (PI) of each study site must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorised parties. Only an identification code (i.e., consists of identification number, sex and year of birth) should be recorded on any form or biological sample submitted to the laboratory, Sponsor, Competent Authorities' or Ethics Committee. The PI must keep a screening and enrolment log showing codes and names for all patients screened and for all patients enrolled in the trial.

## 5.5 Publication Policy

The Sponsor represented by Coordinating Principal Investigator will publish the result of this study considering all legal requirements. The trial will be registered at clinicaltrials.gov.

Beside University Medical Centre Hamburg-Eppendorf, as the Sponsor of the study, is committed to the unrestricted and widespread dissemination of all primary and secondary endpoint results. The publication of the principal results from any single-centre experience within the trial is not allowed.

Following analysis and presentation of the primary endpoint results, active and passive participation of all Committee Members, high enrolling Investigators will be solicited for data analysis, abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary and secondary endpoints from the study requires approval by the Coordinating Principal Investigator and his deputy. Final decision regarding authorship lies at the Coordinating Principal Investigator and his deputy.

The sole acquisition of data does not qualify for authorship. All authors must meet each of the following 3 criteria:

1. Substantial contribution to conception and design of study protocol and/or analysis and interpretation of data
2. Drafted the article or revised it critically for important intellectual content
3. Approved the final version for publication.

# 6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

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# 7 INTRODUCTION AND BACKGROUND

## 7.1 The Medical Problem

About 10% of admissions to ICUs are associated with acute hypoxemic respiratory failure (AHRF) (1). Early in the disease non-invasive respiratory support modalities (e.g., non-invasive ventilation, high-flow nasal oxygen) are used for improving oxygenation and unload respiratory muscles, thereby reducing inspiratory effort and the risk of patient-self-inflicted lung injury (2). However, some patients are suffering from acute respiratory distress syndrome (ARDS), which is associated with a mortality of up to 45% in the severe category (1). The management of ARDS has made considerable progress both regarding supportive and pharmacologic therapies. Lung protective mechanical ventilation is the cornerstone of ARDS management, Besides that Prone positioning (PP) in patients with moderate to severe ARDS has shown improved oxygenation and benefit regarding mortality (3). The response to prone positioning depends on the redistribution of densities and regional perfusion (4). Guidelines recommend early PP alongside with lung protective ventilatory strategies (5). Adverse events during PP can include endotracheal tube obstruction, pressure sores and loss of venous access (6). Of interest, first reports of PP in ARDS go back to the 1970 where Phiel et al. tested a bed which allowed position changes of up to 180 degrees (7). The first effects of PP were reported in 1977 by Douglas and colleagues (8). Since then, studies have focused mainly on mechanically ventilated patients. Prone position of non-intubated, awake patients with AHRF results in many of the same physiological changes improving oxygenation (9). Awake prone positioning (APP) of patients with acute hypoxemic respiratory failure gained considerable attention during the coronavirus disease 2019 (COVID-19) pandemic (9). With the spread of non-invasive respiratory support strategies in wards and ICUs APP in non-mechanically ventilated patients was often performed and became the focus of several clinical trials (5). Prior to the pandemic, reports of APP were limited to case series in patients with influenza and in immunocompromised patients, with encouraging results in terms of tolerance and oxygenation improvement (9-11). High-quality evidence from randomized controlled trials (RCT) derived from studies enrolling only COVID-19 patients (12-15). In a Meta-Trial including six RCTs APP of patients with acute hypoxemic respiratory failure due to COVID-19 reduced the incidence of treatment failure and the need for intubation without any signal of harm (14). A recent RCT showed that prolonged APP (target > 12 h daily for 7 days) reduces the intubation rate without significant harm (12). The most recent ESICM Guideline on acute respiratory distress syndrome suggest awake prone positioning as compared to supine positioning for non-intubated patients with COVID-19-related AHRF to reduce intubation (5). Since the COVID-19 pandemic awake prone positioning has become a medical standard therapy in the intensive care setting worldwide. However, to date there is insufficient data on the effect of APP in non-COVID-19 patients with AHRF. Furthermore, it is of importance that currently there is no evidence of the effect of APP of patients with non-COVID-19 AHRF. Due to its good tolerability and not too complex implementation in spontaneous breathing patients APP could be beneficial in patients with AHRF. Potentially, endotracheal intubation and need for mechanical ventilation and its concomitant side effects could be avoided.

Because of these underlying body of evidence, we hypothesize that APP in non-intubated patients with AHRF in the ICU reduces the need for tracheal intubation and the rate of potentially fatal disease course as compared with supine/semi-recumbent position.

## 7.2 Clinical Use

Currently PP is used as routine therapy for patients with ARDS and mechanical ventilation in moderate to severe severity. PP in patients who are spontaneously breathing gained attention during the COVID-19 pandemic and was proven to be safe in these patient population why it is now also used as routine medical therapy in the intensive care setting worldwide.

## 7.3 Preclinical Results

n/a

## 7.4 Cautions and Tolerability

### 7.4.1 Contraindications

There are absolute and relative contraindication to APP. Similar to prone positioning of mechanically ventilated patients, absolute contraindications include spinal instability or at risk of spinal instability and further relative contraindications include unstable fractures (especially facial and pelvic), anterior burns

(large ventral surface area) and open wounds, severe shock, recent tracheal surgery, and raised intracranial pressure. Contraindications are also listed in the study manual; the feasibility will be assessed by the treating physician on-site. If APP in an individual patient is possible is up to the discretion of the treating physician.

### 7.4.2 Special Warnings and Preventive Measures for the Treatment

#### 7.4.2.1 **Nerval compression injuries**

An important complication of PP is nerve compression injuries, particularly when the prone position is adopted for longer periods of time. Brachial plexus injuries post prone position for patients undergoing IMV is common and well described in the literature. Fortunately, the incidence of brachial or ulnar injuries with in the awake patient is rare. In a case report, a 61-year-old who practiced nocturnal prone positioning for over 2 weeks noted decreased sensation and dysesthesia in his bilateral ulnar forearms and fourth and fifth digits, which resolved completely after 1.5 months without intervention (16). The ulnar nerve may be compressed at the elbow in the condylar groove between the olecranon and the medial epicondyle of the humerus. Flexion narrows the cubital groove by tightening the room and causes bulging of its floor. Advice to reduce the incidence of ulnar injury would include reducing elbow flexion of more than 90 degrees.

### 7.4.3 Side Effects

There are various potential side effects of PP. The most data stems from studies reporting PP in ARDS when patients are invasively mechanically ventilated. Side effects include accidental removal of endotracheal tube, loss of tubes that deliver fluids and medicines to your veins (peripheral or central venous catheter), hemodynamic instability (low blood pressure or arrhythmia), temporary decreases in oxygen levels, blockage of airway. In the study by Guerin at al following side effects were reported, which were all non-significant between the PP and standard of care group (except cardiac arrest) (3).

Side effects in patients with tracheal intubation and mechanical ventilation during prone position:

- Non-scheduled extubation, 25 events (10.9%)
- Mainstem bronchus intubation, 5 (2.2%)
- Endotracheal tube obstruction, 5 (2.2%)
- Hemoptysis, 12 (5.2%)
- Cardiac arrest, 31 (13.5%)
- Oxygen saturation by pulse oximetry < 85% or PaO2 <55 mm Hg > 5 minutes, 164 (71.6%)
- Heart rate < 30 beats.min-1> 1 minute, 27 (11.8%)
- Systolic blood pressure<60 mmHg > 5 minutes, 48 (21.0%)

## 7.5 Rationale

Patients with AHRF are at risk for further worsening of respiratory function and need for oxygen supplementation or even more advanced non-invasive respiratory support or invasive mechanical ventilation if the clinical situation further worsens. Data show a benefit of prone position in invasive mechanical ventilated patients with moderate to severe ARDS. Further data support its benefit in COVID-19 patients with need for non-invasive mechanical ventilation. Since the COVID-19 pandemic APP use increased and became a standard medical therapy in ICUs worldwide. There are currently no RCTs for non-COVID-19 patients with AHRF.

Therefore, this investigator-initiated, prospective, randomized, open, blinded endpoint assessment (PROBE) interventional multi-center trial will investigate whether standard awake prone positioning compared to standard supine/semi-recumbent positioning can improve objective endpoints, relevant for prognosis in patients with AHRF.

Eligible patients will be randomized 1:1 to intervention arm or control arm. Patients enrolled to the interventional arm will receive standard therapy during course of hospital stay and additional standard awake prone positioning for 72h (targeted time in prone position 10 h/day(per 24 h period)) after randomization. Patients enrolled to the control arm will receive standard medical therapy in supine/semi-recumbent position. If patients have to be intubated and mechanical ventilated in both the interventional and control arm treatment should include standard ARDS therapy, including prone positioning in the case of moderate-severe ARDS.

### 7.6 Benefit- Risk Considerations

There is substantial need to improve therapeutic options in AHRF. Awake prone positioning and PP appears to be a safe and promising approach under the light of recent findings.

However, a considerable number of patients with AHRF and with or without APP will eventually need tracheal intubation an invasive mechanical ventilation. Patients with HFNC/NIV will be monitored closely clinically and with continuous vital sign monitoring will detect clinically worsening. An indication for endotracheal intubation won't be deferred. Based on the study hypotheses and previous studies in patients with COVID-19 we expect that there will be a lower rate of tracheal intubation and invasive mechanical ventilation which prevents complications associated with invasive mechanical ventilation.

Since the therapy is unblinded for both the patients and the supervising investigators, an unblinding procedure is not necessary. A Data Safety and Monitoring Board (DSMB) will be established to further minimise the risk for the patients.

Due to the fact that prone positioning is a standard manoeuvre in patients with AHRF/ARDS it can be defined as intensive care medical standard procedure. Therefore, no dedicated patient insurance will be needed.

The identifying data of patients will be kept securely at the participating sites. Clinical patient data will be stored central electronic data capture tool provided by the sponsor.

All aspects of the trial will be conducted in accordance with the Declaration of Helsinki principles, ICH-GCP rules and local laws. The study protocol will be submitted for ethical approval to the responsible ethics committees. All participants must provide written informed consent.

Primary aim of this study is to evaluate, if a standard APP strategy compared to a standard supine/semi-recumbent therapy leads to a reduction of all-cause mortality and/or rate of tracheal intubation in patients with AHRF. Furthermore, the safety and tolerability of APP in patients with AHRF will be assessed.

## 8 STUDY OBJECTIVES

Primary aim of the PROSA trial is to evaluate if a standard APP therapy strategy is superior to standard supine/semi-recumbent positioning therapy in reduction of all-cause mortality and/or tracheal intubation endpoints in patients with AHRF due to pneumonia.

All outcome measures were defined in accordance with highest scientific standards. In order to generate meaningful data, patient-related endpoints were chosen as the primary efficacy outcome. The secondary endpoints are also patient-related and can be precisely assessed.

### 8.1 Primary Objective

The primary objective of the PROSA-Study is to evaluate if the application of standard awake prone positioning in spontaneous breathing patients (defined as patients without invasive mechanical ventilation or extracorporeal respiratory support) with acute hypoxic respiratory failure due to pneumonia on the ICU is superior to standard supine/semi-recumbent positioning in reduction of the rate of tracheal intubation and / or all-cause mortality within 28 days after randomization. Furthermore, it should assess safety and tolerability of awake prone positioning in patients with acute hypoxic respiratory failure due to pneumonia on the ICU.

### 8.2 Primary Endpoints

**Primary endpoint:**

- Tracheal intubation and/or all-cause death within 28 days.

### 8.3 Secondary Endpoints

The secondary objectives are to compare the intervention treatment and control groups with respect to:

- All-cause mortality within 28 days
- Tracheal intubation within 28 days
- Duration of awake prone position (per day and total)
- days free from invasive mechanical ventilation or non-invasive ventilation at 28 days (defined as days alive without invasive/non-invasive ventilation)
- Rate of tracheotomy

- Differences in AHRF presumed origin
  - COVID-19
  - Influenza
  - Hospital acquired pneumonia
  - Community acquired pneumonia
  - Pneumonia in immunosuppressed individuals
- Device used
  - HFNO
  - NIV
  - CPAP
  - Combination of the above
- Effect on Oxygenation after awake prone positioning
  - Improvement of spO2
  - Improvement in Horowitz Index
  - Respiratory Rate
- days alive and outside the intensive care unit at 28- days
- days alive and outside the hospital at 28- days
- hospital and intensive care unit length of stay
- Organ support
  - Rate and length of RRT
  - Need for vv-ECMO
  - Need for va-ECMO
- APP Related events

**Primary safety endpoint**

- Interruption of therapy due to intolerability to APP
- New treatment-related events (and changes in severity and frequency in these) related to APP

# 9 INVESTIGATIONAL PLAN

## 9.1 Overall Study Design and Plan-Description

The clinical trial is designed as an investigator-initiated, prospective, randomized, open, blinded end-point assessment (PROBE) interventional multi-center phase 4 trial to assess safety, tolerability, and efficacy of standard APP therapy in patients with AHRF due to pneumonia, and to evaluate if a standard APP therapy strategy is superior to standard supine/semi-recumbent positioning therapy in reduction of mortality and tracheal intubation endpoints in patients with AHRF. The trial has an adaptive design with an interim analysis and re-calculation of the sample size after follow-up of 50% of the planned sample size has been recruited.

APP will be carried out according to the proning strategy described in the study manual. The control group will receive standardized supine positioning therapy. The clinical trial will be conducted in an outcome assessor-blinded manner.

## 9.2 Discussion of Study Design, Including the Choice of Control Groups

So far, PP has shown a reduction in mortality in mechanically ventilated patients with moderate to severe ARDS. However, to date it remains unclear if PP in spontaneous breathing patients with AHRF and need for oxygen supplementation or non-invasive mechanical ventilation methods also benefit from so called awake prone positioning trial. Whether or not standard APP improves prognostic relevant parameters is unclear. Therefore, this trial is of utmost importance.

To this end a standard APP therapy strategy will be compared with a standard supine/semi-recumbent positioning therapy strategy in a clinical trial setting. This is scientifically the strongest possible design and ethically appropriate given the limited evidence for therapeutic options in AHRF.

## 9.3 Selection of Study Population

Since morbidity and mortality in AHRF patients is high, effective therapies are needed to further improve outcome and quality of life are needed. A therapy which is only symptomatic or based on expert consensus is considered to be not fully sufficient. The improvement of prognostic relevant endpoints through a well-tolerated therapy with the potential to also improve quality of life is regarded the ultimate goal.

### 9.3.1 Inclusion Criteria

The focus of this trial is to treat patients with respiratory failure. The inclusion criteria are selected accordingly. Patients meeting all of the criteria listed below will be included in the study:

- Patients in the intensive care unit
- High possibility of Pneumonia (community-acquired pneumonia or hospital-acquired pneumonia) either diagnosed by chest x-ray or computed tomography or clinically diagnosed at least with one of the following signs
    - Appearance of purulent secretions or changes in characteristics (color, odor, quantity, consistency)
    - Cough or dyspnea or tachypnea
    - Evocative auscultation
- Presence of acute hypoxemic respiratory failure (PaO2/FIO2 ≤ 300 mmHg or SpO2/FiO2 ≤ 315)
    - with need for supplementary oxygen via HFNO, NIV or CPAP with at least 40% $FiO_2$

### 9.3.2 Exclusion Criteria

Patients are excluded from the study if any of the following criteria are met at screening or before randomization, a detailed list is shown in the study manual:

- Age below 18
- Pregnant woman
- Patient is unlikely/unable to awake prone positioning, or to be compliant as indicated by the treating team
- Prolonged need (≥ 4 days) for HFNO, NIV or CPAP before study inclusion
- Urgent need for endotracheal intubation
- Invasive Mechanical Ventilation
- Shock
    - Defined as need for vasopressor ≥ 0.4 mcg/kg/min to maintain a mean blood pressure of ≥ 65 mmHg or systolic blood pressure ≥ 90 mmHg
- Participation in another clinical interventional trial in the last 3 months
- Previous Participation in the PROSA Trial
- Long-term oxygenation therapy (LTOT) or continuous positive airway pressure (CPAP) therapy before hospital admission
- Treatment with intention of palliative care and/or Do not intubate order (DNI) at time of randomization

### 9.3.3 Removal of Patients from Therapy or Assessment

The study in its entirety may be discontinued prematurely by the Coordinating Investigator or Sponsor at any time (see below), and/or individual patients may terminate their participation prematurely, or have their participation be terminated by an Investigator.

#### 9.3.3.1 Temporarily Treatment Discontinuation

Treatment may be interrupted, if this is deemed necessary by the treating physician. This might be the case when clinically relevant side effects occur.

Restarting of therapy is allowed and encouraged, but fully lies at the discretion of the investigator.

#### 9.3.3.2 Premature Treatment Discontinuation

Physicians must stop treatment if the patient experiences any kind of relevant side effect. The patient may remain in the study and continue to attend study visits.

APP will be discontinued when the patients meet criteria for endotracheal intubation or the patients develops other criteria as defined in the study manual.

#### 9.3.3.3 Withdrawal of Patients from the Study

The following circumstances may lead to discontinuation of the study by an individual patient who will then be recorded as a drop-out. They include, but are not limited to the following issues:

- Withdrawal for personal reasons
- Adverse events necessitating withdrawal from the study
- Circumstances in which the health of the patient would be endangered upon continued participation in the study
- Lost-to follow-up

If a patient withdraws from the study at any time either at his or her request or at the Investigator's discretion, an "End-of-Study" visit should be performed and the "End-of-Study" eCRF section should be used to collect the relevant information. For the "End-of-Study" visit the same assessments should be made as for the discharge visit. The reason(s) for withdrawal must be recorded on the relevant page of the patient's eCRF and the patient's source data.

It is vital to obtain follow-up data for any patient withdrawn from the study because of an AE. Every effort must be made to undertake protocol-specific safety follow-up procedures. If a patient is discontinued due to an AE, the event should be followed up until resolution or until the event becomes chronic.

If a patient refuses to continue study procedures, the reason for refusal should be fully documented in the patient's source document and recorded in the study-specific eCRF.

It is the patient's right to withdraw from the trial without providing a reason. In this case, the source documents and the eCRF should document the reason for discontinuation as "withdrawal of consent".

#### 9.3.3.4 Criteria for Termination of the Study

The PROSA trial will be supervised by its Steering Committee and an independent Data Safety Monitoring Board (DSMB). All final decisions, however, regarding study termination or modification will be agreed with the Steering Committee and the independent DSMB.

No formal stopping rules will be set. An independent DSMB will monitor safety in the trial. Should safety concerns evolve, they should recommend stopping the study. Stopping the trial for efficacy or futility is an option.

#### 9.3.3.5 Study Termination

Individual study completion is defined as patients having finished the treatment period without early termination and reached the last visit within the specified window per the Flow Chart (28 days).

Overall End of Study is defined as the date of last patient last visit (LPLV). Within 28 days after the End of Study the Coordinating Investigator and the Sponsor must inform regulatory authorities and ethics committees about the completion of the trial.

The Coordinating Investigator and Sponsor may terminate the trial at any time if serious safety concerns rise for the patients. In the case of study termination, participating sites will be informed of the procedures to be followed to ensure that adequate consideration is given to the protection of the patient's safety.

The Coordinating Investigator will be responsible for informing the Sponsor of the trial's termination within 24 hours. The Sponsor has to inform the Competent Authorities and the Ethics Committee within 15 days.

## 9.4 Interventional treatment

### 9.4.1 Study intervention

#### 9.4.1.1 Clinical Intervention

The clinical intervention in the Intervention Group is Awake Prone Positioning, a standard therapy in intensive care units worldwide in ARDS care. The intervention should not be started later than 24 hours after randomization. An earlier start, as soon as possible, after randomization is strongly recommended. In patients in the intervention group standard Awake Prone Positioning for at least 10 hours/day for a length of 72 hours should be applied. The reach the targeted 10 hours / day (per 24 hours), it is strongly

recommended to use blocks of a longer time period (e.g. multiple 3-5 hours blocks) within the 24 h period to reach the anticipated APP goal. It is recommended that the APP therapy within the targeted intervention for 10 hours/day (per 24 h period) is not interrupted for more than 2 hours till reaching the goal of 10 hours / day (per 24 hours). It is further strongly recommended that one APP session should last at least 3 hours. Time in prone position may be prolonged if the patient is comfortable. A detailed instruction for APP can be found in the study manual.

Awake prone positioning will continue daily until the end of the 72 hours intervention period or one of the following stopping criteria is met before:

1) the patient is intubated
2) the patient is discharged from the ICU.

If patients have to be tracheal intubated and mechanically ventilated treatment should follow current ARDS guidelines according to the local protocol. This includes PP in patients with mild to severe ARDS if $PaO_2/FiO_2$ is below 150 mmHg.

#### 9.4.1.2 Control group

Patients randomized to the control arm will receive standard positioning at the discretion of the treating team but excluding APP. Control group patients will remain in their natural choice of position, which is anticipated to favour a supine, semi-recumbent position. The use of awake prone positioning as a so-called rescue intervention is discouraged in the control group and recorded as a protocol violation.

If patients have to be tracheal intubated and mechanically ventilated treatment should follow current ARDS guidelines. This includes PP in patients with mild to severe ARDS if $PaO_2/FiO_2$ is below 150 mmHg.

#### 9.4.1.3 Patient Management

Criteria for endotracheal intubation and guidelines for patient management including invasive mechanical ventilation, fluid management, and sedation will be provided as recommendations within the study manual. The patient management will be up to the discretion of the treating physician team.

#### 9.4.1.4 Follow-up per Patient:

Follow-up for all patients will be according to Table 1 until the last patient recruited has completed 4 weeks (i.e. 28-days) follow-up.

#### 9.4.1.5 Duration of Intervention per Patient:

Interventional Treatment will be administered during the first 72h after randomization.

#### 9.4.1.6 Patient Compliance

Compliance must be assessed by the PI, or an Investigator.

### 9.4.2 Method of Assigning Patients to Treatment Groups

Randomisation will be carried out centrally through a computer-generated sequence (e.g. randomizer.at). Eligible patients will be randomized 1:1 to standard intervention or standard control group. Randomization will be stratified by centre, age and mode of respiratory support at inclusion using block randomization for each stratum with varying block sizes concealed from the investigator to minimize selection bias. The approach of stratified randomisation helps to avoid potential imbalances between the groups that might affect outcome and bias results.

Concealment of randomization will be ensured at each center through a remote dedicated online randomization system.

### 9.4.3 Blinding

Study sites and patients are not blinded, blinding is not possible due to the nature of the awake prone positioning procedure. Assessors of outcome will be blinded.

### 9.4.4 Unblinding

The subject’s treatment group will be disclosed to himself/ herself.

### 9.4.5 Prior and Concomitant Therapy

Prohibited therapy: None

Concomitant therapy: Any concomitant treatment given for any reason during the course of the study must be recorded on the eCRF and in the patient's medical records, including dosage, start and stop dates and reason for use.

### 9.4.6 Treatment Compliance

#### 9.4.6.1 Admission to the Study

A patient will only be admitted to the study if all inclusion and none of the exclusion criteria are met.

#### 9.4.6.2 Patient Identification

The PI of each site will keep a record relating the patient numbers and the names of all patient that have given their informed consent, to allow easy checking of data in patient files, when required. This record will also include the date of the patient's enrolment and completion, as well as patients who could not be included in the study for whatever reason.

## 9.5 Efficacy and Safety Variables

### 9.5.1 Efficacy and Safety Measurement Assessed and Flow Chart

Details regarding scheduled assessments and procedures to be conducted in this study are provided below. For detailed assessment of schedules refer to Table1.

### 9.5.2 Appropriateness of Measurements

#### 9.5.2.1 Screening Procedures

Written, signed, and dated informed consent from the patient prior to the performance of any study related procedures must be obtained by an Investigator. Patients (or legal representatives) will first have ample time to read the patient information before an Investigator will start the information and informed consent process. If the patient is incapable of giving consent personally a legal representative will be informed about the study and can give consent representing the patient. Informed consent from the patient will be obtained as soon as the patient is capable again. If the patient does not agree he/she will be withdrawn from the study.

An Investigator will provide the patients (or legal representatives) with information of the study and explain the nature of the study point by point. During these verbal patient information process, patients (or legal representatives) have already the opportunity to ask questions. After that, the patients (or legal representatives) have the opportunity to individually ask questions in a one-to-one meeting with the Investigator. If the Investigator is convinced that the patient (or legal representatives) understands the nature and risks of the trial, and each patient (or legal representatives) had ample time for consideration and formulation of questions (which could also mean that the patients (or legal representatives) first discuss the decision with friends or family members), and if all questions are answered, the patient (or legal representatives) will ask to personally sign the informed consent form. A copy or a second original of the signed informed consent form must be given to the patients (or legal representatives) for their records.

Only an authorised and trained Investigator may decide on the eligibility of the patient.

##### 9.5.2.1.1 Screening Failure

A screening failure is defined as a patient who has given informed consent and failed to meet at least one inclusion or exclusion criteria as defined by the protocol. Screening failures will not be entered in clinical database.

Eligible patients who meet all inclusion/exclusion criteria but are unable to participate in the study due to different reasons will not be considered screening failures. These patients will not be entered in clinical database.

##### 9.5.2.1.2 Re-screening of Patients

If patients fail screening, re-screening is permitted up to 14 days, if in the opinion of the Investigator the patient may be eligible with a reanalysis of failed variables.

#### 9.5.2.2 Study Examinations

Assessments are to be performed according to the schedule shown in Table 1 and depend on time-point of start of the intervention.

Safety will be evaluated by collecting reported adverse events at regular intervals throughout the study and by the assessment of vital signs, clinical laboratory parameters, ECGs, and adverse events.

##### 9.5.2.2.1 Medical and Medication History

A complete medical and medication history as well as demographic information will be assessed at the time-points indicated in Table 1.

The medical history will be reviewed and recorded, including:

Medical and Medication History

- Recent ingestion of medication (10 days prior to entering the screening period)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, haematological, neurological, psychiatric, musculoskeletal and other diseases.

Demographic information

- Date of birth
- Sex

##### 9.5.2.2.2 Vital Signs

Measurements of vital signs ($spO_2$, systolic and diastolic blood pressure, respiratory rate as well as pulse rate) and treatment parameters on normal ward, IMCU/ICU (Organ support, including resp. settings and $FiO_2$) will be performed at the time-points specified in Table 1. All measurements of vital signs must be recorded in the appropriate source documents.

##### 9.5.2.2.3 Height and Weight

Measurements of height and weight will be performed according to the schedule in Table 1.

Height is measured in centimetres and weight is measured in kilograms. If feasible, measurements are to be taken in light clothing and socks (without shoes) with pockets emptied. The patient's height is recorded to the nearest 1 cm and weight is recorded to the nearest 1 kg.

##### 9.5.2.2.4 Clinical Laboratory Evaluations

All laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges will be supplied by the laboratory and used to assess the laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal laboratory values that are unexpected or not explained by the patient's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible.

###### 9.5.2.2.4.1 Pregnancy Test

Appropriately performed using blood test.

##### 9.5.2.2.5 Concomitant Medication

Concomitant medication will be assessed at the time points described in Table 1.

### 9.5.3 Primary efficacy variable(s)

#### 9.5.3.1 Outcome Measures

Patient-related parameters were defined as outcome measures obtained by the respective gold-standards.

##### 9.5.3.1.1 Clinical Laboratory

All relevant clinical laboratory variables obtained during screening, final examination or the clinical trial periods will be reported in appropriate tables together with descriptive statistics in the CSR.

##### 9.5.3.1.2 Vital Signs

Blood pressure and pulse rate descriptive statistics will be listed by sampling times (screening and follow-up) according to the data captured in the eCRF.

## 9.6 Data Quality Assurance

### 9.6.1 Documentation and Data Collection

The eCRF will be prepared to report at least all clinical data required by the protocol. Site staff will transfer the study data from the source documents into the eCRF. Site staff will check eCRF entries for completeness. Completed eCRF modules will be electronically signed by an Investigator in order to ensure data entry accuracy.

Research Coordinators will enter the study data in a structured Data Collection Form (e.g. REDCap online software (www.project-redcap.org)).

### 9.6.2 Data Quality Monitoring

Site staff will enter data electronically through the validated eCRF system. Quality control will include regular data verification and protocol compliance checks.

Data management will check predefined eCRF entries as defined in the data management plan (DMP), which will be locked after all queries and discrepancies that may occur during data entry are resolved.

Upon request safety reports and interim analysis (50 % of randomized patients) will be generated and provided to the respective members of the DSMB.

After database lock, the data in the study database will be exported and transferred electronically to the responsible biometrician for statistical analysis. The datasets will be used to generate the patient listings, tabulations, and analyses for the CSR.

### 9.6.3 Archival of documents

The research team at each participating site will collect and record study data, as outlined in the data collection system (e.g. REDCap). On all study documents, specific patient data will be identified with unique study identifiers. Trial data will be stored in a secured hospital network drive. Once the trial recruitment period is complete, all study data will be securely stored. The Sponsor will maintain the trial documents and take measures to prevent accidental or premature destruction of these documents. All documents related to the study will be retained until at least 15 years after the end of the study.

## 9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

### 9.7.1 Statistical and Analytical Plan

A Statistical Analysis Plan (SAP) providing greater detail of data derivations and analyses to be performed will be completed prior to randomization of the first patient. The SAP will be reviewed and (if required) updated based on a blind review of the data prior to the analysis and will reflect the protocol and any amendments implemented at the time the SAP is updated.

#### 9.7.1.1 Software to be Used

All statistical analyses will be carried out using SAS® language and procedures (SAS® 9.4 or higher version, SAS-Institute, Cary NC, USA), R (R 4.0.3 Development Core Team, Vienna, Austria.

http://www.R-project.org), Stata (Stata 16.0 or higher version, StataCorp., College Station, TX, USA), or SPSS (24.0 or higher version, IBM Corp., Armonk, NY, USA).

#### 9.7.1.2 Eligibility for Statistical Evaluation

Eligibility of patients will be determined in a BDRM before statistical analysis will be performed.

##### 9.7.1.2.1 Analysis Population

###### 9.7.1.2.1.1 Full analysis set

The full analysis set (FAS) is as complete as possible and as close as possible to the intention-to-treat (ITT) ideal of including all randomised patients. Patients are analysed as belonging to their randomized arm, regardless of whether they received the intervention as planned, or whether other protocol deviations are known.

###### 9.7.1.2.1.2 Per Population set

The per protocol set (PPS) comprises all patients of the FAS who had no relevant violations from the trial protocol. The blinded endpoint committee will define protocol violations that lead to exclusion from the per protocol population. Patients are analysed as belonging to their randomized arm.

###### 9.7.1.2.1.3 Evaluated for safety set

The evaluated for safety set (EFS) comprises all patients of the FAS who received any intervention within the trial. The blinded endpoint committee will define assignment of individual patients to the safety population. Patients are analysed as belonging to their randomized arm.

##### 9.7.1.2.2 Statistical Analyses

All statistical analyses will be carried out by the trial statistician. To preserve the blinding of the study's biometry team until the final analysis, the unblinded interim analysis will be conducted by a separate biometry team from the same institute. Baseline variables will be described by treatment group using appropriate summary statistics.

###### 9.7.1.2.2.1 Primary, Secondary, and Safety Endpoints

The primary efficacy analysis will be performed according to the ITT principle and will therefore be based on the FAS. The adaptive analysis strategy for the primary endpoint follows the Inverse Normal method to independent test statistics derived from adjusted mixed logistic regression models on per-stage data obtained. This strategy allows the use of conventional stopping strategies of group sequential designs. Unbiased parameter estimates and confidence intervals can be obtained by using the theory of repeated confidence intervals. In detail, the null hypothesis will be tested at overall one-sided type-one error of 2.5% with stopping boundaries according to an O'Brien and Fleming α-spending function. To account for the adaptive design of the trial, the Inverse Normal method will be used with weights $w_1=w_2=\sqrt{0.5}$ at the interim and final analysis, respectively. The test on treatment difference at each stage k (k=1,2) will be based on a Wald test statistic originating from a mixed logistic regression model including the treatment group (intervention versus control alone), age and respiratory status at randomization fixed effects and centre as random effect to reflect the stratified randomization. To ensure that the stage-wise test statistics are independent, the data are divided into two subsets, a first-stage and a second-stage data set.

Interim analysis:

After follow-up of 50% of the planned patients, an interim analysis with the possibility to stop for efficacy or futility will be conducted. The treatment effect is tested using the Inverse Normal method applied to the Wald test statistic (originating from the adjusted mixed logistic regression model) at interim significance level which is determined by an O'Brien and Fleming type α-spending function. If the trial is continued to stage 2, the sample size re-calculation will be based on conditional power, with a target conditional power of 80%. After re-calculation, the sample size is adjusted with the originally calculated sample size and the maximum sample size of 342 as lower and 513 upper limit for the adjusted sample size.

Final analysis:

The second-stage data for the final analysis will be based on the Inverse Normal combination of the Wald statistics from the adjusted mixed logistic regression models of the first- and second-stage data

(with weights w_1=w_2=√0.5) at local significance level according to the α-spending function. Parameter estimates and confidence intervals are calculated based on the theory of repeated confidence intervals (RCI), where the midpoint of the two-sided RCI is used as point estimate.

Secondary endpoints: Secondary efficacy endpoints will be analysed in the FAS. Treatment effects will be calculated with two-sided 95% confidence intervals. P-values and confidence intervals derived from these analyses are of descriptive nature only. Secondary outcomes will be analysed depending on the scale type. Time-to-event outcomes will be analysed by Cox proportional hazard models including centre as frailty term. Dichotomous variables will be tested by mixed logistic regression with centre as random effect. Continuous variables will be analysed with linear mixed effects models that include the baseline determinations of the outcome and centre as random effect. Scale transformations will be considered based on the pooled data set. In further secondary analyses, the effect of the number of hours with awake prone positioning on the primary and secondary endpoints is evaluated for the intervention group.

Safety endpoints: Safety analyses will be performed in the EFS. Rates of adverse events and serious adverse events will be tabulated by treatment group, according to type of event and system organ class.

#### 9.7.1.2.2.2 Dropouts

It should be emphasised that as little patients as possible should discontinue treatment (or change to the other treatment arm) and that all patients should be followed up and also documented after discontinuation of the treatment in order to record data required according to the intention-to-treat principle. All efforts will be made to avoid missing data and to collect outcome data for all patients randomized in the trial. In the primary analyses, a negligible number of drop-outs is expected. In case of substantial dropout multiple imputation will be applied in sensitivity analyses.

### 9.7.1.3 Proposed Sample Size

Sample size calculation was performed with rpact 3.3.4, R version 4.2.3 [Wassmer G, Pahlke F (2023). rpact: Confirmatory Adaptive Clinical Trial Design and Analysis. R package version 3.3.4, https://CRAN.R-project.org/package=rpact] using the test for two proportions using the Z-test with unpooled variance. The sample size and power calculation are based on previous similar trials in COVID-19, international ICU databases, observations from small proof-of-concept studies, as well as from our own hospital-based patient information system (3, 9, 12, 14, 15). Based on these data, we estimate the relative decrease of 28-day mortality / need for tracheal intubation by our intervention compared to standard-of-care by 30%. Patients with acute hypoxemic respiratory failure on ICU, as shown by previous studies and own databases, display a 28-day event rate of the combined endpoint of 50%, so that we assume a reduction to a 28-day event rate of 35% in patients with the experimental intervention for sample size calculation (3, 9, 12, 14, 15).

Due to lack of appropriately large data sets, the current assumptions may comprise a certain imprecision. To account for this imprecision, an adaptive design was chosen with one interim analysis (O'Brien and Fleming boundary) after follow-up of 50% of the planned number of patients, in order to allow stopping early for futility or efficacy and to re-estimate the sample size. Only an independent statistician will be unblinded for this purpose and unblinded data will only be reported to the DSMB (including the DSMB statistician). The Sponsor and all other study team members stay blinded till the end of the study.

Based on these assumptions and for an overall one-sided type-one error of 2.5% and statistical power of 80%, 171 patients per group (342 overall) are planned to be enrolled to prove superiority. To avoid an unmanageably large sample size, the sample size after recalculation will be restricted to a maximum of 513 patients (chosen based on practical reasons including feasibility of enrolment and a clinically meaningful effect).

## 9.8 Changes in the conduct of the study or planned analysis

Modifications of the protocol are permitted only if they are authorised by the Sponsor and the Coordinating Investigator in writing.

Deviations and Changes to the study protocol will be classified by the Sponsor and the study site as:

Note-to-File: This refers to clarifications which are not considered changes of the protocol.

Study protocol amendment: This refers to substantial changes of the protocol. If they fulfil the criteria as set out in appropriate law, they need to be approved by the Ethics Committees or the Competent Authorities. Changes to the study protocol may also induce revision of the patient information sheet/informed consent form. Accordingly, patients undergoing trial assessment procedures at the time of implementation of the change have to be given the amended version and have to be asked for consent to continue on this amended trial.

## 9.9 DSMB

A Data and Safety Monitoring Board (DSMB)/ Data Monitoring Committee (DMC) will be constituted to protect the safety of study participants. A DSMB is a group of external independent experts assessing the progress, safety data, and, if needed, critical efficacy endpoints of a clinical study.

The DSMB will receive blinded CRF data in the form of tables and listings (prepared by an independent statistician), and adjudicate on patient status changes. Where appropriate, the DSMB may receive unblinded data (on a patient level or treatment group level) that should be reviewed in a closed session.

The data should include, but is not limited to, demographics, patient enrolment, baseline characteristics, AE data, SAE data (by severity and causality), laboratory data, protocol adherence, and patient withdrawals.

The DSMB will evaluate the progress of the trial, assess data quality and timeliness, participant recruitment, accrual and retention, and participant risk versus benefit. The DSMB will review the accumulating study data after 50% of patients have been randomised. In addition, the DSMB/DMC will monitor external factors relevant to the trial, for example scientific and therapeutic developments that may affect participant safety or ethical status. Based on the observed benefits or adverse effects, the DSMB will make recommendations to the Steering Committee about the conduct of the trial, integrity of the data and trial discontinuation to ensure the overall safety of participants.

The Sponsor will establish a Charta document explaining the working procedures for the DSMB.

In addition, a DSMB meeting will be conducted whenever safety relevant data occur that might have an influence on the trial.

# 10 REPORTS

All reports to the Sponsor will be in English. The Sponsor will receive the original clinical study report (CSR). The CSR is the property of the Sponsor. Publication of the report or of part of it may only be allowed when authorised by the Sponsor in consultation with the study site.

## 10.1 Clinical Study Report

All clinical, analytical and statistical results will be presented in a CSR. The outline of this report will accord to the ICH-GCP E3 document "Structure and Content of Clinical Study Reports" of July 17, 1996.

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