PRone positioN in patients with spontanEous ventiLation and acute hypoxemic respIratory FailurE- The PRONELIFE Randomized Controlled Trial

RESEARCH PROTOCOL

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1. LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

Abbreviation/Acronym	Full Wording
AE	Adverse Event
APACHE II	Acute physiology and chronic health disease classification system II
ARDS	Acute respiratory distress syndrome
BPsys	Systolic blood pressure
CPAP	Continuous positive airway pressure
CRF	Case report form
EELI	End-expiratory lung impedance
FiO2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
HR	Heart rate
IMV	Invasive mechanical ventilation
ICU	Intensive care unit
NIV	Non-invasive ventilation
NPO	Nil per os
PaO_2	Partial arterial oxygen pressure
PEEP	Positive end expiratory pressure
PP	Prone position
SAE	Serious adverse event
SAPS II	Simplified acute physiology score II
SOFA	Sequential Organ Failure Assessment
SP	Supine position
SUSAR	Suspected unexpected serious adverse reaction

2. SUMMARY

Rationale

Acute respiratory failure represents one of the most common causes of intensive care unit admission. Invasive mechanical ventilation (IMV) is the cornerstone support therapy in the most severe patients. Prone positioning is an established evidence-based practice in patients with typical ARDS undergoing IMV, but limited evidence exists in non-ventilated awake patients.

Objectives

To compare awake proning in patients with acute hypoxemic respiratory failure from any cause with standard management.

Hypothesis

Awake prone position in patients with acute hypoxemic respiratory failure is associated with a decreased need for invasive mechanical ventilation.

Study design

Prospective international multicenter randomized controlled trial.

Study population

Adult patients with acute hypoxemic respiratory failure (AHRF) from any cause without respiratory acidosis.

Main study parameters/endpoints

The primary endpoint is the proportion of patients needing invasive mechanical ventilation. Secondary endpoints include the effects of awake proning on the oxygenation parameters, complications, tolerance, length of hospital stay, and 28-day and 90-day mortality.

Nature and extent of the burden and risks associated with participation, benefit, and group relatedness

A significant number of patients under awake proning will eventually require IMV. However, patients will be admitted to the ICU for close monitoring and do not delay intubation when indicated. If the hypothesis proves to be true, there is a potential decrease in intubation and IMV, reducing the risk of complications associated with it, facilitating the early onset of physiotherapy, and early ambulation. All these benefits would hasten recovery, improving short and long-term outcomes. Blood samples will be collected via an existing intravenous catheter or direct vein puncture, but always combined with blood sampling for routine care; the amount of additional blood samples can be considered minimal.

3. INTRODUCTION AND RATIONALE

3.1 Acute respiratory failure

Acute respiratory failure represents one of the most common causes of intensive care unit admission[1]. Initial management of the hypoxemic patient should involve immediate use of supplemental oxygen. If the patient fails to achieve adequate oxygenation with conventional supplemental oxygen, high-flow nasal cannula (HFNC) oxygen or non-invasive positive pressure ventilation (NIPPV) may be used. If patients fail to improve with the non-invasive methods after a time-limited trial or worsen, timely endotracheal intubation should be considered to avoid any harm.

3.2 Complications of mechanical ventilation

Even though mechanical ventilation is a life-saving strategy in patients with respiratory failure, mechanical ventilation is associated with serious complications. These complications may be related to the direct mechanical effects of the intrathoracic pressures generated by the ventilator, to alveolar and systemic inflammation, or to neural stimulation[2]. Experimental[3–5] and clinical[6] studies show that MV has the potential to aggravate or even initiate lung injury (so-called ventilator-associated lung injury, VALI). Patients undergoing MV, sedation with or without paralysis are often required, especially for patients with shock or ARDS or those "fighting the ventilator." [7] The use of sedative agents may unduly prolong MV's duration, precluding mobilization, promoting muscular deconditioning, and leading to detrimental short- and long-term outcomes[8,9].

3.3 Prone position in ARDS

Prone positioning (PP) was first recognized for its ability to improve oxygenation and was historically used in the 1970s to improve gas exchange and salvage therapy for refractory hypoxemia[10]. A seminal multicenter trial and subsequent meta-analyses have made a compelling case that prone positioning in selected patients with severe acute respiratory distress syndrome (ARDS) early in their course improves survival[11]. This survival benefit is likely mediated by reduced VILI, as regional differences in lung aeration, compliance, and shear strain are minimized[12,13].

3.4 Prone position in spontaneously breathing patients

The benefit of prone positioning may not be restricted to invasively ventilated patients. At least, in theory, non-intubated patients could also benefit from being placed in the prone position[14,15], also called "awake proning."

Theoretically, PP benefits may concern spontaneous breathing patients, in whom it could contribute to the success of the non-invasive strategy. Current evidence comes from few studies, mostly case reports and single-center observation case series[15–17] involving patients undergoing NIV or high flow oxygen therapy and suggesting suitable patients' tolerance, significant improvement in oxygenation during the procedure, and no increase in nurse workload. It has been described that the median duration of prone positioning is 3 (2-4) hours with no other respiratory or technical complications, such as displacement of indwelling catheters, facial edema, pressure sores, pressure neuropathies, compression of nerves, and retinal vessels or vomiting[16].

A rapidly growing number of observational studies describe the use of awake proning in patients with acute respiratory failure in whom hypoxemia is refractory to simple supplementary oxygen[18–24].

It is crucial to note that there is no randomized trial evidence for the effect of awake proning in patients with acute respiratory failure so far. The number of studies investigating awake proning is rapidly growing, but thus far, randomized clinical trials remained absent.

Given its tolerability and few complications in spontaneous breathing patients, the prone position could be adjuvant therapy in acute respiratory failure patients. It may avoid the need for invasive mechanical ventilation and its side effects.

4. OBJECTIVES AND HYPOTHESIS

4.1 Objectives

The proposed randomized controlled trial aims at comparing the application of the prone position in spontaneously breathing patients with acute hypoxemic respiratory failure versus standard treatment on the rate of invasive mechanical ventilation, as well as determining the effects of oxygenation, safety, length of ICU, and hospital stay and, mortality at day 28 and day 90. Spontaneous breathing is defined as patients without invasive mechanical ventilation or extracorporeal respiratory support system.

4.2 Hypothesis

We hypothesize that in adult patients with acute hypoxemic respiratory failure from any cause and spontaneous breathing, the prone position application decreases the intubation rate compared to the best standard of care.

5. STUDY DESIGN

Multicenter, international, randomized controlled trial on acute hypoxemic respiratory failure patients with a respiratory rate of more than 25 breaths per minute, SpO_2 < 94% and FiO_2 of at least 40% or more by either Venturi facemask, HFNC or NIV/CPAP and, absence of decompensated respiratory acidosis.

6. STUDY POPULATION

6.1 Population (base)

We intend to recruit acute hypoxemic respiratory failure patients with a respiratory rate of more than 25 breaths per minute, SpO_2 < 94% and FiO_2 of at least 40% or more by either Venturi facemask, HFNC, or NIV/CPAP and, absence of decompensated respiratory acidosis during two years. Currently, we expect about 35 centers to participate in the trial.

Demographic data and clinical characteristics on screened patients, regardless of enrolment criteria match, will be recorded (registry). We will randomize 714 patients admitted to the participating centers' intensive care units and expect each participating center to randomize at least 25 patients who meet all inclusion criteria.

6.2 Inclusion criteria

- >18 years
- Acute respiratory failure from any cause
- Admitted to a participating ICU
- Written informed consent

6.3 Exclusion criteria

- Presence of any contraindication to prone position (APPENDIX i)
- The patient meets the criteria for intubation (APPENDIX ii)
- Participating in other interventional studies with the same primary outcome
- Receiving comfort care only
- Pregnancy

6.4 Sample size calculation

The initial sample size calculation was based on our primary hypothesis and primary study outcome. The required sample size was calculated using data from a multicenter randomized controlled trial reporting intubation rate in patients with acute hypoxemic respiratory failure with a PaO_2/FiO_2 ratio less than 200 using HFNC[25].

These calculations indicated that 322 patients would be required per group, assuming a two-sided significance level of 0.05 and a power of 80%, to detect the expected difference in the

rate of mechanical ventilation between the prone position group of 24 % and the standard treatment group of 34 % (risk ratio of 0.70). Assuming a dropout rate of 10%, **a total of 714 patients** (n= 357 per group) were planned to be included in the study.

7. METHODS

7.1 Study parameter/endpoints

7.1.1 Main study parameters/endpoint

- Rate of invasive mechanical ventilation during the first fourteen days of enrolment

7.1.2 Secondary study parameters/endpoints

- Effects on oxygenation defined by the SpO_2
- Days under the oxygen support device
- Total amount of time the patient remains in the prone position
- Related serious adverse events. The following will be considered serious adverse events:
    - Oxygen desaturations (SpO_2 <90%)
    - Episodes of hemodynamic instability (BPsys < 90mmHg or BPsys drop > 10mmHg if BPsys < 90 before the maneuver)
    - Need of orotracheal intubation
    - Cardiac arrest
    - Displacement of the non-invasive respiratory support device
    - Removal of central venous line, if documented
    - Displacement of an arterial line, if documented
    - Displacement of a urinary catheter, if documented
- Respiratory rate
- Dyspnea defined according to the Borg dyspnea scale (APPENDIX iv)
- ICU-free days and hospital-free days at day 90
- Mortality at day 28 and day 90

7.1.3 Other optional substudy parameters

- Systemic levels of biomarkers of lung injury
- Evaluation of regional ventilation distribution

7.2 Study procedures

Patients admitted to the participating centers' ICUs will be considered eligible if they fulfill the entry criteria. Eligible patients will be screened, their demographic criteria data recorded (registry: age, gender, type of oxygen support device), and those without exclusion criteria will be randomized. In total, 714 patients will be included.

Patient consent

According to local regulations, all patients or legal guardians must provide written informed consent before inclusion in the study. If patients cannot give informed consent due to the effects of acute illness, sedation, or hypoxemia, deferred consent will be obtained.

7.2.1 Randomization

Randomization procedure

Randomization will be performed using a dedicated website and will be balanced per center.

Randomization arms

Central randomization with the use of a permutated-block randomization list (block length 6) will be used. Participants will be allocated to the prone position or standard care on a 1:1 ratio. At each site, at least two investigators will be involved: one who will be aware of the allocated intervention and collect the data; the other will remain blinded to the interventions and evaluate the outcomes.

7.2.2 Prone position

Supine to Prone

The patient will be placed in the prone position for at least 2 hours, which may be prolonged if the patient is comfortable or interrupted if the patient presents any criteria for prone position discontinuation (APPENDIX iii).

During the maneuver, FiO_2 will be increased by 25% above the baseline and then gradually decreased to the baseline value within the first 10 minutes of prone positioning, targeting for a SpO_2 of 94-96%. The total time of the prone position will be recorded.

The maneuver will be performed by two operators and the attending physician, while in patients with impaired mobility, up to 5 operators will be required. Skin protections will be used to avoid pressure sores. Also, the application of cushions will enhance patient tolerance to the

maneuver.

Arms can be at the side, in swimmer position, and can be moved to the patient's comfort.

Vitals, SpO_2, and SpO_2/FiO_2 will be measured before and at the end of the prone position session.

Enteral or oral feeding will be interrupted 1 hour before prone positioning and re-established when the patient is in the semi-recumbent supine position.

Opiates, benzodiazepines, or alpha-2-adrenoceptor agonists can be used during the maneuvering at non-sedative doses to enable adaptation to the maneuver or treat anxiety symptoms related to respiratory failure.

If non-tolerance to the prone position, all clinical data will be collected, and the patients will be promptly rotated in the supine position. The reasons for prematurely unproning the patient will be accurately recorded. In case of sudden worsening of the oxygenation impairment or hemodynamics, 100% FiO_2 will be set, and the patient will be promptly positioned in the supine semi-recumbent position.

Prone to Supine

After the prone position period, the patient will be rotated to the semi-recumbent supine position for at least 2 hours and a maximum of 4 hours. This 2-hour time frame will depend on nursing availability, need for hygiene, complementary explorations, or diet.

As described previously, for the procedure, FiO_2 will be increased up to 25% above the baseline and then gradually decreased to the baseline value within the following 10 minutes targeting a SpO_2 of 94-96%.

Vitals, SpO_2, and SpO_2/FiO_2 will be measured before and at the end of the supine position session.

Opiates, benzodiazepines, or alpha-2-adrenoceptor agonists can be used during maneuvering at non-sedative doses to enable adaptation to the maneuver or treat anxiety symptoms related to respiratory failure.

During the evening, the patient will be asked if the patient would prefer to remain supine or be rotated to prone according to the protocol.

If the patient remains hypoxemic, at clinician's criteria, the prone position could be continued more than 48 hours until respiratory failure improves.

7.2.3 Standard management

The standard management of patients with acute hypoxemic respiratory failure will be done according to the usual practices of each participating center.

7.2.4 Data to be collected

The documentation of the data will adhere to the timetable in APPENDIX v.

Pre-randomization variables

Pre-randomization variables will be collected:

- Gender and age; female + years
- Height and weight; kg + cm
- Date and time of hospital admission
- Source of admission to the ICU (emergency department, hospital ward, transfer from another ICU, transfer from a non-ICU ward of another hospital)
- Date and time of ICU admission
- Type of non-invasive respiratory support (HFNC, NIV, CPAP)
- COPD with inhalation therapy and/or steroids
- Smoking status; never, former (at least three months prior) or current
- History of active cancer; if yes, specify the type of cancer
- History of diabetes mellitus; oral medication or insulin therapy
- History of hypertension
- Use of angiotensin-converting enzyme inhibitor
- Use of angiotensin II receptor blocker
- Use of statins
- Actual organ function evaluation
    - Respiratory rate
    - SpO_2; %
    - SpO_2/FiO_2
    - ROX index; SpO_2/FiO_2: RR
    - Dyspnea defined according to Borg dyspnea scale
    - Chest X-ray

- Non-invasive mean arterial pressure; mmHg
- Heart rate; BPM
- Body temperature; °C
- BUN, Creatinine, AST, ALT, Bilirubin, Hemoglobin, Platelets, PTT, WBC count
- SOFA score
- APACHE II, SAPS II; any of those used by the participating center

Post-randomization variables

One hour before each position change (supine and prone), the following variables will be collected for the duration of the protocol, which will be for 48 hours (APPENDIX v):

- Organ function evaluation:
  - Respiratory rate
  - SpO_2; %
  - SpO_2/FiO_2
  - ROX index; SpO_2/FiO_2: RR
  - Dyspnea defined according to the Borg dyspnea scale (APPENDIX v)
  - Non-invasive mean arterial pressure; mmHg
  - Heart rate; BPM
- Non-invasive support device parameters:
  - HFNC: flow; liters/min. FiO_2; %
  - CPAP: PEEP; cmH_2O. Flow; liters/min; Tidal volume; ml. FiO_2; %
  - NIV: PEEP; cmH_2O. Pressure support over PEEP; cmH_2O. Flow; liters/min. Tidal volume; ml. FiO_2; %
- Complications possibly related to prone position:
  - New hypotension (BPsys < 90mmHg or BPsys drop > 10mmHg, if BPsys < 90 before the maneuver)
  - New bradycardia (HR <50bpm or HR drop > 20%, if HR < 50 before the maneuver)
  - New hypoxemia ($SpO_2 \leq 90\%$ or SpO_2 drop > 5%, if $SpO_2 < 90\%$ before the maneuver)
  - Ulcers
  - Displacements of any of the following: respiratory support device, peripheral or venous central line, oro or nasogastric tube, urinary catheter

Post-protocol variables

The patients will be assessed daily between the third and the fourteenth day after the protocol and the last day before discharge from the ICU and the hospital. Discharge from critical care is defined as the first discharge to a medical or surgical ward in the hospital or another hospital; a transfer between ICUs is not considered a discharge from critical care. Hospital discharge is the first date that the patient is discharged to home/community; a transfer between hospitals is not considered as a hospital discharge. Clinical data and the presence of complications will be registered and the date of the development of any complication documented (see APPENDIX vi). The following variables will be collected:

- Continuation of prone position
- Continuation and time spent under the non-invasive respiratory support device
- Day and time of unassisted breathing; i.e., no ventilatory support and use of conventional supplemental oxygen or room air
- Chest X-ray
- Need for invasive mechanical ventilation
- Any need for anti-arrhythmic and vasoactive medication; if yes: specify
- Date of ICU discharge
- Date of hospital discharge

7.2.5 Blood samples (facultative)

At randomization and the end of the protocol (48 hours) in both groups (supine and prone), and for those centers that have the storage capacity, blood samples (2 x 5 ml in EDTA, citrate, and heparin) will be collected and stored at -80°C for measurement of markers of lung injury (angiopoietin-2, surfactant proteins D, RAGE). Blood samples will be sent and processed at a central laboratory.

7.2.6 Assessment of regional ventilation (facultative)

Before (in supine) and at the end of the first and the last prone position, for those centers with electrical impedance tomography, we plan to investigate the effects of global and regional end-expiratory lung impedance variation (ΔEELI).

8. STATISTICAL ANALYSIS

8.1 Descriptive statistics

Patient characteristics will be compared and described by appropriate statistics.

8.2 Analysis

The goal of the primary outcome is to quantify the effect of prone position versus the standard treatment upon the need for invasive mechanical ventilation during the first fourteen days after randomization.

Interim analyses for efficacy and futility will be conducted at 50% (N= 357), 75% (N= 476), and 100% (N= 714) of the planned enrollment, as needed, using a non-binding group sequential design with gamma spending functions (gamma = -4 for each of alpha and beta).

The table below shows the alpha and beta spent over the trial, z-statistic boundaries for efficacy and futility, and boundary-crossing probabilities under the alternative hypothesis (H1).

The corresponding P-value boundaries for efficacy (futility in parentheses) at the 1st, 2nd and final looks, respectively, are P≤ 0.006 (P>0.82), P≤ 0.015 (P>0.35), and P ≤ 0.044 (P>0.044).

The Figure below displays the z-statistic boundaries for efficacy/harm and futility as a function of accrued sample size.

For the primary efficacy analysis rates of invasive mechanical ventilation will be compared between the two intervention groups, and the odds ratio relative risks with corresponding 95% confidence levels interval will be calculated using logistic regression analysis.

With regard to the remaining parameters: Normally distributed variables will be expressed by their mean and standard deviation; non-normally distributed variables will be expressed by their medians and interquartile ranges. Categorical variables will be expressed as n (%).

Student's t-test will be used to test groups of continuous normally distributed variables.

Conversely, if continuous data is non-normally distributed, the Mann-Whitney-U test will be used. Categorical variables will be compared with the Chi-square test, Fisher's exact tests, or, where appropriate, as relative risks. Time-dependent data will be analyzed using a proportional hazard model adjusted for possible imbalances of patients' baseline characteristics.

COVID-19 status of patients will be taken into account and analyzed in the study to find any

differences in the primary and secondary outcomes between COVID-19 and non-COVID-19 patients.

A stratified analysis will be done by the device used (HFNC, BIPAP, CPAP, and their interfaces).

The statistical analysis will be based on the intention–to–treat principle. Besides, we will perform a per-protocol analysis to check for the robustness of the results. The intention–to–treat analysis includes all patients as randomized regardless of whether they received the randomized treatment or other protocol deviations. Per–protocol group analysis only considers those patients who completed the treatment according to the originally allocated protocol.

Data analyses will follow an a priori documented statistical analysis plan, which will be finalized before the end of data collection. By definition, only the analysis of the primary outcome is confirmatory; all other analyses are exploratory. The analysis strategy follows the intention-to-treat principle. The analysis will be undertaken blinded by a statistical expert. Statistical significance is considered to be at a p-value of 0.05, where 95% confidence levels will express appropriate statistical uncertainty.

The analysis will be performed with R statistics.

8.3 Data Safety Management Board (DSMB)

A DSMB will be installed to monitor safety and the overall conduct of the trial. The DSMB will compose of 5 individuals who will be invited, one of which will be the chairperson.

The DSMB will first convene after the first 100 patients, approximately 6 months after the first patient is enrolled.

- Subsequently, the DSMB will attend videoconferences every six months
- All adverse events will be reported to the DSMB for review. All serious events will be reported within 24 hours after being received by the coordinating center. Non-serious events will be reported within one week of reception by the coordinating center (APPENDIX vi).
- Adverse events possibly occurring during this study include but are not limited to unexpected death or cardiac arrest in either the control or treatment group (APPENDIX vi).

- The DSMB will monitor the overall status of the trial: number of patients enrolled overall and per each center, adherence to protocol overall and per center and results of the interim analysis.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study, and any subsequent amendments to it, conforms/will conform to the World Medical Association Declaration of Helsinki as revised in October 2013 (64th General Assembly of the World Medical Association, Fortaleza, Brazil).

10. ADMINISTRATIVE ASPECTS AND PUBLICATION

10.1 Handling and storage of data and documents

All enrolled patients will receive a random patient identification code. The codebook will be stored digitally, encrypted with a double password, and hard copy under lock and key. All data will be stored for the study's length and afterward as required by local law or for further publication. All handling of personal data will comply with local law.

10.2 Publication

At the appropriate time, and by mutual consent in consultation with the Steering Committee, it is planned that the results of the clinical study will be published in a scientific journal and presented at national and international conferences. Publication of the complete clinical research should generally be the preferred option. The "Uniform requirements for manuscripts submitted to biomedical journals International Committee of Medical Journal Editors" will be applied.

All publications will comply with data protection requirements covering patient data and data relating to the participating clinicians. Any publication or presentation of this clinical study results requires prior notification and submission to the Steering Committee for purposes of comment and approval.

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12. APPENDICES

APPENDIX i. CONTRAINDICATIONS FOR PRONE POSITION

- Suspected increased intracranial pressure (e.g. severe brain injury)
- Hemoptysis
- Vomiting
- Recent abdominal wound (less than 15 days)
- Tracheal surgery or sternotomy during the previous 15 days
- Facial trauma or facial surgery during the previous 15 days
- Deep venous thrombosis treated for less than 2 days
- Cardiac pacemaker inserted in the last 2 days
- Unstable spine, femur, or pelvic fractures
- Hemodynamic instability (defined by a systolic blood pressure below 90 mmHg, a mean blood pressure below 65 mmHg or requirement for vasopressor)
- Pregnant women
- Presence of chest tube

APPENDIX ii. INTUBATION CRITERIA (ANY OF THE FOLLOWING)

- Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:
  - Respiratory rate above 40 breaths/min, lack of improvement of signs of high respiratory-muscle workload, development of copious tracheal secretions, acidosis with a pH below 7.35, SpO_2 below 90% for more than 5 minutes not attributed to technical device dysfunction, or
  - Intolerance to oxygenation techniques
- Deterioration of neurologic status (Glasgow coma scale below 12 points)

APPENDIX iii. PRONE POSITION DISCONTINUATION (ANY OF THE FOLLOWING)

- Occurrence of contraindications (see APPENDIX i)
- Worsening of dyspnea according to the Borg scale after 15 minutes
- Drop in SpO_2 <90% after 15 minutes
- Nausea/vomiting
- BPsys < 90mmHg or BPsys drop > 10mmHg, if BPsys < 90 before the maneuver

APPENDIX iv. BORG DYSPNEA SCALE

0	Nothing at all
0.5	Very, very slight (just noticeable)
1	Very slight
2	Slight breathlessness
3	Moderate
4	Somewhat severe
5	Severe breathlessness
6	
7	Very severe breathlessness
8	
9	Very, very severe (almost maximal)
10	Maximal

APPENDIX v. TIMETABLE

	Before intervention	During intervention	End of intervention	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14	Day of ICU discharge	Day of hospital discharge	Day 28	Day 90
							All patients eligible for the study								
Screening and Randomization	X														
Daily screening	X														
Demographic data (registry)	X														
Inclusion/Exclusion criteria	X														
Informed consent	X														
Randomization	X														
							Randomized patients								
Before starting protocol															
Demographic data	X														
History of previous disease	X														
Physical examination	X														
SpO_2	X														
Chest X-ray	X														
Routine laboratory tests	X														
During Protocol															
Respiratory variables		X													
Hemodynamic variables		X													
Regional ventilation variables (facultative)		X													
End of Protocol															
Protocol dropout?			X												
Adverse events (possibly related to prone position)			X												
Continuation of prone position after the protocol			X												
Continuation of ventilatory support			X												
Blood sampling (special markers, facultative)			X												
Follow Up															
Physical examination				X	X	X	X	X	X	X					
Actual recovery status (ICU stay, ventilatory support)				X	X	X	X	X	X	X					
SpO_2				X	X	X	X	X	X	X					
Chest X ray (facultative)				X	X	X	X	X	X	X					
Routine laboratory tests (facultative)															
Adverse events (see APPENDIX vi)				X	X	X	X	X	X	X					
Date of ICU discharge												X			
Date of hospital discharge													X		
Alive on day 28														X	X
Alive on day 90														X	X
Hospital-free days on day 90														X	X

APPENDIX vi. ADVERSE EVENTS

1. Definitions

An adverse event (AE) is generally defined as any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding) syndrome or disease which either occurs during the study, having been absent at baseline, or if present at baseline, appears to worsen. Adverse events are to be recorded regardless of their relationship to the study intervention. With respect to intensity, adverse events are classified as follows:

- Mild some awareness of symptoms, but easily tolerated;
- Moderate symptoms causing enough discomfort to interfere with usual activity;
- Severe incapacitating event causing inability to work or to perform usual activity.

A Serious Adverse Event (SAE) is defined as any experience that suggests a significant hazard or side effect with respect to participants participating in a clinical study. This includes any experience which:

- is fatal or life threatening,
- is permanently disabling, i.e. incapacitating or interfering with the ability to resume normal life patterns,
- requires hospitalization or prolongation of hospitalization,
- requires other medically important circumstance (requires medical treatment to avoid one of the above mentioned conditions).

A special form of the SAE is the Suspected Unexpected Serious Adverse Reaction (SUSAR).

Adverse events possibly occurring during this study include but are not limited to unexpected death or cardiac arrest in either the control or treatment group.

2. Documentation of AEs and SAEs

All adverse events that occur between start of randomized intervention and 90-days follow up have to be immediately documented in the participant's electronic CRF. AEs are classified as either serious or non-serious. Details about the clinical symptoms, clinical course and if medical treated, about therapies used should be provided as well as information about relationship to

study intervention, overall intensity and outcome of the adverse event.

3. Reporting of Adverse Events

Reporting responsibilities of the local coordinator

Any AE occurring after start of randomized study intervention will be reported. The participant will be followed until remission of the symptoms. When reporting an AE/SAE, a clinical narrative on each AE/SAE should be added, which gives the clinical context of the event and allows the DSMB to carefully review the AE/SAEs.

AEs are reported via electronic CRF within one week of reception by the coordinating center.

SAEs as well as all related or possibly related events and all unexpected events are reported via electronic CRF within 24 hours after being received by the coordinating center. In case of a SUSAR (suspected unexpected serious adverse reaction) as well as death of study patients the SAE manager has to be informed additionally by email.

Management of AE/SAE

The SAE manager collects and judges the reports within predefined time frames. All related or possibly related events and all unexpected events are forwarded to the DSMB for further review. The DMB members assess forwarded events and review all SAE and AE from all centers every six months or sooner if requested by them. If the DSMB rates an event related to the study therapy, the DSMB should inform the principal investigator.

In case of a SUSAR (suspected unexpected serious adverse reaction) and death of study patients, the ethics committee of the Institut d'Investigació i Innovació Parc Taulí (I3PT) will be informed within seven days. Additionally, a summary of all SAE will be provided twice per year.