# Title: “Assessment of the PEEP responsiveness to titrate end-expiratory pressure and of the need for muscle relaxation during prone positioning in moderate-to-severe acute respiratory distress syndrome: A master Protocol”

ACRONYM: PEPER

INTERVENTIONAL RESEARCH PROTOCOL INVOLVING HUMAN PARTICIPANTS NOT CONCERNING A HEALTH PRODUCT

Version no. 3.0 dated 26/01/2026
Project Code: APHP 240459
/IDRCB no.: **2024-A01624-43**


Coordinating Investigator : Pr Alexandre DEMOULE
Service de Médecine Intensive- Réanimation
Pitié Salpêtrière Hospital
Tel. +33 1 42 16 38 31
Email: alexandre.demoule@aphp.fr

Scientific Directors : Pr Laurent PAPAZIAN
Service de Médecine Intensive Réanimation
Assistance Publique Hôpitaux de Marseille
Tel. + 33 4 95 59 10 39
Email : laurent.papazian@ap-hm.fr

Pr Jean-Daniel CHICHE
Service de Médecine Intensive Adulte
Centre Hospitalier Universitaire Vaudois – Lausanne (CH)
Tel. + 41 79 556 23 93
Lausanne
Email: jean-daniel.chiche@chuv.ch

Pr Sami HRAIECH
Service de Médecine Intensive Réanimation
Assistance Publique Hôpitaux de Marseille
Tel. + 33 4 91 96 58 36
Email sami.hraiech@ap-hm.fr

Sponsor : Assistance Publique – Hôpitaux de Paris (AP-HP)
and by delegation: Délégation à la Recherche Clinique et à l’Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint-Louis
1, avenue Claude Vellefaux
DRCI-Head Office project advisor: Karine SEYMOUR
Tel: + 33 1 44 84 17 42
Email: karine.seymour@aphp.fr





*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| Entity responsible for Safety | Safety department - DRCI<br>Hôpital Fernand Widal<br>200, rue du Faubourg Saint-Denis 75475 Paris<br>Sarra DALIBEY, head of safety department<br>Tel : +33 (0)1 40 27 57 85<br>Email : sarra.dalibey@aphp.fr<br>Valentin HOSANSKY, safety assessor<br>Email : expertisecsi.drc@aphp.fr |
| Entity responsible for monitoring the study: | URC (Clinical Research Unit) Saint Louis<br>1, avenue Claude Vellefaux, 75010 Paris<br>DRCI-URC project advisor : Anissa ZAROUR<br>Tel : + 33 1 42 49 97 99<br>Email : anissa.zarour@aphp.fr |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*

# SIGNATURE page for a research PROTOCOL

Research code number: APHP 240459

Title: Assessment of the PEEP responsiveness to titrate end-expiratory pressure and of the need for muscle relaxation during prone positioning in moderate-to-severe acute respiratory distress syndrome: A Master Protocol, PEPER

Version no. 3.0 dated: 26/01/2026

The study will be carried out in accordance with the protocol, with current good practices and with statutory and regulatory requirements.

**Coordinating Investigator:**
Pr Alexandre Demoule
Service de Médecine Intensive – Réanimation
Pitié Salpêtrière Hospital
75013 Paris

Date: ……/……/……..
Signature:

**Sponsor**
Assistance Publique – Hôpitaux de Paris
Direction de la Recherche Clinique et de l'Innovation - DRCI (Clinical Research and Innovation Department)
Hôpital Saint Louis
1 avenue Claude Vellefaux
75010 PARIS

Date: ……/……/……..
Signature:



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

TABLE OF CONTENTS


**1 SUMMARY ..... 9**

**2 SCIENTIFIC JUSTIFICATION FOR THE STUDY ..... 17**

- 2.1 HYPOTHESIS FOR THE STUDY ..... 17
  - *2.1.1 Hypothesis for the first randomization ..... 17*
  - *2.1.2 Hypothesis for the second randomization ..... 17*
- 2.2 DESCRIPTION OF KNOWLEDGE RELATING TO THE CONDITION IN QUESTION ..... 18
  - *2.2.1 About the condition under investigation (ARDS) ..... 18*
  - *2.2.2 About the studied strategies/procedures ..... 18*
  - *2.2.3 About defining optimal ventilatory strategies in ARDS ..... 18*
  - ***LIMITATION OF INFLATION PRESSURES TO REDUCE VILI ..... 18***
  - ***SETTING PEEP TO IMPROVE OUTCOME IN MODERATE TO SEVERE ARDS ..... 19***
  - ***THE USE OF NEUROMUSCULAR BLOCKING AGENTS IN LUNG-PROTECTIVE STRATEGIES ..... 19***
- 2.3 SUMMARY OF RELEVANT PRE-CLINICAL EXPERIMENTS AND CLINICAL TRIALS ..... 20
  - *2.3.1 Rationale for the proposed PEEP responsiveness test ..... 20*
  - **METHOD TO ASSESS LUNG RECRUITMENT AND THEIR LIMITS ..... 20**
  - **MAIN RESULTS OF THE PILOT STUDY ..... 21**
  - **MAIN RESULTS OF THE LAST STUDIES ..... 22**
- 2.4 DESCRIPTION OF THE POPULATION TO BE STUDIED AND JUSTIFICATION FOR THE CHOICE OF PARTICIPANTS ..... 22
- 2.5 SUCCINCT DESCRIPTION OF THE INVESTIGATIONAL PRODUCT(S) OR INTERVENTION(S) ..... 22
  - *2.5.1 First randomization ..... 23*
  - *2.5.1.1 First Randomization, Arm A: Minimal distension ..... 23*
  - *2.5.1.2 First Randomization, Arm B: Maximal recruitment ..... 23*
  - *2.5.1.3 First Randomization, Arm C: PRT-guided ventilation strategy ..... 24*
  - *2.5.2 Second randomization ..... 24*
  - *2.5.2.1 Second Randomization, Control arm: Early & Systematic Use of PP with NMBAs indicated only as rescue ..... 24*
  - *2.5.2.2 Second randomization, intervention: Early and systematic use of PP and NMBAs ..... 24*
- 2.6 SUMMARY OF THE KNOWN AND FORESEEABLE BENEFITS AND RISKS FOR THE RESEARCH PARTICIPANTS ..... 24

**3 OBJECTIVES ..... 25**

- 3.1 PRIMARY OBJECTIVES ..... 25
- 3.2 SECONDARY OBJECTIVES ..... 25
- 3.3 OBJECTIVE OF ANCILLARY STUDIES ..... 26
  - *3.3.1 Influence of lung morphology on PEEP responsiveness ..... 26*
  - *3.3.2 Reassessment of the PRT with determination of EELV and the R/I ratio ..... 26*
  - *3.3.3 Distribution of ventilation using electrical impedance tomography ..... 27*

**4 STUDY DESIGN ..... 27**

- 4.1 STUDY ENDPOINTS ..... 27
  - *4.1.1 Primary endpoint ..... 27*
  - *4.1.2 Secondary endpoints ..... 27*
- 4.2 DESCRIPTION OF RESEARCH METHODOLOGY ..... 28
  - *4.2.1 Design of the study ..... 28*
  - *4.2.2 Number of participating sites ..... 29*
  - *4.2.3 Identification of participants ..... 29*
  - *4.2.4 Randomisation ..... 29*
  - *4.2.5 Blinding methods and measures put in place to protect blinding ..... 30*

**5 IMPLEMENTATION OF THE STUDY ..... 31**

- 5.1 INCLUSION/RANDOMISATION VISIT (J0) ..... 31
  - *5.1.1 Screening visits (standard of care) ..... 31*
  - *5.1.2 Inclusion visit ..... 31*
  - *First randomization ..... 31*
  - *Second randomization ..... 32*
- 5.2 DURATION OF VENTILATION INTERVENTIONS & WEANING STRATEGY ..... 33





*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- 5.3 FOLLOW-UP VISITS ..... 34
  - *5.3.1 Data to be collected on first randomization:* ..... *34*
  - *5.3.2 Data to be collected on second randomization* ..... *34*
  - *5.3.3 Data to be collected at ICU discharge:* ..... *34*
  - *5.3.4 Data to be collected at hospital discharge:* ..... *34*
  - *5.3.5 Day 90 Follow-up visit* ..... *35*
  - *5.3.6 Day 180 Follow-up visit* ..... *35*
  - *5.4 Last study visit* ..... *35*
- 5.5 EXPECTED LENGTH OF PARTICIPATION AND DESCRIPTION OF THE CHRONOLOGY AND DURATION OF THE STUDY. 35
- 5.6 CHRONOLOGY OF THE STUDY ..... 36
- 5.7 DISTINCTION BETWEEN STANDARD CARE AND STUDY ..... 37

**6 ELIGIBILITY CRITERIA ..... 37**

- 6.1 INCLUSION CRITERIA ..... 37
- 6.2 EXCLUSION CRITERIA ..... 37
- 6.3 RECRUITMENT PROCEDURE ..... 38
- 6.4 TERMINATION RULES ..... 38
  - *6.4.1 Criteria and methods for premature discontinuation of study-related interventions/procedures/strategies or product administration* ..... *38*
  - *6.4.2 Criteria & procedures for premature withdrawal of a participant from the study* ..... *39*
  - *Follow-up of participants following premature withdrawal from the study* ..... *39*
  - *Procedures for replacing participants* ..... *39*
  - *Full or partial discontinuation of the study* ..... *39*

**7 STRATEGY ADMINISTERED TO STUDY PARTICIPANTS ..... 40**

- DESCRIPTION OF THE STUDY STRATEGY ..... 40
  - *7.1 First randomization: using a PEEP responsiveness test to guide therapy following first randomization* ..... *40*
  - *7.2 First Randomization - Arm A: Minimal distension* ..... *41*
  - *7.3 First Randomization - Arm B: Maximal recruitment* ..... *41*
  - *7.4 First Randomization – Arm C – PRT-guided ventilation strategy* ..... *42*
  - *7.5 Second randomization, Intervention arm: Early and systematic use of PP and NMBAs* ..... *42*
  - *7.6 Second Randomization, Control arm: Early & systematic use of PP with NMBAs indicated only as rescue* *43*

**8 EFFICACY ASSESSMENT ..... 43**

- 8.1 DESCRIPTION OF EFFICACY ENDPOINT ASSESSMENT PARAMETERS ..... 43
- 8.2 ANTICIPATED METHODS AND TIMETABLE FOR MEASURING, COLLECTING AND ANALYSING THE EFFICACY ASSESSMENT PARAMETERS ..... 45

**9 SPECIFIC STUDY COMMITTEES ..... 45**

- 9.1 SCIENTIFIC COMMITTEE ..... 45

**10 SAFETY ASSESSMENT - RISKS AND BURDENS ADDED BY THE STUDY ..... 46**

- 10.1 DEFINITIONS ..... 46
- 10.2 THE ROLE OF THE INVESTIGATOR ..... 46
  - *10.2.1 Serious adverse events that require the investigator to notify the sponsor without delay* ..... *47*
  - *10.2.2 Specific features of the protocol* ..... *47*
    - Other events that require the investigator to notify the sponsor without delay ..... 47
    - Serious adverse events that do not require the investigator to notify the sponsor without delay ..... 47
  - *10.2.2.1 Period during which SAEs must be notified without delay by the to thesponsor* ..... *48*
    - 10.2.2.2 Procedures and deadlines for notifying the sponsor ..... 48
- 10.3 ROLE OF THE SPONSOR ..... 49
  - *10.3.1 Analysis and declaration of serious adverse events* ..... *49*
  - *10.3.2 Analysis and declaration of other safety data* ..... *50*
  - *10.3.3 Annual safety report* ..... *50*
- 10.4 DATA SAFETY MONITORING BOARD ..... 51

**11 DATA MANAGEMENT ..... 51**

- 11.1 DATA COLLECTION PROCEDURES ..... 51
- 11.2 IDENTIFICATION OF DATA RECORDED DIRECTLY IN THE CRFS WHICH WILL BE CONSIDERED AS SOURCE DATA 51
- 11.3 RIGHT TO ACCESS DATA AND SOURCE DOCUMENTS ..... 51




*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

*11.3.1 Data access* ..... *51*
*11.3.2 Source documents* ..... *52*
*11.3.3 Data confidentiality* ..... *52*
- 11.4 DATA PROCESSING AND STORAGE OF RESEARCH DOCUMENTS AND DATA ..... 52
*11.4.1 Identification of the data processing manager and location(s)* ..... *52*
*11.4.2 Data entry* ..... *52*
- 11.5 DATA OWNERSHIP ..... 53

**12 STATISTICAL ASPECTS ..... 53**

- 12.1 DESCRIPTION OF STATISTICAL METHODS TO BE USED INCLUDING THE TIMETABLE FOR THE PLANNED INTERIM ANALYSES 53
*Initialisation and Optimal allocation computation* ..... *53*
- 12.2 CALCULATION HYPOTHESES FOR THE NUMBER OF PARTICIPANTS REQUIRED AND THE RESULT ..... 54
- 12.3 ANTICIPATED LEVEL OF STATISTICAL SIGNIFICANCE ..... 54
*Method for taking into account missing, unused or invalid data* ..... *55*
- 12.4 STATISTICAL CRITERIA FOR TERMINATION OF THE FIRST INTERVENTION ..... 55
*12.4.1 Choice of individuals to be included in the analyses* ..... *55*
*12.4.2 Subgroup analysis* ..... *55*

**13 QUALITY CONTROL AND ASSURANCE ..... 55**

- 13.1 GENERAL ORGANISATION ..... 56
*13.1.1 Strategy for centers opening* ..... *56*
*13.1.2 Scope of centre monitoring* ..... *56*
- 13.2 QUALITY CONTROL ..... 56
- 13.3 CASE REPORT FORMS ..... 56
- 13.4 MANAGEMENT OF NON-COMPLIANCES ..... 57
- 13.5 AUDITS/INSPECTIONS ..... 57
- 13.6 PRINCIPAL INVESTIGATOR'S COMMITMENT TO ASSUME RESPONSIBILITY ..... 57

**14 ETHICAL AND LEGAL CONSIDERATIONS ..... 57**

- 14.1 METHODS FOR INFORMING RESEARCH PARTICIPANTS AND OBTAINING THEIR CONSENT ..... 57
- 14.2 PROHIBITION FROM PARTICIPATING IN ANOTHER CLINICAL STUDY OR EXCLUSION PERIOD SET AFTER THE STUDY 58
- 14.3 LEGAL OBLIGATIONS ..... 58
*14.3.1 Role of the sponsor* ..... *58*
*14.3.2 Request for approval from the CPP (Research Ethics Committee)* ..... *59*
*14.3.3 Request for authorisation from ANSM* ..... *59*
*14.3.4 Procedures relating to data protection regulations* ..... *59*
*14.3.5 Amendments to the research* ..... *59*
*14.3.6 Final study report* ..... *59*
*14.3.7 Archiving* ..... *59*

**15 FUNDING AND INSURANCE ..... 60**

- 15.1 FUNDING SOURCES ..... 60
- 15.2 INSURANCE ..... 60

**16 PUBLICATION RULES ..... 60**

- 16.1 MENTION OF AP-HP AFFILIATION FOR PROJECTS SPONSORED BY AP-HP ..... 60
- 16.2 MENTION OF THE SPONSOR AP-HP (DRCI) IN THE ACKNOWLEDGEMENTS OF THE TEXT ..... 60
- 16.3 MENTION OF THE FINANCIAL BACKER IN THE ACKNOWLEDGEMENTS OF THE TEXT ..... 61

**17 BIBLIOGRAPHY ..... 61**

**18 LIST OF ADDENDA ..... 64**

- 18.1 SERIOUS ADVERSE EVENTS NOTIFICATION FORM ..... 64
- 18.2 PREGNANCY NOTIFICATION FORM ..... 64
- 18.3 QUESTIONNAIRES OR SCALES ..... 64
*SAPS II score* ..... *65*
*SOFA score* ..... *65*
*RASS score* ..... *66*



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

*MRC score* ..... *66*
*CAM-ICU score* ..... *67*
*EQ-5D-5L score* ..... *67*
*IES-R score* ..... *69*
*T-MoCA score* ..... *70*
- 18.4 RECOMMENDATIONS ON THE MONITORING OF VENTILATORY PARAMETERS IN ARDS PATIENTS (BEFORE INCLUSION): ..... 70



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

# ABREVIATIONS

- ABG: Arterial blood gas
- ACV: Assisted volume-control ventilation
- ARDS: Acute Respiratory Distress Syndrome
- BIPAP: Bilevel positive airway pressure
- CAM-ICU: Confusion Assessment Method for the Intensive Care Unit
- CPAP: Continuous positive arway pressure
- CPP: Committee for the Protection of Persons
- CRS: Respiratory system compliance
- CT: Computed tomographic
- ECCO2R: Extracorporeal $CO_2$ removal
- ECMO: Extracorporeal membrane oxygenation
- EELV: End-expiratory lung volumes
- FRC: Functioncal residual capacity
- PBW: Predicted body weight
- ICU: Intensive Care Unit
- IES-R: Impact Event Scale-Revised
- ITT: Intention-to-treat
- MAP: Mean arterial pressure
- MRC: Medical research council
- MV: Mechanical ventilation
- NMBAs: Neuromuscular blockade agents
- PBW: Predicted body weight
- PEEP: Positive end-expiratory pressure
- PP: Prone positioning
- PRT: PEEP responsiveness test
- PTSD: Posttraumatic stress disorder
- RCTs: Randomized controlled trials
- SAPS: Simplified acute physiology score
- SOFA: Sequential Organ Failure Assessment
- VFD: Ventilator Free Days
- VILI: Ventilator-induced lung injury
- $V_T$: Tidal volume


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

# 1 SUMMARY

| | |
|---|---|
| Full title | Assessment of the PEEP responsiveness to titrate end-expiratory pressure and of the need for muscle relaxation during prone positioning in moderate-to-severe acute respiratory distress syndrome: A Master Protocol |
| Acronym/reference | PEPER |
| Coordinating investigator | *Pr Alexandre Demoule, Service de Médecine Intensive-Réanimation, Pitié Salpêtrière Hospital, Paris* |
| Scientific Director | *Pr Laurent Papazian, Service de Médecine Intensive Réanimation, AP-HM, Marseille*<br>*Pr Sami Hraiech, Service de Médecine Intensive Réanimation, AP-HM, Marseille*<br>*Pr Jean-Daniel Chiche, Service de Médecine Intensive Adulte, Centre Hospitalier Universitaire Vaudois, Lausanne* |
| Sponsor | Assistance Publique – Hôpitaux de Paris |
| Scientific justification | Despite best supportive care, mortality of the Acute Respiratory Distress Syndrom (ARDS) remains around 35-46%[1,2]. In the absence of specific treatments, providing safe and efficient mechanical ventilation (MV) is key to survival.<br>There are still management issues for ICU of patients with moderate-to-severe ARDS.<br>First, the use of low tidal volumes ($V_T$) (6 mL/kg of predicted body weight – PBW) and plateau pressures ($P_{PLAT}$) improves survival in randomized controlled trials (RCTs)[2], but the safest $V_T$ to be applied for each patient remains unknown. Normalizing $V_T$ to respiratory system compliance ($C_{RS}$) and using the ratio as an index of the "functional" size of the lung could improve outcomes[3]. Driving pressure ($\Delta P = P_{PLAT}$-total PEEP) has been reported to be a more accurate indicator of the risk of VILI and death. Whether targeting low $\Delta P$ instead of a 6 mL/kg $V_T$ improves outcome has not been tested prospectively. The optimal method to set PEEP is also a matter of debate. A meta-analysis of the 3 main RCTs showed that higher PEEP improved survival in patients with $PaO_2/FiO_2$<200 mmHg[4]. Still, there is considerable equipoise as to the optimal PEEP settings in patients with ARDS. A strategy of lung recruitment and PEEP titration according to the best $C_{RS}$ applied irrespective of the potential for lung recruitment increased mortality[5]. As the amount of potentially recruitable lung vary widely among patients and is strongly associated with the response to PEEP, it may be necessary to tailor PEEP settings based on the response to a PEEP trial.<br>As the first aim, we wish to test a personalized approach to set PEEP widely supported by the literature. **We first hypothesized that i) patients with greater amounts of recruitable lung may benefit from higher PEEP levels, if attention is paid to maintain $\Delta P$ below 14 $cmH_2O$, ii) setting PEEP based on results of a PEEP-responsiveness test improves survival as compared to low- and high-PEEP strategies applied independently of the patient response.** |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | Apart from the reduction of $V_T$ and the control of $P_{PLAT}$ below 30 $cmH_2O$, only 2 interventions demonstrated a reduction of mortality in large RCTs: a 48-hour continuous infusion of neuromuscular blocking agents (NMBAs) at the acute phase of ARDS and the use of prone positioning (PP)[6,7] . Whereas there is little doubt on the utility of PP in patients with $PaO_2/FiO_2$ ratio < 150 mmHg, there is more controversy on the impact of NMBAs on survival. In the ACURASYS study, early treatment with cisatracurium for 48 hours improved the adjusted 90-day survival rate in the group of severe ARDS patients[6]. The beneficial effect of cisatracurium particularly affected patients presenting a $PaO_2/FiO_2$<120 mmHg. A recent study re-evaluated the beneficial effects of NMBAs on mortality by comparing the use of cisatracurium with management by light sedation very early in the course of moderate-to-severe ARDS[8]. Neither in-hospital mortality nor ventilator-free days at day 90 were different between the 2 groups. Significant methodological differences may explain these inconsistent results between the ACURASYS and ROSE studies. Despite a strong rationale and a very widespread use in clinical practice, no current guidelines answer the question of the best timing of muscle relaxation in moderate to severe ARDS patients treated with PP.<br>**As a second aim, we thus hypothesized that the early systematic and combined use of NMBAs improved survival of patients with moderate to severe ARDS requiring prone positioning after optimization of PEEP settings**. |
| Main objective and primary endpoint | The main objective of this Master Protocol is to test the benefit of two management strategies of patients with moderate or severe ARDS:<br><br>- To test whether titration of PEEP based on the patients' response to a standardized PEEP responsiveness test improves survival<br>- To test whether the early and systematic combined use of PP and NMBAs is superior regarding all-cause mortality to the early and systematic use of PP with NMBAs prescribed only as a rescue strategy.<br><br>For both interventions, **the primary endpoint is 28-day all-cause mortality after randomisation.** |
| Secondary objectives and endpoints | As secondary objectives, we aim:<br><br>- To test whether implementing a high-PEEP strategy only in patients with a positive response to a PRT is superior to using PEEP levels regardless of lung recruitability.<br>- To assess if the systematic and early use of prone positioning (PP) and neuromuscular blockade agents (NMBAs) is superior to initiating PP early and using NMBAs only as a rescue strategy.<br><br>We will investigate these strategies across multiple objectives, including:<br><br>• Physiological effects: evaluate the impact of the interventions on physiological parameters such as $PaO_2/FiO_2$, oxygenation index, and ventilator parameters at at H24, H48, H72, and on day 7 and 14. |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | • Organ dysfunctions: assess the development and progression of organ dysfunctions, including acute kidney injury, hepatic dysfunction, and cardiovascular compromise, through detailed evaluations of the Sequential Organ Failure Assessment (SOFA) score at 24, 48, and 72 hours post-intervention, as well as on days 7 and 14.<br>• Clinical/Patient-centered efficacy outcomes: measure clinical endpoints such as mortality rates, ventilator-free days length of ICU stay and hospital-free days.<br>• Safety objective: assess the occurrence of barotrauma and of acute cor pulmonale through day 7. Additionally, evaluate ICU-acquired weakness using the Medical Research Council (MRC) score at ICU discharge, where a score less than 48 defines ICU-acquired weakness.<br>• Use of Other Rescue Procedures: record and monitor the use of other rescue procedures and of NMBAs during the follow up of the patients. Additionnaly, calculate the number of muscle relaxants-free days between inclusion in the study and day 7.<br>• Sedatives/Analgesic Use: measure the number of days alive and without continuous IV administration of sedatives and/or analgesics at day 7 and day 28 post-intervention. Evaluate the presence of delirium using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) at days 14 and ICU discharge.<br>• Quality of Life: assess the impact of interventions on patients' physical, psychological, and social well-being, using validated quality of life measures and questionnaries.<br>• Exploratory objective: assess death with refractory hypoxemia, refractory acidosis, and barotrauma within 7 days. Monitor initiation or significant increase in vasopressors or hypotension within 8 hours post-randomization. Identify cases of refractory hypoxemia and severe acidosis within 8 hours post-randomization.<br><br>***Secondary endpoints:***<br><br>- ***Physiological outcomes:***<br>• $PaO_2/FiO_2$, oxygenation index and ventilatory parameters ($V_T$, respiratory rate, total PEEP, $P_{PEAK}$, $P_{PLAT}$, $C_{RS}$) at H24, H48, H72, and on day 7 and 14<br>- ***Organ dysfunctions:***<br>• Detailed Sequential Organ Failure Assessment (SOFA) score at H24, H48, H72, and on day 7 and 14<br>- ***Clinical / Patient-centered efficacy outcomes***<br>• All-cause mortality at days 90 and 1 year<br>• All-cause ICU and hospital mortality<br>• Duration of mechanical ventilation<br>• Ventilator Free Days at day 28 (VFD28). The number of VFD is defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or died prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.<br>• ICU and hospital length of stay<br>• ICU-free days at day 28<br>• Hospital-free days at day 28 and day 90<br>- ***Safety outcomes***<br>• Occurrence of barotrauma (defined as any pneumothorax, pneumomediastinum, subcutaneous emphysema, or pneumatocele of more than 2 cm detected on image examinations) through day 7<br>• Occurrence of acute cor pulmonale defined by the combination of a right/left ventricular diameter ratio greater than 0.6 and a paradoxical septum through day 7<br>• ICU acquired weakness assessed by the medical research council (MRC) score at ICU discharge. A score < 48 defines ICU acquired weakness.<br>- ***Use of other rescue procedures***<br>• Use (days) of other rescue procedures such as inhaled nitric oxide, almitrine, epoprostenol sodium, extracorporeal membrane oxygenation (ECMO), extracorporeal $CO_2$ removal (ECCO2R)<br>• Use of NMBAs during the first 3 days following inclusion<br>• Use of NMBAs following inclusion in the rescue arm of the second randomization<br>• Muscle relaxants-free days between inclusion and day 7<br>- ***Sedatives and analgesics use***<br>• Number of days alive and without continuous IV administration of sedatives/analgesics at day 7 and day 28<br>• Presence of delirium (CAM-ICU) at day 14 & ICU discharge<br>• Paralysis recall assessment at ICU discharge using a modified Brice questionnaire<br>- ***Quality of life at 1 year***<br>• Disability assessed by the Activities of Daily Living score (Lawton IADL)<br>• Quality-of-life, using the EuroQOL (EQ-5D-5L)<br>• Posttraumatic stress disorder (PTSD), using the Impact Event Scale-Revised (IES-R)<br>• Subsequent return to work. Return to work status: employment statut<br>• Cognitive dysfunction using T-MoCA score<br>• Place of residence<br>- ***Exploratory outcomes***<br>• Death with refractory hypoxemia (defined as $PaO_2/FiO_2$< 80 mmHg outside a care incident) within 7 days<br>• Death with refractory acidosis within 7 days<br>• Death with barotrauma within 7 days<br>• Need of commencement or 30% increase in vasopressors or hypotension (MAP<60 mmHg) within 8 hours after the first randomization<br>• Refractory hypoxemia within 8 hours after randomization |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | (defined as $PaO_2/FiO_2$< 50 mmHg for more than one hour)<br>• Severe acidosis (pH<7.10) within 8 hours after randomization |
| Design of the study | **Master Protocol**, including two randomized, controlled, clinical trials with Bayesian adaptive designs<br>• **First randomization** with 3 parallel arms (first ratio 1:1:1)<br>A. Minimal distension<br>B. Maximal recruitment<br>C. PRT-guided ventilation strategy<br>• **Second randomization within 4 to 72 hours**, if persistent $PaO_2/FiO_2$ <150 mmHg, with two parallel arms (ratio 1:1)<br>1. Prone position with systematic NMBAs<br>2. Prone position without systematic NMBAs |
| Population of study participants | Patients with moderate to severe ARDS at the early phase of the disease process |
| Inclusion criteria | - Inclusion within 96 hours of ICU admission and within 72 hours of tracheal intubation <u>for first randomization</u> and then within 72 hours of the first randomization for the second randomization<br>- Patients meeting the Berlin ARDS definition criteria with hypoxemia characterized as:<br>• <u>for first randomization</u>: $PaO_2/FiO_2$ <200 mmHg on a PEEP ≥5 $cmH_2O$ with $FiO_2$≥0.6 while $V_T$ is 6 ml/kg PBW and adequate sedation level to adjust mechanical ventilation settings<br>• <u>for second randomization</u>: $PaO_2/FiO_2$ <150 mmHg on optimized ventilatory settings according to the first randomization, confirmed by two ABG analyses separated by an interval time of 4 hours (besides emergency situations) and observed within 72 hours of the first randomization<br>- Informed consent signed:<br>• by the patient<br>• Or informed consent signed by a family members / trustworthy person if his condition does not allow him to express his consent by written as per L. 1111-6<br>• Or in a situation urgently and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow him to consent.<br>- Health insurance coverage |
| Exclusion criteria | - Age < 18 years<br>- Known pregnancy or breathfeeding<br>- Participation in another interventional studies evaluating ventilator settings and neuromuscular blocking agents at the initial phase of ARDS.<br>- Intracranial pressure > 30 mm Hg or cerebral perfusion pressure < 60 mmHg<br>- Severe chronic respiratory disease requiring long-term $O_2$ therapy or home mechanical ventilation (except CPAP/BIPAP used for sleep apnea syndrome)<br>- Chronic interstitial lung disease<br>- Continuous neuromuscular blockade infusion at enrolment<br>- Previous hypersensitivity or anaphylactic reaction to any NMBA<br>- Neuromuscular disease that may potentiate neuromuscular blockade or impair spontaneous ventilation: amyotrophic lateral |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | sclerosis, Guillain-Barré syndrome, myasthenia gravis, upper spinal injury at level C5 or above<br>- Patients on ECMO or any technique of extracorporeal $CO_2$ removal<br>- Sickle cell disease<br>- Actual body weight >1 kg/cm of height<br>- Severe chronic liver disease defined as a Child-Pugh score of 12-15 (Appendix)<br>- Pneumothorax at randomization<br>- Expected duration of mechanical ventilation <48 hours<br>- SAPS II score >75 at the time of ICU admission or suffering from a disease with an estimated survival time of less than two months<br>- Decision to withhold life-sustaining treatment<br>- Patients deprived of freedom or under legal authority<br>- Unstable spine fracture |
| Interventions or product under investigation | - First part of the trial<br>• Decision of the ventilation strategy (maximal recruitment or minimal distention) according to the result of the PRT.<br>▪ If the PRT shows no response to PEEP, a minimal distension ventilation strategy will be applied. Ventilation will strictly follow the intervention protocol used in the ARMA trial[2]. In brief, this includes assisted volume-control ventilation (ACV) with $V_T$= 6 mL/kg PBW and $P_{PLAT}$≤ 30 $cmH_2O$) and a $FiO_2$/PEEP combination chart titration until weaning criteria are met.<br>▪ If the PRT shows a response to PEEP, a maximal recruitment ventilation strategy will be applied. Patients will be ventilated using ACV with a $V_T$ initially set at 6 mL/kg and the highest possible PEEP to obtain a $P_{PLAT}$ = 27 $cmH_2O$ with a $V_T$ = 6 mL/kg PBW. Then, driving pressure $\Delta P$ will be measured and a further reduction of $V_T$ (0.5 mL/kg steps) will be eventually performed if necessary to achieve $\Delta P \leq 14$ $cmH_2O$.<br><br>- Second part of the trial<br>• Interventional arm: early NMBAs will be used as soon as possible after randomization and no later than 6 hours of it. NMBAs are used for 48h but can be stopped early if $PaO_2/FiO_2$ is ≥ 150 mmHg at a PEEP ≤ 12 $cmH_2O$ and plateau pressure ≤ 28 $cmH_2O$ while the patient is in the supine position. |
| Comparator arm | - First part of the trial:<br>• Decision of the ventilation strategy (maximal recruitment or minimal distention) according to the routine care<br>▪ **Minimal distension**, ventilation will strictly follow the intervention protocol used in the ARMA trial[2]. In brief, this includes assisted volume-control ventilation (ACV) with $V_T$= 6 mL/kg PBW and $P_{PLAT}$≤ 30 $cmH_2O$) and a $FiO_2$/PEEP combination chart titration until weaning criteria are met.<br>▪ **Maximal recruitment,** patients will be ventilated using ACV with a VT initially set at 6 mL/kg and the highest possible PEEP to obtain a $P_{PLAT}$ = 27 $cmH_2O$ with a $V_T$ = 6 mL/kg PBW. Then, driving pressure $\Delta P$ will be measured and a further reduction of $V_T$ (0.5 mL/kg steps) will be |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | eventually performed if necessary to achieve $\Delta P \leq 14$ $cmH_2O$.<br>– Second part of the trial<br>• In the control arm, NMBAs will only be used as a rescue if $P_{PLAT}$ exceeds 30 $cmH_2O$ for at least 10 minutes despite increasing doses of sedatives and decreasing $V_T$ (while maintaining a pH > 7.20) and also PEEP by 2 $cmH_2O$ (only if pH ≤ 7.20) if tolerated. |
| Interventions added by the study | • Two successive randomizations<br>• A PRT will be performed in all patients enrolled following the same procedure. Baseline characteristics will be obtained with a PEEP of 5 $cmH_2O$ then a lung recruitment maneuver will be performed then PEEP will be increased from 5 to 15 $cmH_2O$, while $V_T$ will be maintained at 6 mL/kg PBW. After 20 min, investigators will record changes in $PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$.<br>• In centers participating to ancillary studies, a second PRT will be performed for reassessement with the R/I ratio, distribution of ventilation will be studied using electrical impedence tomography and end-expiratory lung volume will be measures (GE brand ventilators only). Also, the relationships between chest X-ray appearance and effect of high PEEP on gas exchange will be assessed<br>• In the control arm, sedation will be adjusted to ensure clinically acceptable patient-ventilator synchrony, and NMBAs will only be used as a rescueFollow up visits at day 90, 180 and 360<br>• Questionnaires at day 180 and 360<br>• Blood or urinary pregnency test at inclusion |
| Expected benefits for the participants and for society | With nearly 1.2 million deaths worldwide, ARDS is a major public health issue. Any intervention that could potentially impact mortality, time on mechanical ventilation and the need for expensive rescue therapies would have important human, social and financial benefits and warrant investigation. ARDS is also associated with prolonged ICU and hospital stays, high hospital costs, and with significant morbidity. Survivors of the ARDS exhibit exercise limitation, physical and psychological sequelae, decreased physical quality of life, and increased costs and use of health care services. Less than 50% of them have returned to normal work after 1 year. We anticipate that a personalized approach to mechanical ventilation and the early use of NMBAs and PP will reduce mortality, decrease the time to resolution of ARDS and shorten duration of MV, ICU and hospital stay. We also expect that such an approach will reduce the risk of ventilator-induced lung injury and life-threatening complications. |
| Risks and burdens added by the study | Interventions under investigation in the study carry no significant additional risk as compared to usual care of patients with moderate to severe ARDS in intensive care units.<br>The following risks associated with the different strategies: pneumothorax, pneumomediastinum, subcutaneous emphysema, refractory hypoxemia, severe acidosis, cor pulmonale, anaphylaxis due to NMBAs use, and catheter or endotracheal tube accidental removal during PP.<br><br>Risks associated with the PRT are barotrauma and a decrease in arterial blood pressure. |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| | *The risk level of the study:* B |
| Number of participants included | *1200 patients* |
| Number of centres | The study is a national multicenter trial including 60 centers |
| Duration of the study | • Inclusion period: 36 months<br>• Participation period (treatment + follow-up): 360 days (12 months)<br>• Total duration: 48 months |
| Number of enrolments expected per site and per month | 0.55patient per site and per month |
| Statistical analysis | For the first randomization, a Bayesian enrichment design with response-adaptive randomization will be used to evaluate the primary outcome (28-day mortality). Interim analyses will be conducted every 300 patients to detect early efficacy of the intervention and update randomization allocation probabilities. Regarding the second randomization, the primary outcome will be evaluated using a stratified chi-square test based on the results of the first randomization. Secondary outcomes will be assessed at the final analysis. All analyses will be conducted on an intention-to-treat (ITT) basis. |
| Funding sources | *Ministry of Health, PHRC National 2020* |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

# 2 SCIENTIFIC JUSTIFICATION FOR THE STUDY

Acute respiratory failure is one of the most frequent and severe organ failures in the intensive care unit (ICU). Acute Respiratory Distress Syndrome (ARDS) is the most severe form of acute respiratory failure[1]. Recently, the COVID-19 pandemics has resulted in an unprecedented number of patients with ARDS. There are still open questions regarding the ideal modalities of ventilatory support in patients with ARDS. We aim to combine 2 trials to assess the best ventilatory strategy for patients who develop moderate or severe form of ARDS as defined by the ARDS Definition Taskforce[1]. Specifically, we plan to investigate i) whether a novel strategy that includes a specific test to assess lung recruitability can help determine the optimal level of positive end-expiratory pressure (PEEP) in patients with ARDS, ii) whether the early and systematic combined use of neuromuscular blocking agents (NMBAs) and prone position (PP) improve outcome as compared with the systematic use of PP while NMBAs will be prescribed as rescue therapy in moderate-to-severe ARDS patients.

## 2.1 Hypothesis for the study

### *2.1.1 Hypothesis for the first randomization*

The amount of potentially recruitable lung varies widely in ARDS patients[9]. Thus, being able to identify the potential for recruitment at the bedside may be a key factor to success in our ability to implement safe and efficient mechanical ventilation. Patients with a higher percentage of potentially recruitable lung have poorer oxygenation, worse CRS and higher levels of dead space than patients with a lower percentage of potentially recruitable lung[9]. Caironi et al. have shown that there is a good correlation between the proportion of potentially recruitable lung and the severity of ARDS estimated with PEEP set to 5 $cmH_2O$ rather than with higher PEEP levels[10]. Whereas improvements in arterial oxygenation with increased PEEP often reflect lung recruitment, arterial oxygenation is also influenced by other factors affected by PEEP (i.e., cardiac output), rendering the correlation imperfect. As discussed below (Section 2.2.3), finding a practical yet reliable method to detect who might benefit from higher PEEP levels at the bedside remains complex despite the availability of various options to evaluate lung recruitability.

**We hypothesize that patients with a greater percentage of recruitable lung may benefit from higher PEEP strategies, provided that attention is paid to maintain $\Delta P$ within clinically acceptable ranges, whereas patients with limited potential for recruitment may have better outcomes when treated with more conservative PEEP levels. To test this hypothesis, we plan to investigate the effect on 28-day mortality of a strategy that involves the use of a PEEP responsiveness test (PRT) to decide whether patients should be treated with high PEEP with $V_T$ set at 6 mL/kg or less in order to limit $\Delta P$ to a maximum of 14 $cmH_2O$, or with more conservative PEEP settings aiming at minimal distention.** Specifically, we will test whether the use of a PRT confers any advantage in selecting PEEP levels as compared to low- and high-PEEP strategies applied independently of the patient response. We hypothesize that patients with the greatest amount of recruitable lung and/or with the most severe hypoxemia will benefit the most from a high PEEP / maximal recruitment strategy.

### *2.1.2 Hypothesis for the second randomization*

The aim of the second randomization is to bring high level of evidence to characterize the place of NMBAs in the management of moderate-to-severe ARDS patients ventilated in PP. A survey in 20 French intensivists (all of them having participated into at least one major academic trial on ARDS) and a sample of 5 patients revealed that both intensivists and patients were reluctant to discard any possibility to use PP and/or NMBAs when indicated. It is the reason why **the present study will evaluate the early and systematic combined use of NMBAs and PP as compared with the systematic use of PP while NMBAs will be prescribed as rescue therapy (North American strategy) in moderate-to-severe ARDS patients**. **We will conduct a superiority trial comparing the combination of PP and NMBAs early in the course of ARDS patients presenting with a $PaO_2/FiO_2$ < 150 mmHg on PEEP of at least 5 $cmH_2O$ and with a $FiO_2$ of at least 0.60 with the early use of PP associated with the use of NMBAs only as rescue (when $P_{PLAT}$ exceeds 30 $cmH_2O$)**. **This study will be the first to evaluate the timing of NMBAs (early**



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

**vs. only if needed as rescue) on mortality of ARDS patients requiring PP after optimization of PEEP settings.**

## 2.2 Description of knowledge relating to the condition in question

### *2.2.1 About the condition under investigation (ARDS)*

- ***ARDS is a major public health problem***

More than 50 years after its description, ARDS remains a major public health issue. Globally, ARDS affects approximately 3 million patients annually, accounting for 10% of ICU admissions, and 24% of patients receiving mechanical ventilation in the ICU[11]. The incidence of ARDS has dramatically increased with the COVID-19 pandemics that killed more than 2.5 million patients out of the estimated 114.6 million affected. Data from 24 countries indicate that the concomitant number of ARDS patients on a single day may have culminated well above 25,000 in January 2021 (https://bit.ly/3b6ArZZ). Mortality from ARDS remains high, ranging from 35% to 46% with higher mortality being associated with greater degrees of lung injury severity at onset[11]. Despite decades of research, specific treatment options for ARDS remain limited. Supportive care with mechanical ventilation remains the mainstay of management. Key to the survival of patients with ARDS is the ability to provide safe and efficient ventilatory support in the subset of patients that develop overt acute respiratory failure and ARDS.

Despite best supportive care, ARDS remains a global problem worldwide and is commonly associated with significant mortality and morbidity[12]. As an example, during the spring wave of the COVID-19 pandemics, 53% of the 4244 patients admitted in the 149 ICUs of the COVID-ICU Registry during the first wave of the pandemics met the ARDS criteria and 38% of these patients tragically died in hospital[13]. ARDS is also associated with prolonged ICU and hospital stays, high hospital costs, and with significant morbidity. Survivors of the ARDS exhibit exercise limitation, physical and psychological sequelae, decreased physical quality of life, and increased costs and use of health care services. Less than 50% of them have returned to normal work after 1 year[14] .

So, any intervention that could potentially impact mortality, time on mechanical ventilation and the need for expensive rescue therapies would have important human, social and financial benefits and warrant investigation.

### *2.2.2 About the studied strategies/procedures*

- ***Ventilator-induced lung injury increases mortality of ARDS***

While mechanical ventilation is a life-saving intervention which maintains satisfactory gas exchange, it can also damage the lung via increased alveolar strain due to high $V_T$ (volutrauma) and ventilation pressures (barotrauma), and shear stress-induced injury caused by cyclic opening and closure of unstable alveoli (atelectrauma)[15,16]. Application of PEEP during mechanical ventilation can also decrease the amount of permanently collapsed, non-ventilated lung that contributes to alter gas exchanges and increase shear stress[17]. Ventilator-induced lung injury (VILI) results from these repetitive mechanical assaults that also promote a deleterious pulmonary and systemic inflammatory injury, called biotrauma[16]. Experimental and clinical studies have shown that VILI significantly increases morbidity and mortality in experimental models as well as in patients with ARDS[12].

### *2.2.3 About defining optimal ventilatory strategies in ARDS*

Extensive research has been conducted to define optimal ventilatory strategies in patients with ARDS, with the dual goal of limiting the development of VILI while ensuring adequate gas exchange. Nevertheless, clinical recommendations highlight areas of uncertainty regarding ventilatory settings in specific subsets of patients[18–20].

- ***Limitation of inflation pressures to reduce VILI***



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Mechanical ventilation strategies that use lower end-inspiratory (plateau) airway pressures ($P_{PLAT}$) and lower $V_T$ have been associated with survival benefits in randomized clinical trials (RCTs) involving patients with the ARDS[2,21]. Investigators from the NIH ARDSNet have shown that reducing $V_T$ from 12 to 6 mL/kg of predicted body weight (PBW) decreases mortality and facilitates weaning from mechanical ventilation[2]. Still, it is difficult to estimate what is the safe $V_T$ to be applied for each patient. Depending on the severity of illness and the reduction of functional residual capacity (FRC), some patients may still be at significant risk of VILI when treated with a $V_T$ of 6 mL/kg IBW[22]. Clinical data indicate that the most severe patients might benefit from ventilation with ultra-low $V_T$ (4 mL/kg), provided that adjunct techniques are used to remove $CO_2$ and maintain arterial pH above 7.25[23,24].

In fact, most studies have scaled $V_T$ to predicted PBW to normalize $V_T$ to lung size in order to minimize VILI. However, in patients with ARDS, the proportion of lung available for ventilation is markedly decreased, which is reflected by lower respiratory system compliance ($C_{RS}$)[9]. Normalizing $V_T$ to $C_{RS}$ and using the ratio as an index indicating the "functional" size of the lung could provide a better predictor of outcomes in patients with ARDS than $V_T$ alone. In patients who are not making inspiratory efforts, this ratio ($\Delta P = V_T/C_{RS}$) termed the driving pressure can be routinely calculated as the plateau pressure minus total PEEP. Mediation analysis of data obtained in randomized clinical trials testing lung-protective strategies has pointed to $\Delta P$ as a more accurate indicator of the risk of VILI[3]. Amato et al. reported that among all ventilatory variables, $\Delta P$ was most strongly associated with survival. In this cohort, mortality increased significantly when $\Delta P$ was greater than 14 $cmH_2O$. **Whether targeting low $\Delta P$ provides a survival advantage over targeting a 6 mL/kg $V_T$ has not been tested prospectively**.

- ***Setting PEEP to improve outcome in moderate to severe ARDS***

Setting PEEP in ARDS patients is another ongoing topic of controversy. Several trials have tested whether the use of high-PEEP strategies confer a survival advantage as compared to more conservative PEEP setting. Using PEEP-$FiO_2$ algorithms to determine optimal levels of PEEP, the NIH ARDSNet investigators and the Canadian Critical Care Trials Group failed to detect any significant benefit of high PEEP strategies in patients with acute lung injury or ARDS[25,26]. Similarly, Mercat et al. compared a low PEEP strategy (minimal distension) to a strategy based on setting PEEP to the highest possible value while maintaining $P_{PLAT}$ between 28-30 $cmH_2O$ with 6 mL/kg $V_T$ (maximal recruitment)[27]. There was no statistically significant difference in survival, although a trend toward lower mortality was observed when higher PEEP was applied to the most severe subset of patients. A patient-level data meta-analysis of these 3 trials suggests that higher PEEP may be beneficial in patients with $PaO_2/FiO_2$ <200 mmHg[4]. Recently, another multicenter trial tested if lung recruitment associated with PEEP titration according to the best respiratory-system compliance decreased 28-day mortality of patients with moderate to severe ARDS[5]. Compared with a conventional low-PEEP strategy, the experimental group strategy increased 28-day and 6-month mortality, decreased the number of mean ventilator-free days, and increased the risk of barotrauma. Application of high PEEP levels in patients with little potential for lung recruitment may have contributed to poor outcomes in this study.

**Altogether, these data suggest that only severe patients with a high potential for lung recruitment benefit from high PEEP strategies. However, all studies testing the effect of high PEEP in patients with ARDS have randomized patients irrespective of their potential for recruitment.**

- ***The use of neuromuscular blocking agents in lung-protective strategies***

Apart from the reduction of $V_T$ and the control of $P_{PLAT}$ below 30 $cmH_2O$[2], only 2 interventions demonstrated a reduction of mortality in large RCTs: a 48-hour continuous infusion of NMBAs at the acute phase of ARDS[6] and the use of PP[7]. In these 2 latter studies, only patients presenting with a moderate-to-severe ARDS with a $PaO_2/FiO_2$ ratio < 150 mmHg were considered. Whereas there is little doubt on the utility of PP in patients with $PaO_2/FiO_2$ ratio < 150 mmHg, there is more controversy on the impact of NMBAs on survival.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Four RCTs specifically addressed the impact of NMBAs on the prognosis of ARDS patients in the era of lung-protective ventilation. Using a multicentric design, the 2 first studies showed a significant beneficial effect on the course of $PaO_2/FIO_2$ ratio in the NMBAS-treated group of patients, as well as a greater decrease in $P_{PLAT}$, PEEP and $FiO_2$ requirements in the NMBAs group during the study period[28,29]. In the ACURASYS study, 340 patients were randomly assigned to receive either cisatracurium besylate or placebo for 48 hours[6]. Early treatment with cisatracurium for 48 hours improved the adjusted 90-day survival rate in the group of severe ARDS patients. The beneficial effect of cisatracurium on the 90-day survival rate particularly affected patients presenting a $PaO_2/FiO_2$<120 mmHg. Furthermore, the cisatracurium group had significantly more ventilator-free days than the placebo group during the first 28 and 90 days, and more days free of organ failure (other than the lung) during the first 28 days. However, a recent large RCT evaluating the role of NMBAs in ARDS has tempered the enthusiasm for their use as a front-line adjunctive therapy. The PETAL (Prevention and Early Treatment of Acute Lung Injury) network aimed to re-evaluate the beneficial effects of NMBAs on mortality by designing the ROSE study comparing the use of cisatracurium with management by light sedation very early in the course of moderate-to-severe ARDS[8]. The primary endpoint was hospital mortality from any cause at day 90. The trial was stopped at the second interim analysis for futility. Neither in-hospital mortality nor ventilator-free days at day 90 were different between the 2 groups. Significant methodological differences may explain these inconsistent results between the ACURASYS and ROSE studies[30]. In the ROSE trial[8], patients were included earlier than in ACURASYS, sometimes with a $PaO_2/FiO_2$ > 150 mmHg at the time of randomization, and a high PEEP strategy was applied in both arms of the ROSE study while a moderate PEEP strategy was used in the ACURASYS study[6]. In addition, an open-label administration of NMBAs as a rescue therapy was allowed in the control group of ROSE and sedation strategies were also different during the first two days in the control group—light sedation in ROSE, heavy sedation in ACURASYS. These differences in PEEP and sedation strategies may have altered the level of ventilator-induced lung injury (VILI) experienced in the control and intervention arms in both studies, highlighting the complex interplay among patient efforts, sedation, NMBAs and ventilator management in ARDS[30]. To summarize, **despite a relevant rational and a very widespread use in clinical practice, no current guidelines strongly answer the following question: in moderate to severe ARDS patients, after optimization of PEEP settings, should NMBAs be systematically associated when PP is initiated?** In addition, although PP and NMBAs have been shown to ensure protective ventilation through common pathophysiological effects, their synergistic or additional benefits remain to be proven.

## 2.3 Summary of relevant pre-clinical experiments and clinical trials

### *2.3.1 Rationale for the proposed PEEP responsiveness test*

- **Method to assess lung recruitment and their limits**

Despite the availability of multiple techniques to assess lung recruitability, none has emerged as an easy, reliable, widely applicable method at the bedside.

- Computed tomographic (CT) scanning can identify tissue compartments that are well aerated, poorly aerated, and non-aerated[31]. By comparing images obtained at different PEEP levels, the amount of lung tissue that is recruited at a higher PEEP in relation to the baseline lung volume can be estimated[32]. Although scientifically rigorous, this method is too cumbersome, costly, and it requires transportation to the CT-scanner suite that may be risky for critically-ill ARDS patients. Constantin et al. tested whether a mechanical ventilation strategy personalized to individual patients' lung morphology on the CT-scanner would improve the survival of patients with ARDS when compared with standard of care[33]. Unfortunately, CT-scanner was performed in only 34% of the 400 patients, confirming the practical difficulties to use CT-scanner for therapeutic purposes in these severe patients. Interestingly, misclassification of patients as having focal or non-focal ARDS by the investigators was observed in 21% of patients and was associated with worse outcomes whereas analysis of patients whose lung morphology was correctly classified at inclusion revealed a significant increase in survival for those in the personalized group.
- Helium dilution or nitrogen washout techniques have been used to measure changes in end-expiratory lung volumes (EELV) at different PEEP levels. Initially performed in physiology laboratories, measurements of EELV (also named functional residual capacity – FRC) can now


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

be performed at the bedside with the nitrogen washout technique using specific ventilators. The increase in EELV from a lower to a higher PEEP level is estimated from the product of the change in PEEP and the $C_{RS}$ measured at the lower PEEP level. If the change in EELV exceeds the predicted change in EELV, the difference is presumed to represent recruitment. This method is reliable, but it requires specific equipment that is not available in every ICU[34,35].

- The use of electrical impedance tomography (EIT), which permits real-time visualization of changes in the distribution of ventilation as PEEP is adjusted, has been proposed to assess lung recruitability. Comparison of actual and predicted increases in lung impedance after an increase in PEEP permit estimates of recruited lung volume. However, this technique also requires a specific device and more studies are needed to evaluate correlations with established techniques (CT-scanner, EELV)[36] . Similarly, the use of lung ultrasound to quantitatively assess lung recruitment and identify recruiters or non-recruiters is not yet validated and is a user-dependent technique[37] .
- Construction of low-flow airway pressure–volume (P-V) curves during tidal ventilation at different PEEP levels can also be used to assess lung recruitment. After a P-V curve is established at a given PEEP level, the airway is opened to atmospheric pressure for a prolonged exhalation to FRC. Measuring the exhaled volumes at different PEEP levels to FRC allow curves to be plotted on the same axes, with the origin at FRC and an airway pressure of zero. The volume recruited when PEEP is raised from the lower to the higher PEEP level is calculated as the difference in volume between the two curves at a given airway pressure.
- Recently, Chen et al. described a technique to quantify the R/I ratio and assess the potential for lung recruitment[38] . The R/I ratio estimates how much of an increase in EELV induced by PEEP is distributed between the recruited lung (recruitment) and the inflation and/or hyperinflation of the “baby lung” when a higher PEEP is applied. Values of R/I ratio range from 0 to 2.0. The higher the R/I ratio, the higher the potential for lung recruitment. An R/I ratio of 1.0 suggests a high likelihood of recruitment, as the volume will be distributed similarly to the recruited lung and the baby lung, and a threshold of 0.5 has been proposed to distinguish recruiters from non-recruiters. The R/I ratio correlates with oxygenation and alveolar dead space, can be performed at the bedside and requires only a single-breath maneuver.

- **Main results of the pilot study**

All studies testing the effect of high PEEP in patients with ARDS have randomized patients irrespective of their potential for recruitment.
For these reasons, our group had established a test for assess lung recruitability (named “Patient Recruitment Test” or PRT), based on variations of the $PaO_2/FiO_2$ ratio, $C_{RS}$ and $PaCO_2$ between two predefined PEEP levels.
Before this pilot study, we assumed that if recruitment occurs, $PaO_2/FiO_2$ ratio will increase and $PaCO_2$ will be reduced primarily because of increased alveolar ventilation, as part of the minute ventilation is delivered to the newly recruited and perfused lung regions.
We also supposed that changes in $C_{RS}$ could help identify recruitment or overdistension and were thus added to the PRT.
To be an easy, reliable, widely applicable method at the bedside, we wanted to make a test:

- easy to implement in all ICUs,
- independent of the available equipment
- reliable to identify patient with significant amounts of potentially recruitable lung.

To assess whether our PRT can reliably identify recruitment, we have performed a pilot study as suggested by reviewers of the previous protocol submission to the PHRC-2019. PRT in 51 hemodynamically stable patients with ARDS ($PaO_2/FiO_2$ 139±55 mmHg) from various etiologies (including 24 COVID-19 patients) and have measured i) EELV using the nitrogen washout technique with a COVX module on R860 ventilators (GE Healthcare, Madison, USA), ii) $PaO_2/FiO_2$, iii) $PACO_2$ iv) and $C_{RS}$ at PEEP levels of 5 and 15 $cmH_2O$. We calculated the volume recruited ($V_{rec}$) as $V_{rec}$= $EELV_{PEEP15}$ – ($EELV_{PEEP5}$ + 10x$C_{RS\text{-}PEEP5}$). We arbitrarily defined recruiters as patients whom exhibited a $V_{rec}$ greater than 10% of $EELV_{PEEP5}$. Using this definition, 31 of our patients were defined as recruiters. We then calculated ROC curves for threshold values of changes in $PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$ in order to detect lung recruitment as defined by EELV with the best accuracy. **Using values of 15%, 9% and 11% for changes in $PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$ respectively**, **our proposed PRT identified lung recruitment with a sensitivity of 83%, a**


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

**specificity of 75%, a positive predictive value of 84% and a negative predictive value of 74% (AUC 0,804)**. Of note, no adverse effect occurred during the PRT. More specifically, when PEEP was dropped to 5 $cmH_2O$, we did not observe any significant episode of hypoxemia. In the few episodes that occurred, increasing $FiO_2$ was sufficient to maintain $SaO_2$ within acceptable ranges.

- **Main results of the last studies**

There are still important questions to be answered regarding optimal ventilatory strategies in patients with ARDS. The most recent expert guidelines recommend using PEEP levels greater than 12 $cmH_2O$ in patients with moderate to severe ARDS[20] . However, physicians are often reluctant to use higher PEEP levels. In LUNG-SAFE, the large (>13,000 patients) international multicenter observational study conducted by the ESICM Trials Group[11] , the levels of PEEP used in the mild, moderate and severe ARDS patients were lower than the levels recommended by the most conservative algorithm of the ALVEOLI trial[26] . In the same trial, continuous NMBAs were used at baseline in 30% and 25.4% of the lower and higher PEEP groups, respectively, and in 45% and 33% of patients with lower and higher PEEP between day 0 and day 28. Whereas the accurate place of NMBAs is internationally admitted in moderate-to-severe ARDS patients, NMBAs can be considered either in an early use as they were used in RCTs and as suggested by the French guidelines[6,7,30], or as "rescue therapies" for hypoxemic patients with a $PaO_2/FiO_2$ ratio < 100 mmHg for PP and/or when $P_{PLAT}$ exceeds 30 $cmH_2O$ (as in the ROSE study and in North-American guidelines)[8,18] . Altogether, these data suggest that there is still considerable equipoise as to the optimal ventilatory settings in patients with ARDS.

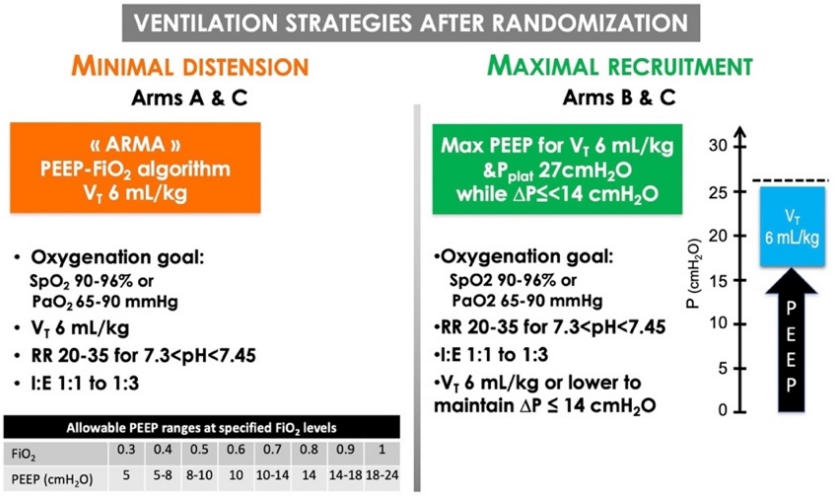
## 2.4 Description of the population to be studied and justification for the choice of participants

We plan to enroll **adult patients with moderate to severe ARDS**, irrespective of the etiology of ARDS. For these patients, there is still equipoise as to the optimal strategy to set PEEP. As it is essential to implement lung protective strategies with optimal PEEP as quickly as possible in order to optimize potential benefits, we will randomize patients at the early phase of the disease process, within 96 hours of ICU admission and within 72 hours of tracheal intubation.

## 2.5 Succinct description of the investigational product(s) or intervention(s)

Whereas both parts of the study are testing strategies widely used in the management of moderate to severe ARDS in clinical practice, the main objective of the trials is to determine the ideal target population and the adequate timing of interventions.
The study will compare two ventilation strategies, Minimal distension and Maximal recruitment.
As explain in part 2.2, clinical trials have failed to show a significant difference in outcome between low- and high-PEEP strategies used in arms A & B can be viewed as suitable comparator arms.
Ventilation strategies in each comparator arm will be detailed below, and the differences between strategy of minimal distension and maximal recruitment are resumed in Figure 1.

**Figure 1.** Ventilation strategies






*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### *2.5.1 First randomization*

#### *2.5.1.1 First Randomization, Arm A: Minimal distension*

Ventilation strategy in this arm is a slightly modified version of the ARDSnet protocol as used in the ARMA and LOVS studies[2,25]. In brief, this includes ventilation with $V_T$= 6 mL/kg and $P_{PLAT}$ ≤ 30 $cmH_2O$) and $FiO_2$/PEEP combination chart titration.

i) **Adjusting tidal volume:** ACV will be used until weaning criteria are met. Tidal volume will be set at 6 ml/kg, computed using the predicted body weight determined as follows: PBW = X + 0.91 (height in cm – 152.4), with X = 50 for males and 45.5 for females. Inspiratory flow will be 50 to 70 L/min and end-inspiratory pause duration 0 to 0.5 s, and the I:E ratio will be kept between 1:1 to 1:3. All ventilators used in study will correct the measurements of tidal volume for gas compression. Measurement of $P_{PLAT}$ using a 0.5-1 sec tele-inspiratory occlusion maneuver will be performed to confirm that $P_{PLAT}$ is lower than 30 $cmH_2O$. If $P_{PLAT}$ is >30 $cmH_2O$ despite a $V_T$ of 6 ml/kg, PEEP will be reduced to a minimum of 5 $cmH_2O$. If $P_{PLAT}$ is >32 $cmH_2O$ with 6 ml/kg $V_T$ and 5 $cmH_2O$ PEEP, $V_T$ will be reduced by 1 ml/kg steps to 4 ml/kg, provided pH remains ≥ 7.15 (see below).

ii) **Respiratory rate & acidosis management:** Respiratory rate will be kept at no more than 35/min and adjusted to achieve $PaCO_2$ values such that arterial pH is between 7.2 and 7.45. When pH remains lower than 7.25 despite a breathing rate of 35/min, tidal volume will be increased stepwise to 8 ml/kg by 1 mL/kg steps until pH is ≥7.25, provided $PaCO_2$ is kept ≥38 mm Hg and $P_{PLAT}$<32 $cmH_2O$, if needed by decreasing the PEEP level to 5 $cmH_2O$. Detailed management strategies of severe respiratory acidosis will be described in the investigator manual.

iii) **Setting of $F_IO_2$ & oxygenation targets:** $FiO_2$ (0.21 to 1) will be set to achieve the following oxygenation targets: 90% ≤ $SpO_2$ ≤96% or 65 mmHg ≤ $PaO_2$ ≤90 mmHg. When $PaO_2$ measurements are available, they will take priority over $SpO_2$.

iv) **Setting PEEP:** PEEP will be set according to ARMA lung protective algorithm (see below) taking into account total PEEP (the sum of applied PEEP and intrinsic PEEP)[2]. In patients who are completely relaxed or on neuromuscular blockade, total PEEP will be measured using the end-expiration occlusion method. Estimation of total PEEP when muscle activity precludes the use of this method is described in the Investigator's manual.

| | Fraction of Inspired Oxygen ($FIO_2$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 |
| Control PEEP ranges, cm $H_2O$ | 5 | 5-8 | 8-10 | 10 | 10-14 | 14 | 14-18 | 18-24 |

#### *2.5.1.2 First Randomization, Arm B: Maximal recruitment*

As in Arm A, patients will be ventilated with a $V_T$ initially set at 6 mL/kg using ACV.

i) **Setting PEEP:** The PEEP setting strategy is adapted from the Express trial[27]. Immediately after a recruitment maneuver performed as described in section 2.4.3.1, PEEP will be adjusted based on airway pressure and will be kept as high as possible to obtain a $V_T$ equal to 6 mL/kg BW without increasing the maximal inspiratory $P_{PLAT}$ above 27 $cmH_2O$ - a value shown in several studies to limit the risk of distension-related lung injury. Measurement of $P_{PLAT}$ using a 0.5-1 sec tele-inspiratory occlusion maneuver will be performed to confirm that $P_{PLAT}$ ≤27 $cmH_2O$. The PEEP will be assessed twice daily and increased / decreased if necessary to achieve a $P_{PLAT}$ ≤ 27 $cmH_2O$.

ii) **Adjusting tidal volume to limit ΔP:** After setting PEEP to the maximal level for an inspiratory $P_{PLAT}$ of 27 $cmH_2O$ and $V_T$ 6 mL/kg, the driving pressure ΔP will be measured. If ΔP exceeds 14 $cmH_2O$, a further reduction of $V_T$ will be performed by 0.5 mL/kg steps to achieve the ventilation goals. In case of severe acidosis, respiratory rate will be increased to a maximal rate of 35 rpm. Management of severe respiratory acidosis is described below.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

iii) **Respiratory rate & acidosis management:** Respiratory rate will be kept at no more than 35/min and adjusted to achieve $PaCO_2$ values such that arterial pH is between 7.25 and 7.45. When pH remains lower than 7.2 despite a breathing rate of 35/min, tidal volume will be increased stepwise to 8 ml/kg by 1 ml/kg steps until pH is ≥7.25, provided $PaCO_2$ is kept ≥38 mm Hg and $P_{PLAT}$<32 $cmH_2O$, if needed by decreasing the PEEP level to 5 $cmH_2O$.

iv) **Setting of $F_IO_2$ & oxygenation targets:** $FiO_2$ (0.21 to 1) will be set to achieve the following oxygenation targets: 90% ≤ $SpO_2$ ≤96% or 65 mmHg ≤ $PaO_2$ ≤90 mmHg. When $PaO_2$ measurements are available, they will take priority over $SpO_2$.

#### *2.5.1.3 First Randomization, Arm C: PRT-guided ventilation strategy*

All randomized patients will undergo a **PEEP responsiveness test** (PRT) before activation of the allocated ventilation strategy. Changes in $PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$ will be used to define the outcome of the PRT and the ventilation settings to be used.
Results of the PRT will be entered in the eCRF platform for all patients. **The ventilator strategy to be used for the patient (minimal distension / maximal recruitment) will then be notified to the investigator, who will remain blinded as to the study arm**. PEEP responsiveness status will be used to select the ventilator strategy only in patients randomized to Arm C

- Patients with a negative PRT will be treated with the strategy defined in Arm A (minimal distension)
- Patients with a positive PRT will be treated with the strategy defined in Arm B (maximal recruitment).

### *2.5.2 Second randomization*

#### *2.5.2.1 Second Randomization, Control arm: Early & Systematic Use of PP with NMBAs indicated only as rescue*

Prone positioning will be initiated in all patients with $PaO_2/FiO_2$<150 mmHg once secondly randomized. Sedation will be adjusted to ensure clinically acceptable patient-ventilator synchrony. In the control arm, NMBAs will only be used as a rescue if $P_{PLAT}$ exceeds 30 $cmH_2O$ for at least 10 minutes despite increasing doses of sedatives and decreasing $V_T$ (while maintaining a pH > 7.20) and also PEEP by 2 $cmH_2O$ (only if pH ≤ 7.20) if tolerated[6,8].

#### *2.5.2.2 Second randomization, intervention: Early and systematic use of PP and NMBAs*

In the second randomization interventional arm, early PP and NMBAs will be used as soon as possible after randomization and no later than 6 hours after the second randomization. NMBAs are used for 48h but can be stopped early if $PaO_2/FiO_2$ is ≥ 150 mmHg at a PEEP ≤ 12 $cmH_2O$ and plateau pressure ≤ 28 $cmH_2O$ while the patient is in the supine position.

## 2.6 Summary of the known and foreseeable benefits and risks for the research participants

Considering the frequency and the gravity of ARDS, even a 5% absolute reduction in 28-day mortality would significantly reduce its burden. We hypothesize that combination of standardized PEEP settings to assess the severity of ARDS and implementation of a PEEP responsiveness test to evaluate the potential for lung recruitment and titrate PEEP will reduce the heterogeneity of treatment effect in patients with ARDS. We anticipate that a personalized approach to mechanical ventilation will reduce mortality, decrease the time to resolution of ARDS and shorten duration of MV, ICU and hospital stay. We also expect that such an approach will reduce the risk of VILI and life-threatening complications.

By selecting the ventilation strategy based on the results of their physiologic response to high PEEP, we expect that the strategy tested in Arm C will improve survival as well as other patient-centered efficacy outcomes. In addition, our study design includes Bayesian response-adaptive randomization. Based on actual patients' outcome, the randomization algorithm will favor patient


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

allocation to the arm with better 28-day survival, thereby increasing the likelihood of individual patient benefit.

We will investigate the effects of procedures that are routinely used in the treatment of patients with ARDS. Both ventilatory strategies (minimal distension and maximal recruitment) that will be implemented in the study have been safely used in clinical studies in the past. They are routinely implemented in ICUs of the REVA network and thus carry no additional risks for the patients studied.

The PEEP-responsiveness test proposed in the study derives from a procedure that has been widely and safely used in physiological studies. The inflation pressure selected for the recruitment maneuver to be performed as part of the PRT is moderate, and those maneuvers have been designed to minimize their hemodynamic effects. Although we do not anticipate any significant side-effect of these procedures, their safety will be assessed and reported to the Data Safety & Monitoring Board of the study. The expected possible adverse effects of PRT are mainly barotrauma (pneumothorax, subcutaneous emphysema, pneumo-mediastinum, etc…) and a decrease in arterial blood pressure.

About the risks carried by ancillary studies:
i/ The determination of lung morphology does not imply any additional intervention,
ii/ Reassessment of the PRT with determination of EELV and the R/I ratio implies to repeat the PRT twice times. Considering the relatively short duration of the test and the moderate inflation pressure, the total duration of the PRT with this determination is not consider enough to carry significant additional risk
iii/ Electrical impedance tomography (EIT) is a non-invasive intervention, routinely used in ICU equipped and thus carry no additional risks for the research participants.

PP and NMBA are part of standard of care, separately or associated, and thus carry no additional risks for the patients studied in compare with usual care. It is possible that their combination could provide the highest benefit regarding outcomes such as mortality. It is therefore important to evaluate if the early use of these two adjuvants early in the course of moderate-to-severe ARDS is superior regarding mortality than the rescue use of NMBAs in patients submitted to PP.
If the early use of NMBAs is not superior to their use as rescue therapy, it could help to decrease the duration of mechanical ventilation and/or critical illness myopathy. In contrast, if there is a superiority of their systematic early association, then the early use of the combination of PP and NMBAs could be recommended in moderate-to-severe ARDS patients who remain hypoxemic ($PaO_2/FiO_2$<150 mmHg) despite adjustment of ventilation settings and sedation optimization.

# 3 OBJECTIVES

## 3.1 Primary objectives

The main objective of this Master Protocol is to test the benefit on mortality in moderate-to-severe ARDS of two management strategies of patients with moderate or severe ARDS:

- To test whether titration of PEEP based on the patients' response to a standardized PEEP responsiveness test improves survival
- To test whether the early and systematic combined use of PP and NMBAs is superior regarding all-cause mortality to the early and systematic use of PP with NMBAs prescribed only as a rescue strategy.

For both interventions, the primary endpoint is **28-day all-cause mortality after randomisation.**

## 3.2 Secondary objectives

As secondary objectives, we aim:

- to test whether implementing a high-PEEP strategy only in patients with a positive response to a PRT is superior to using PEEP levels regardless of lung recruitability.
- to assess if the systematic and early use of prone positioning (PP) and neuromuscular blockade agents (NMBAs) is superior to initiating PP early and using NMBAs only as a rescue strategy.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

We will investigate these strategies across multiple objectives, including:

- Physiological effects: evaluate the impact of the interventions on physiological parameters such as $PaO_2/FiO_2$, oxygenation index, and ventilator parameters at H24, H48, H72, and on day 7 and 14.
- Organ dysfunctions: assess the development and progression of organ dysfunctions, including acute kidney injury, hepatic dysfunction, and cardiovascular compromise, through detailed evaluations of the Sequential Organ Failure Assessment (SOFA) score at 24, 48, and 72 hours post-intervention, as well as on days 7 and 14.
- Clinical/Patient-centered efficacy outcomes: measure clinical endpoints such as mortality rates, ventilator-free days length of ICU stay and hospital-free days.
- Safety objective: assess the occurrence of barotrauma and of acute cor pulmonale through day 7. Additionally, evaluate ICU-acquired weakness using the Medical Research Council (MRC) score at ICU discharge, where a score less than 48 defines ICU-acquired weakness.
- Use of other rescue procedures: record and monitor the use of other rescue procedures and of NMBAs during the follow up of the patients. Additionnaly, calculate the number of muscle relaxants-free days between inclusion in the study and day 7.
- Sedatives/Analgesic use: measure the number of days alive and without continuous IV administration of sedatives/analgesics at day 7 and day 28 post-intervention. Evaluate the presence of delirium using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) at days 14 and ICU discharge.
- Quality of Life: assess the impact of interventions on patients' physical, psychological, and social well-being, using validated quality of life measures and questionnaries.
- Exploratory objective: assess death with refractory hypoxemia, refractory acidosis, and barotrauma within 7 days. Monitor initiation or significant increase in vasopressors or hypotension within 8 hours post-randomization. Identify cases of refractory hypoxemia and severe acidosis within 8 hours post-randomization.

We plan to collect clinical information and plasma samples in order to test whether i) there is an association between a positive PRT and the “hyper-inflammatory” sub-phenotype described by Calfee et al[39] .

In this cohort of patients with moderate or severe ARDS, we will also seek to identify a sub-phenotype associated with i) lower mortality, more ventilator-free days and organ failure-free days, ii) positive PRT, iii) improved outcome with early use of NMBAs.

## 3.3 Objective of ancillary studies

Considering the large sample size and the extensive patient phenotyping in this project, we anticipate that at least three ancillary studies, that bear no additional cost to the project, will be carried out.

### *3.3.1 Influence of lung morphology on PEEP responsiveness*

Investigators will be asked to analyze the chest X-ray used to characterize the ARDS on inclusion in order to assess the radiological severity using the score recently proposed by Warren et al[40]. They will be instructed to qualify the ARDS as « focal » or « non-focal ». These data will be used in ancillary studies to assess the relationships between chest X-ray appearance and effect of high PEEP on gas exchange and outcome.

### *3.3.2 Reassessment of the PRT with determination of EELV and the R/I ratio*

One of the key aspects of this study is to try to identify patients with a high percentage of recruitable lung. We hypothesize that these patients may benefit from higher PEEP levels and plan to identify them using a PRT based on the analysis of changes in $PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$. The nitrogen washout technique allows an accurate measurement of EELV at the bedside[34]. Determination of the R/I ratio has been recently proposed to distinguish recruiters from non-recruiters. In centers that have the expertise to routinely determine the R/I ratio and the technical



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

possibility to measure EELV (i.e., equipped with GE Carestation or GE R860 ventilators), we will test whether defining recruiters according to changes in EELV or to the R/I ratio lead to different thresholds for changes in $PaCO_2$ and $C_{RS}$ and improve the correlation between EELV measurements, R/I ratio and results of the PRT.

#### *3.3.3 Distribution of ventilation using electrical impedance tomography*

We hypothesize that in patients with a high potential for lung recruitment, application of a maximal recruitment strategy could improve homogeneity in lung aeration and lung mechanics, without affecting hemodynamics. Electrical impedance tomography (EIT) is a recently introduced technique that allows quantification of regional distribution of ventilation at the bedside. In centers equipped with an EIT devices, we will measure changes in regional distribution of ventilation (with particular attention to areas of lung recruitment or overdistension). We will seek to establish correlations between results of the PRT, changes in the distribution of ventilation and outcome.

# 4 STUDY DESIGN

## 4.1 Study endpoints

#### *4.1.1 Primary endpoint*

The primary efficacy endpoint is **all-cause mortality before or at day 28** after inclusion.

#### *4.1.2 Secondary endpoints*

- ***Physiological outcomes*****:** $PaO_2/FiO_2$, oxygenation index and ventilatory parameters ($V_T$, respiratory rate, total PEEP, $P_{PEAK}$, $P_{PLAT}$, compliance of the respiratory system) at H24, H48, H72, and on day 7 and 14
- ***Organ dysfunctions*****:** Sequential Organ Failure Assessment (SOFA) Score at H24, H48, H72, and on day 7 and 14
- ***Clinical / Patient-centered efficacy outcomes:***

- All-cause mortality at days 90 and 1 year
- All-cause ICU and hospital mortality
- Duration of mechanical ventilation
- Ventilator Free Days at day 28 (VFD28). The number of VFD is defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or died prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.
- ICU and hospital length of stay
- ICU-free days at day 28
- Hospital-free days at day 28 and day 90

- ***Safety outcomes:***

- Occurrence of barotrauma (defined as any pneumothorax, subcutaneous emphysema, pneumomediastinum, or pneumatocele of more than 2 cm detected on image examinations) through day 7
- Occurrence of acute cor pulmonale defined by the combination of a right/left ventricular diameter ratio greater than 0.6 and a paradoxical septum through day 7



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- ICU acquired weakness assessed by the medical research council (MRC) score at ICU discharge. A score < 48 defines ICU acquired weakness.

- ***Use of other rescue procedures:***

- Use (days) of other rescue procedures such as inhaled nitric oxide, almitrine, epoprostenol sodium, extracorporeal membrane oxygenation (ECMO), extracorporeal $CO_2$ removal (ECCO2R)
- Use of NMBAs during the first 3 days following the first randomization or following inclusion in the rescue arm of the second randomization
- Muscle relaxants-free days between inclusion and day 7

- ***Sedatives and analgesics use:***

- Number of days alive and without continuous IV administration of sedatives/analgesics at day 7 and at day 28
- Presence of delirium (CAM-ICU) at days 14 & ICU discharge
- Paralysis recall assessment at ICU discharge using a modified Brice questionnaire

- ***Quality of life at 1 year***
- Disability assessed by the Activities of Daily Living score (Lawton IADL)
- Quality-of-life, using the EuroQOL (EQ-5D-5L)
- Posttraumatic stress disorder (PTSD), using the Impact Event Scale-Revised (IES-R)
- Subsequent return to work. Return to work status: employment status
- Cognitive dysfunction using T-MoCA score
- Place of residence

- ***Exploratory outcomes:***

- Death with refractory hypoxemia (defined as $PaO_2/FiO_2$< 80 mmHg outside a care incident) within 7 days
- Death with refractory acidosis (defined as pH<7.10 despite RR ≥ 35 /min & $V_T$ 8 ml/kg) within 7 days
- Death with barotrauma within 7 days
- Initiation or 30% increase in vasopressors or hypotension (MAP<60 mmHg) within 8 hours after randomization
- Refractory hypoxemia within 8 hours after randomization (defined as $PaO_2/FiO_2$< 50 mmHg for more than one hour)
- Severe acidosis (pH<7.10) within 8 hours after randomization

## 4.2 Description of research methodology

### *4.2.1 Design of the study*

The master protocol involves two randomized, controlled clinical trials utilizing Bayesian adaptive designs. Patients with moderate-to-severe ARDS will be enrolled prospectively to test two interventions, successively assessed using a randomized, multicenter, controlled design.

- **First Randomization:**

Patients meeting moderate or severe ARDS criteria within 96 hours of ICU admission and 72 hours of tracheal intubation will be randomized to one of three arms:

Arm A. **Minimal Distension Arm:** Patients receive tidal volume ($V_T$) of 6 mL/kg and conservative positive end-expiratory pressure (PEEP) setting.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Arm B. **Maximal Recruitment Arm:** Patients receive tidal volume adjusted to limit plateau pressure ($\Delta P$) to 14 $cmH_2O$ and the highest possible PEEP while maintaining plateau pressure ($P_{PLAT}$) ≤ 27 $cmH_2O$.

Arm C. **PRT-Guided PEEP Arm:** Maximal recruitment strategy in patients with positive PEEP responsiveness test (PRT) or minimal distension strategy in patients with negative PRT.

Allocation between randomization arms is based on a Bayesian response-adaptive randomization procedure, using current data to compute the randomization probability for each patient at enrollment. A PEEP responsiveness test (PRT) is performed within 1 - 2 hours after randomization, recording changes in $PaO_2/FiO_2$ ratio, $PaCO_2$, and $C_{RS}$.

- **Second Randomization:**

Patients meeting the second randomization $PaO_2/FiO_2$ criteria ($PaO_2/FiO_2$ < 150 mmHg on PEEP ≥ 5 $cmH_2O$ & $FiO_2$ ≥ 0.6 on 2 ABGs separated by at least 4h after setting PEEP) can be secondarily randomized. The first qualifying ABG corresponds to the gas realized 1 hour after application of the ventilation strategy (H1). In case of severe hypoxemia, defined as a $PaO_2/FiO_2$ < 50 mmHg for at least 1h or a $PaO_2/FiO_2$ < 80 mmHg for at least 2h with $FiO_2$ and PEEP settings set according to instructions derived from the first randomization, the second randomization will be allowed without waiting for the 4h delay in order to rapidly allow prone positioning.

Patients with $PaO_2/FiO_2$ ≥ 150 mmHg will be managed without NMBAs and screened at least twice daily for 72 hours after the first randomization to be subsequently randomized if they meet the $PaO_2/FiO_2$ criteria.

After second randomization, deep sedation followed by neuromuscular blockade/prone position will be initiated as soon as possible after randomization and no later than 6 hours of it. Data collection timelines will be adjusted to ensure adequate assessment of primary and secondary endpoints.

Patients whose $PaO_2/FiO_2$ ratio remains ≥150 mmHg for more than 72 hours after the first randomization will not be secondarily randomized and managed according to French ARDS treatment guidelines.

#### *4.2.2 Number of participating sites*

The study is a national multicenter trial involving academic as well as non-academic centers.

- **Recruitment centres**

It is a multicentre study involving 60 intensive care units at a national level.

#### *4.2.3 Identification of participants*

The participants in this research will be identified as follows:
Site number (3 digits) - Sequential enrolment number for the site (4 digits) - Surname initial - first name initial
This reference number is unique and will be used for the entire duration of the study.

#### *4.2.4 Randomisation*

Randomization will be centralized and performed with the use of a centralized Web-based system to ensure appropriate allocation concealment. After obtaining a signed and dated informed consent, investigators will enter the subject into a web-based randomization system.

- **First randomization**

Patients that meet the definition of moderate or severe ARDS within 96 hours of ICU admission and within 72 hours of tracheal intubation and who do not present any exclusion criteria will be randomized to one of the 3 arms of the first randomization (A, B, C), described below.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Allocation between randomization arms (A, B, C) will be based on a **Bayesian response-adaptive randomization procedure** that uses the current data to compute the randomization probability for each patient at the time of enrolment. Response-adaptive randomization or allocation is a randomization technique in which the allocation of patients to treatment groups is based on the responses (outcomes) of the previous patients. The main purpose is to provide a better chance of randomizing the patients to a superior treatment group based on the knowledge about the treatment effect at the time of randomization. As a result, response adaptive randomization takes ethical concerns into consideration. Randomization will first be based on a fixed randomization design, 1:1:1, for the first 300 patients. Then, it will use the Bayesian posterior distribution of treatment effect given the observed response data (in terms of the primary outcome measure) between the different arms, with allocation ratios that aim to minimize expected treatment failures (see Statistical section for details of allocation probabilities computation).

- **Second randomization**

Those patients who also meet within 4-72 hours of the first randomization will be secondly randomized in one of 2 arms testing the second intervention.

- For the second randomization, lists will be computer-generated in a 1:1 ratio, using permuted blocks of varying sizes to ensure allocation concealment. Randomization will be stratified on center, on whether receiving corticosteroids on inclusion or not (no or yes, yes if: Hydrocortisone ≥ 200 mg/J, Méthylprednisolone ≥ 0.5 mg/kg/j, Dexaméthasone : whatever the dosage), on COVID-19 pneumonia being responsible for ARDS (no or yes) and on the ventilation strategy indicated by the first randomization (minimal distension/maximal recruitment). The stratification on the site allows accounting for center effect that is, site-specific practice heterogeneity. The stratification on the first allocated strategy aims at ensuring the distribution of those patients equally between the randomization groups of PP. Regarding COVID-19 pneumonia, as mechanisms of lung injury and respiratory drive being different from other causes, this potential confounding factor must be taken into account, as well as the previous use of corticosteroids.

The overall randomization scheme and sequence are summarized in Figure 2.

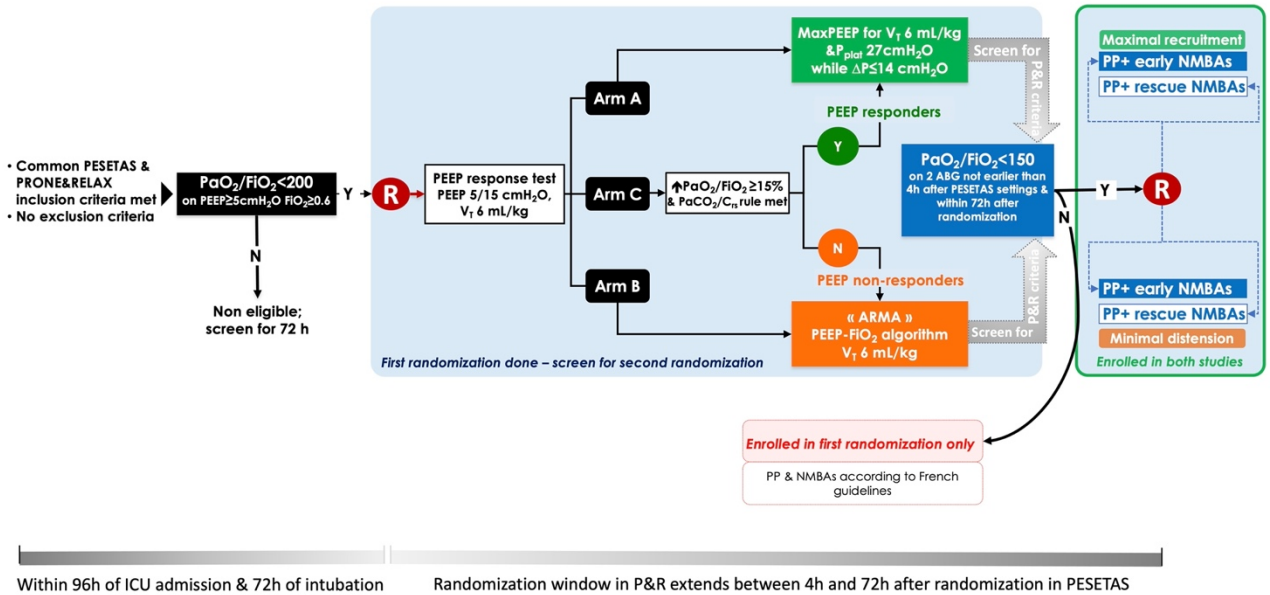



**Figure 2.** Randomization scheme and sequence.

### *4.2.5 Blinding methods and measures put in place to protect blinding*

By nature, studies on mechanical ventilation cannot be conducted with full blinding of the investigators. We aim to test the influence of a PRT on outcome when results of this test determine the ventilatory strategy to be used in an individual patient. To facilitate blinding of investigators as to the randomization, the $\Delta C_{rs}$ and $\Delta PaCO_2$ criteria used in conjunction with the $\Delta PaO_2/FiO_2$ will not



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

be disclosed to clinicians in charge of the patient care. As a result, clinicians will just be instructed to implement one of the 2 ventilation strategies described below (in Arms A & B) after data entry ($PaO_2/FiO_2$ ratio, $PaCO_2$ and $C_{RS}$) in the eCRF, without actually knowing whether the patient response to the PRT has been taken into account in selecting the strategy.

Statistical analyses will be conducted blinded to treatment assignment, with treatment arms denoted by letters instead of explicit labelling of intervention arms. All analyses will be based on the intent-to-treat (ITT) basis. Nevertheless, a per-protocol population will be used as the secondary analysis to assess the robustness of the results. Per protocol population will include all included patients.

# 5 IMPLEMENTATION OF THE STUDY

By definition, Day 0 starts on the day of inclusion and ends at midnight on the same day. Then, all days will be counted as calendar days (00h00 to 23h59). As patients may be enrolled up to 3 days later in the second randomization, we have planned to adjust time-points for consistent data collection in both parts of the study.

## 5.1 Inclusion/randomisation visit (J0)

### *5.1.1 Screening visits (standard of care)*

This visit take place between the day of ICU admission and no later than 96 hours and/or 72 hours of invasive mechanical ventilation for the first randomization, and 72h after the first randomization for the second one. All intubated patients meeting the ARDS criteria in a participating center will be screened twice daily during a maximum of 72 hours after the time of intubation for the first randomization, and 4-72h after the first randomization to the second randomization.

Screening will rely on the verification of ARDS Berlin definition criteria and on the assessment of the $PaO_2/FiO_2$ ratio to determine ARDS severity. Investigators will need to evaluate the patient medical history (including the cause of ARDS and documentation of the absence of cardiogenic pulmonary edema), obtain a chest x-ray, and will assess $PaO_2$ with standard ventilatory settings including PEEP ≥ 5 $cmH_2O$ and $V_T$ set at 6 mL/kg PBW. These procedures are part of usual care in patients with ARDS and thus no consent need to be obtained to accomplish the screening visit.

During the whole screening period, investigators will be strongly encouraged to use ventilator settings consistent with standard best practice described above (see section 2.2.3)[2,20]. Attention will also be paid to ensure hemodynamic stabilization following recommendations on the management of hemodynamics in ARDS patients[52].

### *5.1.2 Inclusion visit*

***First randomization***

| **Whose consent must be obtained** | **Who informs the individuals and collects their consent** | **At what point the individuals are informed** | **At what point the consent is obtained** |
|---|---|---|---|
| *The individual participating in the study;*<br>*Or*<br>*the relative*<br>*Or*<br>*Inclusion according to deferred consent* | *Investigators declared and trained in the study ICU* | *At the inclusion visit*<br>*or*<br>*as soon as available and able to approve in case of deferred consent* | *After a time reflexion at least of 15 minutes*<br>*During the inclusion visit*<br>*Or*<br>*As soon as available and able to approve in case of deferred consent* |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

The inclusion visit happens at the time an intubated patient meets all inclusion criteria (including consent). During this visit, investigators will need to evaluate the severity of ARDS, the patient medical history (including the cause of ARDS and documentation of the absence of cardiogenic pulmonary oedema) and the biological and radiologic tests to assess eligibility criteria of the patients.

On this day, investigators will document and will record the following elements obtained before realization of the PRT:

- Demographic data: DOB, height, weight, Date of hospital admission, ARDS diagnosis date, main suspected ARDS etiology
- Baseline patient characteristics: significant medical history, date of ICU admission, reason for admission in ICU, IGS2 score at admission, date of intubation, Charlson score (components), SAPS II (components), McCabe score
- SOFA score
- Ventilatory parameters: mode, $FiO_2$, $V_T$, RR, VE (minute ventilation), PEEP set, Total PEEP, $P_{PLAT}$, $P_{PEAK}$, $\Delta P$, CRS
- Physiological data: arterial pressure (systolic, diastolic, mean), heart rate, temperature, $SpO_2$, urine output (prior 24h), Glasgow score
- Laboratory test including:
  - Arterial blood gas (ABG) analysis, obtained with the ventilation parameters recorded; (may be the qualifying ABG if performed no more than 2h before implementation of the PRT for inclusions)
  - Baseline biological data: glycemia, creatinine, leukocytes, platelets, Kaliemy, natremy, bilirubin, Bicarbonate
  - Blood or urine pregnancy test in women with childbearing potential
- Chest X-ray (may be the one obtained for screening)
- Treatments: sedative drug infusion
- Presence of acute cor pulmonale (defined by the combination of a right/left ventricular diameter ratio greater than 0.6 and a paradoxical septum) at inclusion
- Any adverse event /serious adverse events

**Data to be collected 1 and 8 hours after initiation of the allocated treatment by the first randomization:**

- Ventilatory parameters: mode, $FiO_2$, $V_T$, RR, $V_E$ (minute ventilation), PEEP set, Total PEEP, $P_{PLAT}$, $P_{PEAK}$, $\Delta P$, $C_{RS}$
- Arterial Blood Gaz (ABG)
- Physiological data: arterial pressure (systolic, diastolic, mean), heart rate, temperature, $SpO_2$, urine output (prior 24h), Glasgow score
- Vital status
- Need for adjunctive ventilation.

***Second randomization***

Starting one hour after application of the ventilation strategy indicated by the first randomisation, if the patient fulfills the eligibility criteria for the second randomization, he (she) will be randomized across one of the 2 arms of this second part of the trial.

For patients who have increased their $PaO_2/FiO_2$ ratio above 150 mmHg, investigators will monitor the $PaO_2/FiO_2$ ratio at least twice daily for 72 h following the first randomization. Within those 72 h, patients whose $PaO_2/FiO_2$ will drop below 150 mmHg (with PEEP and a $FiO_2$ set accordingly to the first randomization arm) on 2 ABGs separated by at least 4 hours (besides emergency situations) will then be secondly randomized. The first qualifying ABG corresponds to the ABG realized 1 hour after application of the ventilation strategy (H1).



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Patients whose $PaO_2/FiO_2$ will remain greater than 150 mmHg for more than 72h following the first randomization will not process to the second randomization and will be managed following the French guidelines regarding the use of PP and NMBAs[20] .

## 5.2 Duration of ventilation interventions & weaning strategy

The overall weaning strategy encompasses: i) a PEEP-weaning trial, ii) an attempt to safely establish spontaneous breathing, iii) if possible, a spontaneous breathing trial.

i) PEEP-weaning trial. Starting 48h after the first randomization, a "PEEP weanability" test should be performed once a day in all patients with a $PaO_2/FiO_2$ ratio > 200 mmHg with an $FiO_2$<0.6. Briefly, $FiO_2$ will be set to 0.4 and the PEEP will be gradually decreased (over 20-30 min) to 8 $cmH_2O$ by keeping the $V_T$ constant. If, during this maneuver, persistent desaturation ($SpO_2$<88%) occurs (> 5 min), the previous PEEP and $FiO_2$ settings will be restored. If this is not the case, arterial blood gases will be drawn after 10-20 minutes of ventilation with PEEP set to 8 $cmH_2O$. If the $PaO_2/FiO_2$ ratio is greater than or equal to 150 under these conditions (PEEP= 8 $cmH_2O$, and $FiO_2$ 0.4), the patient will be considered "weanable from PEEP" and investigators will be allowed to decrease PEEP as clinically indicated. If this is not the case, the previous PEEP and $FiO_2$ settings will be restored.
ii) Attempt to establish spontaneous breathing. The continuation of the MV of patients "weanable from PEEP" will be performed with the ventilation mode used at the time of the PEEP weaning trial or, preferably, using inspiratory pressure support (PSV) with pressure level adjusted to obtain a $V_T$< 8 mL/kg PBW, an inspiratory pressure lower than 30 $cmH_2O$ and a respiratory rate lower than 35 breath per min with a PEEP ≤ 10 $cmH_2O$ and an $FiO_2$ ≤0.4. If prolonged (> 15 min) desaturation ($SpO_2$ <88%) occurs under these conditions, the settings for controlled ventilation mode will be re-established according to the allocated ventilation strategy defined after randomization.
iii) Spontaneous breathing trials. In patients that tolerate PSV, weaning criteria will be sought every day according to standard recommendations and to the protocol in place in each center13. Spontaneous breathing trials will be performed using a T-piece or pressure support at +7 cm $H_2O$ without PEEP (30 min-2h). The trial will be repeated once a day until extubation as long as the criteria for the trial are met. Extubation, as well as decisions about whether and when to perform tracheostomy, will be at the discretion of the attending physician. All patients who pass the unassisted breathing trial will be extubated or allowed to receive oxygen without positive pressure via tracheostomy. Patients, who require invasive ventilation within 48 hours, will continue in the same study group(s).

Patients at high-risk of extubation failure (ie, older than 65 years or having underlying chronic cardiac or respiratory disease) will receive prophylactic non-invasive respiratory support to prevent post extubation acute respiratory failure that may occur. This support can be either non-invasive ventilation (12 hours per day during 2 days, if possible) or high flow nasal oxygen (during 2 days, if possible) or a combination of both. For all patients, days with high flow nasal oxygen will be considered as ventilatory-free days if the patient does not exhibit signs of acute respiratory failure. For patients on noninvasive ventilation (NIV), days with total duration of NIV lower than or equal to 4 hours will be considered as ventilatory-free days.

In the study, unassisted breathing is defined as:
- Extubated with face mask, nasal prong oxygen, or room air, OR
- T-tube breathing, OR
- Tracheostomy mask breathing, OR
- CPAP ≤ 5 $cmH_2O$ without PS or intermittent non-invasive ventilation for less than 4h per day or high flow nasal oxygen.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## 5.3 Follow-up visits

Follow-up visits during ICU hospitalization have to be planned at day 1, 2, 3, 7, 14 and 28 after first randomization. Others data have to be collected 1, 2, 3, 7, 14 and 28 days after the second randomization.

Following ICU discharge, investigators will be automatically reminded in due time the need to organize the follow-up visit.

The following data will be recorded as planned in Table 2.

### *5.3.1 Data to be collected on first randomization:*

These data have to be collected everyday from day 1, 2, 3, 7 and 14, or until ICU discharge, and at day 28.

- SOFA score (components)
- Ventilator parameters: mode, $FiO_2$, VT, RR, VE (minute ventilation), PEEPset, Total PEEP, $P_{PLAT}$, $P_{PEAK}$, $\Delta P$, $C_{RS}$
- Physiological data: arterial pressure (systolic, diastolic, mean), heart rate, temperature, $SpO_2$, urine output (prior 24h), glycemia
- Input/output fluid balance (to be collected only from day 1 to 14)
- Arterial blood gas analysis
- Patient outcome status: ICU discharge, Hospital discharge, alive, cause of death (if applicable), still on mechanical ventilation
- Treatments: vasopressor, corticosteroids, sedative, analgesic, insulin and modality (intravenous or not, continuous infusion or not)
- Presence of study barotrauma (pneumothorax, subcutaneous emphysema, pneumo-mediastinum, etc.)
- Presence of acute cor pulmonale or other complications (refractory hypoxemia, refractory acidosis, multiple organ failure, ventilator-associated pneumonia, pulmonary embolism)
- Adverse events/serious adverse events

### *5.3.2 Data to be collected on second randomization*

All the data collected on first randomization (listed in section 5.1.3) have also to be collected at 1, 2, 3, 7, 14 and 28 days after the second randomization.

In addition of this, the data listed below have also to be collected at the same days:

- Neuromuscular blocking agent (systematic used of NMBA group)
- Neuromuscular blocking agent used as rescue therapy (NMBA used as rescue)
- Prone Position
- RASS score
- CAM-ICU score (at day 14 after second randomization)

### *5.3.3 Data to be collected at ICU discharge:*

- Patient outcome status: alive, cause of death (if applicable), still on mechanical ventilation
- MRC Score Paralysis recall assessement (modified Brice questionnaire)
- CAM-ICU

### *5.3.4 Data to be collected at hospital discharge:*

- Patient outcome status: alive, cause of death (if applicable), still on mechanical ventilation



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

#### *5.3.5 Day 90 Follow-up visit*

On Day 90, the follow-up visit aims to evaluate the patient outcome status.

- Patient outcome status: alive, cause of death (if applicable), still on mechanical ventilation

We anticipate that the majority of patients alive will be discharged by Day 90. For those patients, the follow-up visit will be conducted by a research technician or a clinical research assistant. For practical reasons, we will tolerate a time interval of ± 5 days.

This visit can be done by phone call.

#### *5.3.6 Day 180 Follow-up visit*

On Day 180, this follow-up visit will evaluate the patient outcome status and the presence of

i) impaired quality of life (EQ-5D-5L score)
ii) cognitive dysfunction (T-MoCA) score
iii) place of residence
iv) post-traumatic stress disorder (IES-R score)
v) autonomy in daily life (Lawton IADL)
vi) employment status

This visit will be conducted during a telephone call led by a research technician or a clinical research assistant trained to perform these evaluations as we anticipate that the vast majority of patients alive will be discharged by Day 180. For practical reasons, we will tolerate a time interval of ± 30 days.

### *5.4 Last study visit*

The last study visit will be organized on Day 360. This follow-up visit will aim to evaluate the patient outcome status and the presence of

i) impaired quality of life (EQ-5D-5L score)
ii) cognitive dysfunction (T-MoCA) score
iii) place of residence
iv) post-traumatic stress disorder (IES-R score)
v) autonomy in daily life (Lawton IADL)
vi) employment status

This visit will be conducted during a telephone call led by a research technician or a clinical research assistant trained to perform these evaluations as we anticipate that the vast majority of patients alive will be discharged by Day 360. For practical reasons, we will tolerate a time interval of ± 30 days.

## 5.5 Expected length of participation and description of the chronology and duration of the study.

| | **Time** |
|---|---|
| Duration of enrolment period | 36 Months |
| Total duration of participation, of which | 12 Months (360 days) |
| • Moment of first randomization<br>• Moment of second randomization | Max 96 hours after ICU admission<br>Max 72 hours after the first randomization |
| • Duration of follow-up period: | 12 Months (360 days) |
| Total study duration: | 48 months |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## 5.6 Chronology of the study

| Schedule of the assessment (calendar days) | J0 | H1[1] | H8[1] | D1-D2-D3 after R1 | D1-D2-D3 after R2 | D7after R1 | D7 after R2 | D14 after R1 | D14 after R2 | D28 after R1 | D28 after R2 | ICU discharge | Hospital discharge | J90 | J180 | J360 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Demographic data | • | | | | | | | | | | | | | | | |
| Inclusion criteria | • | | | | | | | | | | | | | | | |
| Written informed consent (patient/proxy) | • | | | | | | | | | | | | | | | |
| Baseline patients characteristics | • | | | | | | | | | | | | | | | |
| PEEP responsiveness test | • | | | | | | | | | | | | | | | |
| 1st Randomization (R1) | • | | | | | | | | | | | | | | | |
| 2nd Randomization (R2)[2] | • | | | • | | | | | | | | | | | | |
| SOFA score[3, 4] | • | | | • | • | • | • | • | • | • | • | | | | | |
| Physiological data (HR,BP,RR,Temp)[3,4] | • | • | • | • | • | • | • | • | • | • | • | | | | | |
| Ventilatory parameters[3, 4] | • | • | • | • | • | • | • | • | • | • | • | | | | | |
| Arterial blood gas analysis[3, 4] | • | • | • | • | • | • | • | • | • | • | • | | | | | |
| Baseline biological data | • | | | | | | | | | | | | | | | |
| Frontal Chest X-ray | • | | | | | | | | | | | | | | | |
| Need for adjunctive ventilation | | • | • | | | | | | | | | | | | | |
| Neuromuscular bloking agents (Bolus) | • | | | | • | | • | | • | | • | | | | | |
| Prone position | | | | | • | | • | | • | | • | | | | | |
| Neuromuscular Blocking Agent (NMBA)[3] | | | | | • | | • | | • | | • | | | | | |
| NMBA used as rescue therapies (control group) | | | | | • | | • | | • | | • | | | | | |
| RASS | | | | | • | | • | | • | | • | | | | | |
| Input/output fluid balance | | | | • | • | • | • | • | • | | | | | | | |
| Patient outcome status | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • | • |
| Ventilator-free days | | | | | | | | | | • | • | | | | | |
| Treatments | • | | | • | • | • | • | • | • | • | • | | | | | |
| Routine blood tests [5] | • | | | | | | | | | | | | | | | |
| CAM-ICU | | | | | | | | | • | | | • | | | | |
| MRC score | | | | | | | | | | | | • | | | | |
| Activities of DailyLiving (Lawton IADL) | | | | | | | | | | | | | | | • | • |
| Employment status- | | | | | | | | | | | | | | | • | • |
| Place of residence | | | | | | | | | | | | | | | • | • |
| Quality of life EuroQOL (EQ-5D-5L) | | | | | | | | | | | | | | | • | • |
| T-MOCA | | | | | | | | | | | | | | | • | • |
| PTSD evaluation (IES-R) | | | | | | | | | | | | | | | • | • |
| Paralysis recall assessement (modified Brice questionnaire) | | | | | | | | | | | | • | | | | |
| Presence of study barotrauma | • | • | • | • | • | • | • | • | • | • | • | | | | | |
| Presence of acute cor pulmonale | • | • | • | • | • | • | • | • | • | • | • | | | | | |
| AEs/SAEs | • | • | • | • | • | • | • | • | • | • | • | | | | | |

**Table 2. Chronology of the study**

1 : after the first administration of the treatment allocated by the ventilation strategy
2 : after 4-72 hours of 1st randomization if the condition of second randomization are filled
3 : if patient still in mechanichal ventilation
4 : if patient is still in the ICU
5 : routine test- may use pre-inclusion value if obtained within 12 hours; and blood or urine pregnancy test


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## 5.7 Distinction between standard care and study

**"Standard care" vs. "additional interventions" required specifically for the study**

| **Interventions, procedures and treatments carried out for research purposes** | **Interventions, procedures and treatments associated with standard care** | **Interventions, procedures and treatments added for research purposes** |
|---|---|---|
| **Clinical interventions** | Mechanical ventilation<br>Treatment of organ failures | PEEP-responsiveness test |
| **Visits** | All visits | PEEP-responsiveness test<br>Day 90, Day 180, Day 360 |
| **Blood samples** | At inclusion | Blood or urine pregnancy test |
| **Questionnaire** | | At day 180, and 360 |
| **Imaging** | Chest X-ray, CT-scanner | None |

# 6 ELIGIBILITY CRITERIA

## 6.1 Inclusion criteria

- Inclusion within 96 hours of ICU admission and within 72 hours of tracheal intubation for first randomization and then within 72 hours of the first randomization for the second randomization
- Patients meeting the Berlin ARDS definition criteria with hypoxemia characterized as
  - for first randomization: $PaO_2/FiO_2$ <200 mmHg on a PEEP ≥5 $cmH_2O$ with $FiO_2$≥0.6 while $V_T$ is 6 ml/kg PBW and adequate sedation level to adjust mechanical ventilation settings
  - for second randomization: $PaO_2/FiO_2$ <150 mmHg on optimized ventilatory settings according to the first randomization, confirmed by two ABG analyses separated by an interval time of 4 hours (besides emergency situations) and observed within 72 hours of the first randomization
- Informed consent signed:
  - by the patient
  - Or informed consent signed by a family members/trustworthy person if his condition does not allow him to express his consent by written as per L. 1111-6
  - Or in a situation urgently and in the absence of family members/trustworthy person, the patient can be enrolled. The consent to participate to the research will be requested as soon as the condition of the patient will allow him to consent.
- Health insurance coverage

## 6.2 Exclusion criteria

- Age < 18 years
- Known pregnancy or breathfeeding
- Participation in another interventional studies evaluating ventilator settings and neuromuscular blocking agents at the initial phase of ARDS.
- Intracranial pressure > 30 mm Hg or cerebral perfusion pressure < 60 mmHg
- Severe chronic respiratory disease requiring long-term $O_2$ therapy or home mechanical ventilation (except CPAP/BIPAP used for sleep apnea syndrome)
- Chronic interstitial lung disease
- Continuous neuromuscular blockade infusion at enrolment
- Previous hypersensitivity or anaphylactic reaction to any NMBA
- Neuromuscular disease that may potentiate neuromuscular blockade or impair spontaneous ventilation: amyotrophic lateral sclerosis, Guillain-Barré syndrome, myasthenia gravis, upper spinal injury at level C5 or above
- Patients on ECMO or any technique of extracorporeal $CO_2$ removal
- Sickle cell disease
- Actual body weight >1 kg/cm of height
- Severe chronic liver disease defined as a Child-Pugh score of 12-15 (Appendix)



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- Pneumothorax at randomization
- Expected duration of mechanical ventilation <48 hours
- SAPS II score >75 at the time of ICU admission or suffering from a disease with an estimated survival time of less than two months
- Decision to withhold life-sustaining treatment
- Patients deprived of freedom or under legal authority
- Unstable spine fracture

## 6.3 Recruitment procedure

We aim to conduct the study in 60 centers. Most centers are affiliated to the REVA (*Réseau Européen de recherche sur l'insuffisance respiratoire aiguë et la Ventilation Artificielle*) network, all have a high potential to enroll patients and have expressed interest in the study. The overwhelming response of centers approached for participation highlights the importance of the study questions.

| | N |
|---|---|
| **Total number of participants to enrol** | 1200 |
| **Number of centers** | 60 |
| **Enrolment period** | 36 months |
| **Number of participants/center** | 25 |
| **Number of participants/center/month** | 0.55 |

Identification of patients and recruitment will take place during standard ICU hospitalization and treatment of ARDS patients. Patients with conditions known to cause ARDS will be actively screened at least twice a day during 48h after intubation and no later than 72h after ICU admission. For each center, investigators will establish a screening log that include reasons of non-inclusion in the study. This screening log will be provided to the Steering committee in order to analyze the overall rate of patient recruitment in the study.

## 6.4 Termination rules

### *6.4.1 Criteria and methods for premature discontinuation of study-related interventions/procedures/strategies or product administration*

Several situations are possible
- Temporary suspension of study-related interventions/procedures/strategies or of the product used, the investigator must document the reason for suspending and resuming the treatment in the participant's source file and the case report form (CRF)
- Premature discontinuation of study-related interventions/procedures/strategies or of the product used, but the participant remains enrolled in the study until the end of their participation
- Premature discontinuation of study-related interventions/procedures/strategies or of the product used, and withdrawal from the study

**The investigator must:**
- Document the reason(s)
- Collect the assessment criteria at the time of ending participation in the study, if the participant agrees
- Schedule a follow-up for the participant, particularly in case of a serious adverse event.

  In the case of severe adverse events, the investigator must notify the sponsor and follow up the participant until resolving. Notification of a serious adverse event must be sent by email (eig-vigilance.drc@aphp.fr ) to the sponsor.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### *6.4.2 Criteria & procedures for premature withdrawal of a participant from the study*

As in all clinical studies, participants may exit the study at any time and for any reason.

The investigator can temporarily or permanently withdraw a participant from the study for any safety reason or if it is in the participant's best interests. Thus, several situations are possible:

- Temporary discontinuation: the investigator will document the reason for discontinuing the study and its recovery in the source file of the subject and in the CRF.
- Premature and permanent discontinuation: the participant remains enrolled in the study until the end of his/her participation and the investigator must document the reason.
- Participant lost to follow-up: the participant cannot be located. The investigator must make every effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead

The case report form must list the various reasons why the participant has discontinued the study:

- ☐ Lack of efficacy
- ☐ Adverse reaction
- ☐ Another medical issue
- ☐ Personal reasons of the participant
- ☐ Explicit withdrawal of consent
- ☐ Lost to follow-up

Discontinuation of a patient's participation to the study will not change his or her clinical management or the relationship with the clinical team in charge of patient care. In the event of an adverse event, serious or not, precise follow-up may be considered depending on the severity of the adverse event despite the study discontinuation.

***Follow-up of participants following premature withdrawal from the study***

Even in the event of premature discontinuation, the investigator is bound to ensure proper follow-up for a total time equal to the duration of maximum time of participation since the inclusion of this patient. Investigators will inform patients about this possibility and a precise follow-up plan may be considered depending on the severity adverse events that may have occurred.
If a participant enrolled in the study cannot be located for follow-up visits, the investigator must make every possible effort to reconnect with the participant (and document his attempts in the source file), at least to determine whether the participant is alive or dead.

***Procedures for replacing participants***

Participants who leave the study prematurely will not be replaced. As any data collected prior to the date of premature discontinuation may still be used, we will include in the analysis all patients who discontinued the study after a time allowing evaluation of the primary endpoint (Day 28).

***Full or partial discontinuation of the study***

AP-HP as sponsor or the Competent Authority (ANSM) can prematurely discontinue all or part of the study, temporarily or permanently, further to the recommendations of the Data Safety Monitoring Board in the following situations:

- first of all, if suspected unexpected serious adverse reactions (SUSARs) are observed in one of the study arms or if there is a discrepancy in the serious adverse reactions between the study arms, requiring a reassessment of the benefit-risk ratio for the study [adapt as necessary].
- if an interim analysis confirms the efficacy of one of the study arms or, alternatively, the lack of efficacy.

Similarly, AP-HP as the sponsor or the Competent Authority (ANSM) may decide to prematurely discontinue the study due to unforeseen issues or new information about the intervention performed or the product used [adapt as necessary], in light of which the objectives of the study or clinical programme are unlikely to be achieved [adapt as necessary].


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

AP-HP as sponsor reserves the right to permanently suspend enrolment at any time if it appears that the inclusion objectives are not met.

In all cases in which a study is discontinued, the care options must be specified for participants currently enrolled in the study. Notably, it must be specified if the participants included in the study must be monitored until the end of their participation, as set forth in the protocol.

If the study is prematurely discontinued for safety reasons, the decision and justification will be provided by the sponsor (AP-HP) to the Competent Authority (ANSM) and to the CPP (Research Ethics Committee) within a period of 15 days, along with recommendations from the Data Safety Monitoring Board in the case of substantial modification.

# 7 STRATEGY ADMINISTERED TO STUDY PARTICIPANTS

## Description of the study strategy

Whereas both parts of the study are testing strategies widely used in the management of moderate to severe ARDS in clinical practice, the main objective of the trials is to determine the ideal target population and the adequate timing of interventions.
Principles of ventilator treatment after randomization in each comparator arm are summarized below and will be detailed in specific operating procedures provided to all participating centers.

### *7.1 First randomization: using a PEEP responsiveness test to guide therapy following first randomization*

Patients that meet the definition of moderate or severe ARDS within 96 hours of ICU admission and within 72 hours of tracheal intubation will be randomized to one of the three arms of the first randomization. Within 2 hours after first randomization and before activation of the ventilation strategy allocated by the first randomization, patients will undergo a PEEP responsiveness test (PRT).

i) First, right after inclusion in the first part, patients will be evaluated with PEEP set to 5 $cmH_2O$. Briefly, PEEP will be adjusted to reach a total PEEP of 5 $cmH_2O$, $V_T$ will be kept at 6 mL/kg PBW and other ventilatory settings will remain set as they were during the screening test that resulted in qualification of the patient for the study. After 20 min of ventilation with PEEP set to 5 $cmH_2O$, lung mechanics ($P_{PLAT}$, $\Delta P$, $C_{RS}$) measurement will be performed and ABGs will be obtained to calculate the $PaO_2/FiO_2$ ratio and assess $PaCO_2$.
ii) Then, a lung recruitment maneuver (LRM) will be performed by applying one minute of controlled ventilation with $V_T$ set to result in a 45 $cmH_2O$ inspiratory plateau pressure, 15 $cmH_2O$ PEEP, 10 breaths/min respiratory rate, and 1:1 inspiratory to expiratory ratio.
iii) PEEP will then remain set to 15 $cmH_2O$, while $V_T$ will be decreased to 6 mL/kg PBW and settings of respiratory rate and inspiratory to expiratory ratio will be brought back to baseline values. An ABG analysis will be performed after 20 minutes, without any other change to the $FiO_2$ or any other ventilator parameter.

If an hypoxemia occur when PEEP is set at 5 $cmH_2O$, $FiO_2$ will be increased to maintain $SaO_2$ within acceptable ranges. If severe hypoxemia persists despite increased $FiO_2$, the test will be shortened and aborted right after ABG sampling.

After entering the values measured at PEEP 5 and PEEP 15 in the eCRF, the investigator will be notified of the ventilation strategy to use for this patient.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### *7.2 First Randomization - Arm A: Minimal distension*

Ventilation strategy in this arm is a slightly modified version of the ARDSnet protocol as used in the ARMA and LOVS studies [2,25] . In brief, this includes ventilation with $V_T$= 6 mL/kg and $P_{PLAT}$ ≤ 30 $cmH_2O$) and $FiO_2$/PEEP combination chart titration.

i. **Adjusting tidal volume:** ACV will be used until weaning criteria are met. Tidal volume will be set at 6 ml/kg, computed using the predicted body weight determined as follows: PBW = X + 0.91 (height in cm – 152.4), with X = 50 for males and 45.5 for females. Inspiratory flow will be 50 to 70 L/min and end-inspiratory pause duration 0 to 0.5 s, and the I:E ratio will be kept between 1:1 to 1:3. All ventilators used in study will correct the measurements of tidal volume for gas compression. Measurement of $P_{PLAT}$ using a 0.5-1 sec tele-inspiratory occlusion maneuver will be performed to confirm that $P_{PLAT}$ is lower than 30 $cmH_2O$. If $P_{PLAT}$ is >30 $cmH_2O$ despite a $V_T$ of 6 ml/kg, PEEP will be reduced to a minimum of 5 $cmH_2O$. If $P_{PLAT}$ is >32 $cmH_2O$ with 6 ml/kg $V_T$ and 5 $cmH_2O$ PEEP, $V_T$ will be reduced by 1 ml/kg steps to 4 ml/kg, provided pH remains ≥ 7.15 (Appendix).

ii. **Respiratory rate & acidosis management:** Respiratory rate will be kept at no more than 35/min and adjusted to achieve $PaCO_2$ values such that arterial pH is between 7.2 and 7.45. When pH remains lower than 7.25 despite a breathing rate of 35/min, tidal volume will be increased stepwise to 8 ml/kg by 1 mL/kg steps until pH is ≥7.25, provided $PaCO_2$ is kept ≥38 mm Hg and $P_{PLAT}$<32 $cmH_2O$, if needed by decreasing the PEEP level to 5 $cmH_2O$. Detailed management strategies of severe respiratory acidosis will be described in the investigator manual.

iii. **Setting of $F_IO_2$ & oxygenation targets:** $FiO_2$ (0.21 to 1) will be set to achieve the following oxygenation targets: 90% ≤ $SpO_2$ ≤96% or 65 mmHg ≤ $PaO_2$ ≤90 mmHg. When $PaO_2$ measurements are available, they will take priority over $SpO_2$.

iv. **Setting PEEP:** PEEP will be set according to ARMA lung protective algorithm (see below) taking into account total PEEP (the sum of applied PEEP and intrinsic PEEP)[2]. In patients who are completely relaxed or on neuromuscular blockade, total PEEP will be measured using the end-expiration occlusion method. Estimation of total PEEP when muscle activity precludes the use of this method is described in the Investigator's manual.

| | Fraction of Inspired Oxygen ($FIO_2$) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 0.3 | 0.4 | 0.5 | 0.6 | 0.7 | 0.8 | 0.9 | 1.0 |
| Control PEEP ranges, cm $H_2O$ | 5 | 5-8 | 8-10 | 10 | 10-14 | 14 | 14-18 | 18-24 |

### *7.3 First Randomization - Arm B: Maximal recruitment*

As in Arm A, patients will be ventilated with a $V_T$ initially set at 6 mL/kg using ACV.

i. **Setting PEEP:** The PEEP setting strategy is adapted from the Express trial[27] . Immediately after a recruitment maneuver performed as described in the PRT, PEEP will be adjusted based on airway pressure and will be kept as high as possible to obtain a $V_T$ equal to 6 mL/kg PBW without increasing the maximal inspiratory $P_{PLAT}$ above 27 $cmH_2O$ - a value shown in several studies to limit the risk of distension-related lung injury. Measurement of $P_{PLAT}$ using a 0.5-1 sec tele-inspiratory occlusion maneuver will be performed to confirm that $P_{PLAT}$ ≤27 $cmH_2O$. The PEEP will be assessed twice daily and increased / decreased if necessary to achieve a $P_{PLAT}$ ≤ 27 $cmH_2O$.

ii. **Adjusting tidal volume to limit ΔP:** After setting PEEP to the maximal level for an inspiratory $P_{PLAT}$ of 27 $cmH_2O$ and $V_T$ 6 mL/kg, the driving pressure ΔP will be measured. If ΔP exceeds 14 $cmH_2O$, a further reduction of $V_T$ will be performed by 0.5 mL/kg steps to achieve the ventilation goals. In case of severe acidosis, respiratory rate will be increased



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

to a maximal rate of 35 rpm. Management of severe respiratory acidosis is described in Appendix.

iii. **Respiratory rate & acidosis management:** Respiratory rate will be kept at no more than 35/min and adjusted to achieve $PaCO_2$ values such that arterial pH is between 7.25 and 7.45. When pH remains lower than 7.2 despite a breathing rate of 35/min, tidal volume will be increased stepwise to 8 ml/kg by 1 ml/kg steps until pH is ≥7.25, provided $PaCO_2$ is kept ≥38 mm Hg and $P_{PLAT}$<32 $cmH_2O$, if needed by decreasing the PEEP level to 5 $cmH_2O$. Detailed management strategies of severe respiratory acidosis will be described in the Investigator's manual.

**iv. Setting of $F_IO_2$ & oxygenation targets:** $FiO_2$ (0.21 to 1) will be set to achieve the following oxygenation targets: 90% ≤ $SpO_2$ ≤96% or 65 mmHg ≤ $PaO_2$ ≤90 mmHg. When $PaO_2$ measurements are available, they will take priority over $SpO_2$.

Ventilation strategies that will be implemented in study arms are illustrated in Figure 1 (page 22).

### *7.4 First Randomization – Arm C – PRT-guided ventilation strategy*

In the first randomization Arm C, the results of the PRT will be used to tailor the ventilatory strategy.

- Patients with a negative will be treated with the strategy defined in Arm A (minimal distension)
- Patients with a positive PRT will be treated with the strategy defined in Arm B (maximal recruitment).

### *7.5 Second randomization, Intervention arm: Early and systematic use of PP and NMBAs*

In the second randomization interventional arm, early PP and NMBAs will be used as soon as possible after randomization and no later than 6 hours after it . NMBAs are used for 48h but can be stopped early if $PaO_2/FiO_2$ is ≥ 150 mmHg at a PEEP ≤ 12 $cmH_2O$ and plateau pressure ≤ 28 $cmH_2O$ while the patient is in the supine position.

- Initiation and dosage

Study staff will ensure a RASS score of -5 to -4 is achieved and documented prior to initiation of neuromuscular blockade and that patients are receiving controlled modes of mechanical ventilation. Initiation of neuromuscular blockade must begin within 6 hours of randomization in the group with early and systematic use of NMBAs. If the first administration is not done within 6 hours following randomization, this will be considered as a deviation to the protocol but the patient will remain in the study and in the ITT analysis. Cisatracurium will be the preferred muscle relaxant used. This NMBA is usually used in France and has obtained a European Medicines Agency approval. NMBAs will be systematically used in the interventional group and only if requested as a rescue therapy in the control group. Regarding the dose, we propose to use cisatracurium in the interventional group in order to obtain 0 to 1 response to the train-of-four (TOF) performed at the orbicular site (orbicularis oculi), or no response (0/4) if the TOF is done at the ulnar site (adductor pollicis). TOF will be monitored 1 hour after the initiation of NMBAs infusion and 1 hour after every dose regimen change. An initial dose of 0.25 mg/kg/hour of cisatracurium besylate can be proposed, as already described[41] . In case of insufficient neuromuscular block (TOF above the objectives) a bolus of 0.2 mg/kg and an increase of 20% in the continuous infusion will be performed[41]. In the absence of TOF evaluation, we propose to use cisatracurium as in the ACURASYS and ROSE studies (cisatracurium besylate bolus of 15 mg, followed by a continuous infusion of 37.5 mg/hour)[6,8] . If atracurium is used, posology should be according to the center local protocol.

- Sedation

The sedation dosage required to achieve a RASS score of -5 to -4 prior to cisatracurium administration should be continued during the neuromuscular blockade period. After



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

neuromuscular blockade ceases or when there is no administration of NMBAs, sedation should be adapted to ensure the safety of mechanical ventilation supply. We do not mandate sedative type or dose.

- Stopping rules for neuromuscular blockade

During the 48-hours study intervention period can be stopped prematurely if $PaO_2/FiO_2$ is ≥ 150 mmHg at a PEEP ≤ 12 $cmH_2O$ and a plateau pressure ≤ 28 $cmH_2O$ and maintained for at least 4 hours while the patient is in the supine position. If after the discontinuation of neuromuscular blockade, the oxygenation significantly worsens ($PaO_2/FiO_2$ < 120 mmHg), neuromuscular blockade should be resumed. After the 48-hours study intervention period, if the oxygenation significantly worsens ($PaO_2/FiO_2$ < 120 mmHg), neuromuscular blockade can also be resumed (clinician decision).

### *7.6 Second Randomization, Control arm: Early & systematic use of PP with NMBAs indicated only as rescue*

Prone positioning will be initiated in all patients with $PaO_2/FiO_2$ < 150 mmHg once secondly randomized. Sedation will be adjusted to ensure clinically acceptable patient-ventilator synchrony. In the control arm, NMBAs will only be used as a rescue if $P_{PLAT}$ exceeds 30 $cmH_2O$ for at least 10 minutes despite increasing doses of sedatives and decreasing $V_T$ (while maintaining a pH > 7.20) and also PEEP by 2 $cmH_2O$ (only if pH ≤ 7.20) if tolerated[6,8] .

We will encourage sites to minimize neuromuscular blockade use in the control group of the second randomization and during the first 72 hours following the first randomization before the second randomization occurs. We will encourage non-neuromuscular blockade interventions for refractory hypoxemia without neuromuscular blockade.

**Recommendation:** If the end-inspiratory $P_{PLAT}$ remains > 30 $cmH_2O$ for at least 10 minutes, it is recommended that the patient receives the administration of increasing doses of sedatives and decreasing $V_T$ and also PEEP (if tolerated) before considering using cisatracurium. If needed, an intravenous injection of 20 mg of cisatracurium is recommended for patients in the NMBAS rescue arms of the study. If this rapid, intravenous injection results in a decrease of the end-inspiratory plateau pressure by less than 2 cm $H_2O$, a second injection of 20 mg of cisatracurium will be allowed. If after injection, the end-inspiratory plateau pressure does not decrease or decrease by less than 2 cm of water, cisatracurium should not be administered again during the following 24-hour period. In the presence of a patient/ventilator asynchrony or dyssynchrony, it is recommended first to adapt the ventilator settings and if necessary to use deeper sedation levels. NMBAS infusion is not allowed if plateau pressure is ≤ 30 $cmH_2O$.
If a NMBA is used it is recommended to use it for the shortest period with a minimal interruption of the infusion every 24 hours, to insure not to prolong the treatment longer than necessary.

- Sedation

In the absence of neuromuscular blockade, as in the ROSE study[6,8] , sedation is let to the clinician discretion but it is recommended to target a RASS score 0 to -1 or the absence of respiratory distress, and/or daily sedation breaks if no contraindication and to document reasons for sedation given for RASS < -1.

# 8 EFFICACY ASSESSMENT

## 8.1 Description of efficacy endpoint assessment parameters

The objectives, primary and secondary endpoints of the study have been clearly defined (see sections 4.1 & 4.2).


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- The primary endpoint of the study is **28-day all-cause mortality** after inclusion.
- The secondary endpoints of the study are detailed in the table below:

| Secondary objectives | Secondary endpoints |
|---|---|
| • **To test whether cautious implementation of a high-PEEP strategy only in patients with a positive response to a PRT is superior to PEEP levels selected irrespective of the potential for lung on:**<br>• **To assess if the systematic and early use of PP and NMBAs is superior to the early and systematic use of PP with NMBAs prescribed only as rescue strategy on:** | |
| Physiological effects | - $PaO_2/FiO_2$, oxygenation index and ventilatory parameters ($V_T$, respiratory rate, total PEEP, $P_{PLAT}$, compliance of the respiratory system) at H24, H48, H72, and on day 7 and 14 |
| Organ dysfunctions | - Detailed Sequential Organ Failure Assessment (SOFA) Score at H24, H48, H72, and on day 7 and 14 |
| Clinical / Patient-centered efficacy outcomes | - All-cause mortality at days 90 and 1 year<br>- All-cause ICU and hospital mortality<br>- Duration of mechanical ventilation<br>- Ventilator Free Days at day 28 (VFD28). The number of VFD is defined as the number of days from the time of initiating unassisted breathing to day 28 after randomization, assuming survival for at least two consecutive calendar days after initiating unassisted breathing and continued unassisted breathing to day 28. If a patient returns to assisted breathing and subsequently achieves unassisted breathing to day 28, VFDs will be counted from the end of the last period of assisted breathing to day 28. A period of assisted breathing lasting less than 24 hours and for the purpose of a surgical procedure will not count against the VFD calculation. If a patient was receiving assisted breathing at day 27 or died prior to day 28, VFDs will be zero. Patients transferred to another hospital or other health care facility will be followed to day 28 to assess this endpoint.<br>- ICU and hospital length of stay<br>- ICU-free days at day 28<br>- Hospital-free days at day 28 and day 90 |
| Safety outcomes | - Occurrence of barotrauma (defined as any pneumothorax, subcutaneous emphysema, pneumomediastinum, or pneumatocele of more than 2 cm detected on image examinations) through day 7<br>- Occurrence of acute cor pulmonale defined by the presence of both paradoxical septal movement and RV dilatation (RVEDA/LVEDA >0.6 ACP; RVEDA/LVEDA >1 severe ACP) through day 7<br>- ICU acquired weakness assessed by the Medical research council (MRC) score at ICU discharge. A score < 48 defines ICU acquired weakness. |
| Use of other rescue procedures | - Use (days) of other rescue procedures such as inhaled nitric oxide, almitrine, epoprostenol sodium, extracorporeal membrane oxygenation (ECMO), extracorporeal $CO_2$ removal ($ECCO_2R$)<br>- Use of NMBAs during the first 3 days following inclusion<br>- Use of NMBAs following inclusion in the rescue ARM of the second randomization<br>- Muscle relaxants-free days between inclusion and day 7 and day 28 |



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

| | |
|---|---|
| Sedatives use | - Number of days alive and without continuous IV administration of sedatives/analgesics at day 7 and at day 28<br>- Presence of delirium (CAM-ICU) at days 14 & ICU discharge<br>- Paralysis recall assessment at ICU discharge using a modified Brice questionnaire |
| Quality of life | – One-year outcome assessments<br>• Disability assessed by the Activities of Daily Living score (Lawton IADL)<br>• Quality-of-life, using the EuroQOL (EQ-5D-5L)<br>• Posttraumatic stress disorder (PTSD), using the Impact Event Scale-Revised (IES-R)<br>• Subsequent return to work. Return to work status: employment status<br>• cognitive dysfunction using T-MoCA score<br>• Place of residence |
| Exploratory outcomes | - Death with refractory hypoxemia (defined as $PaO_2/FiO_2$< 80 mmHg outside a care incident) within 7 days<br>- Death with refractory acidosis within 7 days<br>- Death with barotrauma within 7 days<br>- Need of commencement or 30% increase in vasopressors or hypotension (MAP<60 mmHg) within 8 hours after first randomization<br>- Refractory hypoxemia within 8 hours after randomization<br>- Severe acidosis (pH<7.10) within 8 hours after randomization |

## 8.2 Anticipated methods and timetable for measuring, collecting and analysing the efficacy assessment parameters

We have carefully planned sequential collection and recording of all parameters allowing to assess the primary and secondary endpoints of the study. All the data will be collected prospectively as intensive care is provided to the participants to the research. The vast majority of data will be collected during the ICU stay by investigators, research technicians or clinical research assistant. This will require minimal arrangements. The organization of follow-up after ICU discharge (including necessary telephone interviews up to 12 months after inclusion) requires time of research technicians or clinical research assistants to collect and analyze the long-term efficacy assessment parameters. This has been considered in the proposed budget.

# 9 SPECIFIC STUDY COMMITTEES

## 9.1 Scientific Committee

***Role***

Members of the Scientific committee determine the study design and methodology, define the general organization and course of the project and coordinate the information. The Scientific committee initiates the project, drafts the protocol and may suggest modifications to the protocol during the enrolment period of the study in response to information collected during the trial (i.e., inclusion rate, treatment allocation, separation of PEEP levels between arms, etc.). It is also responsible for writing and validating the CRF (importantly, there will one common CRF for both parts of the study). During the trial, they monitor the course of the project and provide responses to unforeseen events that may happen, especially concerning safety and side effects. Members of the Scientific committee oversee the analysis of data and are responsible for the writing of scientific documents derived from the study, eventually helped by a writing committee.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

***Composition***
The Scientific Committee is constituted by the investigators that initiated the study and include clinical experts in the condition and treatments investigated in the study. Current members (in alphabetical order) of the Scientific Committee include: Pr S. Chevret, Pr JD. Chiche, Pr A. Demoule, Pr JM. Forel, Pr S. Hraiech, Pr A. Mercat, Pr L. Papazian.

# 10 SAFETY ASSESSMENT - RISKS AND BURDENS ADDED BY THE STUDY

## 10.1 Definitions

According to Article R.1123-46 of the *Code de la Santé Publique* (French Public Health Code):

- **Adverse event**

Any untoward medical occurrence in a study participant, which does not necessarily have a causal relationship with the study or with the product subject to the study.

- **Adverse reaction**

Adverse event occurring in a person enrolled in a study involving human participants, when this event is related to the study or to the product being studied.

- **Serious adverse event or reaction**

Any adverse event or reaction that results in death, threatens the life of the research participant, requires hospitalisation or prolongs hospitalisation, causes a serious or long-term disability or handicap, or results in a congenital abnormality or deformity.

- **Unexpected adverse reaction**

Any adverse reaction for which the nature, severity or progression are not consistent with information pertaining to the products, acts practiced and methods used during the study.

Pursuant to article R. 1123-46 of the Code de la Santé Publique and the opinion of the clinical trial sponsor not relating to a health product (ANSM):

- **Emerging safety issue**

Any new information that may lead to a reassessment of the risk/benefit ratio of the study or the product under investigation, modifications to the use of the product, the conduct of the clinical trial, or the clinical trial documents, or to a suspension, interruption or modification of the clinical trial or of similar studies.

For example, this concerns:

- any clinically significant increase in the frequency of an expected serious adverse reaction;
- early termination or a temporary halt for safety reasons for a trial carried out in another country with the same product (act or method) as the one being studied in France;
- recommendations from the Data Monitoring Committee, if applicable, if they are relevant to the safety of the participants;
- suspected unexpected serious adverse reactions in participants who have terminated the trial and of which the sponsor has been notified by the investigator, in addition to any possible follow-up reports.

## 10.2 The role of the investigator

**For each adverse event, the investigator must assess its severity** and report all serious and non-serious adverse events in the e-CRF


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

The investigator must **document** serious adverse events **as thoroughly as possible** and provide a definitive medical diagnosis, if possible.

The investigator must **assess the intensity** of the adverse events by using a rating scale for adverse events appended to the protocol

- *CTCAE V5.0 (Common Terminology Criteria for Adverse Events version 5.0)*

The investigator must **assess the causal relationship between** a serious adverse events and interventions/procedures added by the study.

The method to be used by the investigator is based on 2 causality terms (EudraVigilance Clinical Trial Module (EVCTM) method):

- Related
- Not related

### *10.2.1 Serious adverse events that require the investigator to notify the sponsor without delay*

As per Article R.1123-49 of the *Code de la Santé Publique* (French Public Health Code), the investigator notifies informs the sponsor without delay on the day he become aware of any serious adverse event which occurs during a study that meets the description in line 1° of Article L.1121-1 of the *Code de la Santé Publique*, with the exception except any event which is listed in the protocol (see section 10.2.2) and, if applicable, in the investigator's brochure as not requiring notification.

A serious adverse event is any untoward medical occurrence that:

1- results in death
2- is life-threatening to the participant enrolled in the study
3- requires hospitalisation or prolongation of existing hospitalisation
4- results in persistent or significant disability/incapacity
5- is a congenital anomaly/birth defect

### *10.2.2 Specific features of the protocol*

***Other events that require the investigator to notify the sponsor without delay***

Serious Adverse events deemed "medically significant"

- Pneumothorax or other clinical manifestation of barotrauma
- Refractory hypoxemia defined as $PaO_2/FiO_2$< 80 mmHg for > 6 hours outside a care incident, and its consequences
- Severe acidosis defined as pH<7.10 despite RR ≥ 35 /min & $V_T$ 8 ml/kg, and its consequences
- Acute cor pulmonale
- Anaphylaxis due to NMBAs use
- Catheter or endotracheal tube accidental removal during PP

The investigator must notify the sponsor without delay on the day the investigator becomes aware of these adverse events, in the same manner and within the same deadline as for serious adverse events (see above).

***Serious adverse events that do not require the investigator to notify the sponsor without delay***

Patients with the ARDS are severe and they often present life-threatening conditions. These serious adverse events do not need to be reported without delay to the sponsor but need to be recorded in the eCRF on the "adverse event" form of the eCRF, specifying the date of


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

occurrence, description, intensity, duration, resolution mode, etiology, study interventions imputability and decisions made.

Serious adverse events in the course of ARDS include:

- Death due to the evolution of the ARDS
- Death following a decision to limit active therapies
- Multi-organ failure
- Death or deterioration due to the progression of an underlying disease
- Septic shock and its consequences (distal ischemia, mesenteric, cardiac...)
- Nosocomial infection
- Severe ventricular arrythmia
- Complications of intubation (unplanned extubation, tube obstruction, mucous plugs,...)
- Complications after extubation (inhalation, acute respiratory failure requiring reintubation)
- Difficult weaning requiring tracheotomy

Each adverse event will be monitored until its full resolution (stabilized to a level deemed acceptable to the investigator or return to the previous condition) even if the patient has been discharged from the ICU.

The primary objective of the study is the mortality at 28 days. The mortality rate linked to the studied condition of acute distress respiratory syndrome is between 35 and 46% [16]
The interventions added by the study being: a PEEP responsiveness test, who have no serious adverse events in the pilot study, and the early and systematic use of PP with NMBA, **deaths should not have to be notified to the sponsor without delay but are to be recorded in the case report** with exception of SAE medically significant or related acccording to the investigator.
Retrieval of deaths and all serious adverse event listed as SAE that do not required to be reported without delay from the case report will be made every 6 months by the Clinical Research Unit to expertisecsi.drc@aphp.fr.
If there is any discrepancy between the groups or the mortality rate is higher than expected [state the time-to-mortality or number of patients] affecting participant safety and which requires the sponsor to take urgent safety measures, the ANSM (French Health Products Safety Agency) will be informed about the emerging safety issue without delay.

#### *10.2.2.1 Period during which SAEs must be notified without delay by the to thesponsor*

The investigator must notify the sponsor within 24 hours of any serious adverse events as defined in the corresponding section, except those listed in section 10.2.2:

- from the date interventions added by the study
- throughout D28 after second and/or first randomization required for the trial
- Indefinitely, if the SAE is likely to be due to interventions added by the study

#### *10.2.2.2 Procedures and deadlines for notifying the sponsor*

The initial notification of an SAE must be provided in a written report signed by the investigator using a SAE notification form specific to the study and intended for this purpose (in the case report form), and reported by fax to the sponsor, regardless of its causal relationship to the research (except those identified in the protocol as not requiring immediate reporting)

Each item in this form must be completed by the investigator so that the sponsor can carry out the appropriate analysis.

The initial notification to the sponsor of a serious adverse event must be quickly followed by an additional detailed written report (or reports) so that the case outcome may be monitored by the Safety Department or to provide further information.

Whenever possible, the investigator will provide the sponsor with any documents that may be useful (medical reports, laboratory test results, results from additional examinations, etc.). These


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

documents must be non-identifying. In addition, the documents must include the following: study acronym, number and participant's initials.

Any adverse event will be monitored until fully resolved (stabilisation at a level considered acceptable by the investigator, or return to the previous state) even if the participant has left the study.

The initial notification, the SAE follow-up reports and all other documents must be sent to the sponsor's Safety Department by email (eig-vigilance.drc@aphp.fr). It should be noted that it is possible to send SAE reports to the Safety Department by fax to +33 (0)1 44 84 17 99 only in the event of a failed attempt to send the SAE report by email (in order to avoid duplication).

When sending the email, please:
- Adopt a standardized nomming of the email subject in the following form:
<< Objet : YYYYYY_XXXXXX_jjmmaaaa (avec YYYYYY : code de la recherche, XXXXXX : acronyme de la recherche et jjmmaaaa : date de transmission). >>

- Send a SAE initial notification form and/or a follow-up report concerning a single participant for a given SAE, attachment may contain one (or more) document(s) (follow-up and hospitalization reports, for example).
The total size of the email must be less than 8 MB, otherwise please send several e-mails.

- Ensure that all documents transmitted (e.g. hospital reports) are anonymized and identified with the participant's identification number.

For studies using e-CRFs:
- the investigator completes the SAE notification form in the e-CRF, then validates, prints, and signs the form before sending it by email;
- if it is not possible to connect to the e-CRF, the investigator should complete, sign, and send the SAE notification form to the Safety Department. As soon as the connection is restored, the SAE notification form in the e-CRF must be duly completed.

The investigator must respond to all requests from the sponsor for additional information.
For all questions relating to the notification of an adverse event, the Safety Department can be contacted via email: vigilance.drc@aphp.fr

## 10.3 Role of the sponsor

The sponsor, represented by its Safety Department, continuously, throughout the trial, assesses participant safety throughout the study.

### *10.3.1 Analysis and declaration of serious adverse events*

The sponsor assesses:
- the **seriousness** of all the adverse events reported
- the **causal relationship** with each specific intervention/procedure/examination added by the study,
  All serious adverse events which the investigator and/or the sponsor believe could have a causal relationship with the interventions specifically added by the study that could reasonably be considered as having suspected serious adverse reactions.
- the **expected or unexpected nature** of the serious adverse reactions
  Any serious adverse reaction is considered to be unexpected when the nature, severity or progression are not consistent with information pertaining to the interventions practiced over the course of the study.
  The sponsor, represented by its Safety Department, assesses the expected/unexpected nature of a serious adverse reaction based on the information described below**.**


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

**Serious adverse events** likely to be related to the interventions except those leading to death are as follows
- Anaphylaxis due to NMBAs use
- Catheter or endotracheal tube accidental removal during PP
- Pneumothorax or other clinical manifestation of barotrauma
- Refractory hypoxemia defined as $PaO_2/FiO_2$< 80 mmHg for > 6 hours outside a care incident, and its consequences
- Severe acidosis defined as pH<7.10 despite RR ≥ 35 /min & $V_T$ 8 ml/kg, and its consequences
- Acute cor pulmonale

The sponsor will report all suspected unexpected serious adverse reactions (SUSARs), within the regulatory time frame, to the ANSM (French Health Products Safety Agency):

- The sponsor must send the initial report immediately upon learning of the unexpected serious adverse reaction if is fatal or life-threatening, or otherwise within 15 days from learning of any other type of unexpected serious adverse reaction;
- All additional, relevant information must be declared by the sponsor in the form of monitoring reports within a period of 8 calendar days starting from when the sponsor had this information.

The sponsor must notify all the investigators involved about any information that could adversely affect the safety of the research participants.

### *10.3.2 Analysis and declaration of other safety data*

Pursuant to article 1123-46 of the Code de la Santé Publique, a new development is defined by any new data that may lead to a reassessment of the study's risk-benefits ratio or studied product, to modifications in the use of this product, in the conduct of the study, or documents pertaining to the study, or to suspend or halt or modify the study protocol or similar studies.

The sponsor will inform the competent authority and the Research Ethics Committee without delay upon knowledge of any emerging safety issues and, if applicable, describe what measures have been taken.

Following the initial declaration of any emerging safety issues, the sponsor will address to competent authorities any additional relevant information about the emerging safety issue in the form of a follow-up report, which must be sent no later than 7 days from learning of the information.

### *10.3.3 Annual safety report*

Once a year for the duration of the clinical trial, the sponsor must draw up an annual safety report (ASR or annual safety report), which includes, in particular:
- a safety analysis for the research participants,
- a list of all the suspected serious adverse reactions that occurred in France in the concerned study during the period covered by the report,
- summary tables including all of the SAEs that have occurred since the start of the study.

The annual safety report must be sent no later than 60 days after the anniversary of the date on which the first participant was included in the study.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## 10.4 Data Safety Monitoring Board

***Role***

The DSMB will periodically review unblinded and/or blinded safety data at pre-specified intervals defined in the DSMB Charter. The Board will assess the nature, frequency, and severity of safety events and identifies any emerging safety concerns or trends.

The DSMB will also review interim efficacy data to assess whether the interventions studied demonstrate clear benefit, lack of benefit (futility), or unexpected outcomes that may impact participant safety or trial continuation. The DSMB will oversee interim analyses conducted according to the Statistical Analysis Plan, and will ensure that interim analyses are performed in a manner that preserves trial integrity and controls for inflation of type I error. Based on ongoing safety and efficacy evaluations, the DSMB will assess whether the risk–benefit profile of the interventions remains acceptable throughout the trial.

Following each review, the DSMB will provide written recommendations to the Sponsor regarding continuation, modification, temporary suspension, or early termination of the trial due to safety concerns, overwhelming efficacy, or futility. Final decisions will remain the responsibility of the Sponsor. All DSMB proceedings, data reviews, and deliberations willl remain confidential. Access to unblinded data will be restricted to DSMB members and authorized statisticians, as defined in the DSMB Charter, to minimize operational bias.

***Documentation and Charter***

The DSMB will operate under a written DSMB Charter that defines membership, roles, meeting frequency, data to be reviewed, statistical guidelines, decision-making processes, and communication pathways, in alignment with ICH-GCP and applicable regulatory requirements.

***Composition***

To garantee independence, we have selected members that are free of conflicts of interest, have expertise in large RCTs including platform and adaptive-design trials, are familiar with the field and are not involved in trial conduct. The DSMB is constituted by Pr Derek Angus (Pittsburgh, USA, Chair), Pr Kathy Rowan (London, UK, Methodologist), Pr Dan Talmor (Boston, USA), Pr Samir Jaber (Montpellier, F).

# 11 DATA MANAGEMENT

## 11.1 Data collection procedures

Data will be collected prospectively on an e-CRF database specifically designed for both parts of the study. Indeed, both parts of the study share inclusion/exclusion criteria as well as primary and secondary endpoints. Data will be entered by investigators and/or clinical research technicians adhering to good clinical practice.

## 11.2 Identification of data recorded directly in the CRFs which will be considered as source data

Questionnaires such as CAM-ICU, EQ-5D-5L, t-MoCA, BRICE questionnaire or IES-R score will be directly filled inside e-CRF by investigators or designated clinical research assistants and will be considered as source documents.

## 11.3 Right to access data and source documents

### *11.3.1 Data access*

In accordance with good clinical practices (GCPs):



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- the sponsor is responsible for ensuring all parties involved in the study agree to guarantee direct access to all locations where the study will be carried out, the source data, the source documents and the reports, for the purposes of the sponsor's quality control and audit procedures or inspections by the competent authority
- the investigators will ensure the persons in charge of monitoring, quality control and auditing or inspecting the interventional study involving human participants have access to the documents and personal data strictly necessary for these tasks, in accordance with the statutory and regulatory provisions in force (Articles L.1121-3 and R.5121-13 of the French Public Health Code)

#### *11.3.2 Source documents*

Source documents are defined as any original document or item that can prove the existence or accuracy of a data or a fact recorded during the study. These documents will be kept by the investigator, or by the hospital in the case of a hospital medical file, for 15 years.

In the context of the study, source documents include the ICU patient medical file, recorded values derived from patient monitors and ventilators, original biological examination results, chest X-rays and summary from imaging examinations, etc.). Questionnaires such as CAM-ICU, EQ-5D-5L, t-MoCA, BRICE questionnaire or IES-R score will be directly filled by investigators or designated clinical research assistants and will be considered as source documents.

#### *11.3.3 Data confidentiality*

The persons having direct access to the collected data and responsible for the quality control of clinical study (as defined by article L.1121-3 of the *Code de la Santé Publique* (for example, investigators, individuals responsible for quality control, supervisors, clinical research assistants, auditors and all persons called upon to participate in the trial) will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.
These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions set out in Articles 226-13 and 226-14 of the *Code Pénal* (French Criminal Code).
During and after the study, all data collected concerning the participants and sent to the sponsor by the investigators (or any other specialized collaborators) will be rendered non-identifying. Under no circumstances shall the names and addresses of the participants involved be shown. Only the participant's initials will be recorded, accompanied by an encoded number specific to the study indicating study site and the order of enrolment.
The sponsor will ensure that each participant has given written permission for any personal information about him or her which is strictly necessary for the quality control of the study to be accessed.

### 11.4 Data processing and storage of research documents and data

#### *11.4.1 Identification of the data processing manager and location(s)*

The Lariboisière – Saint-Louis – Fernand Vidal Clinical Research Unit (site Saint Louis) will be in charge of the data management of the study.

#### *11.4.2 Data entry*

Data entry will be carried out on an electronic case report form system (e-CRF), filled in on the internet after each visit by the investigator-physicians or authorized trial staff in each center. Access to the online data entry form by the investigator-physicians will be restricted by an access code and a personal and unique password system for each user. Each investigator will, in addition, have access to a specific profile that attributes or withholds access to certain functions of the system (entering data, or simply viewing the data of the enrolled patient or all the study data, possibility of change and validation by the CRAs, etc.). Data will be stored on a secure server, with data encrypted during transmission and automatic internal saving of a copy on the server that will host the electronic case report form.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## 11.5 Data ownership

AP-HP the owner of the data. The data cannot be used or disclosed to a third party without her prior permission.

# 12 STATISTICAL ASPECTS

## 12.1 Description of statistical methods to be used including the timetable for the planned interim analyses

For the first randomization, we plan to use a **Bayesian response-adaptive randomization design with enrichment**, based on sequential Bayesian statistical analyses[42–44] to evaluate the primary outcome of 28-day mortality. Implementation of similar statistical methods in critical care trials performed during the advent of the COVID-19 pandemics has fostered rapid completion of these studies, allowing to obtain answers that rapidly influenced clinical management[45–47] .

Including interim analyses using pre-specified stopping boundaries will allow for the selection or dropping of any treatment arm to move forward when such evidence already exists based on those interim analyses. It will also allow for further assessment of treatment by subset interactions with the pre-specified subsets of interest defined below. To optimize patient allocation, we adopt an adaptive accrual design after an initial "burn-in period", allowing the ratio of patients assigned to experimental versus control arms to evolve based on treatment performance. The simulation setting mimicked the PEPER trial setting under various realistic underlying scenarios, using a fixed sample size of 1,200 patients[48] . In fact, the false-positive rate increased as the number of interim analyses increased, ranging from 0.047 for one interim analysis to 0.066 for nine interim analyses. Therefore, we decided to set a burn-in period of 300 patients (before any interim analyses), then performing 3 interim analyses (that is, every once 300 patients), before the terminal one.

### *Initialisation and Optimal allocation computation*

First, patients are assigned to either arm k = A, B, C, with probabilities of (1/3,1/3, 1/3) that is, using a 1:1:1 balance fixed-randomisation design. After a burn-in enrolment period of the first 300 patients patient outcomes will be recorded. Then, actualization of randomization probabilities can be performed.

We considered that reactualization of the randomization ratios are scheduled to be performed after every 300 patients have been allocated to either arm, A, B and C.

Data collected on the previous cohort of enrolled patients are used to calculate the posterior mean of the 28-day death rate in each arm k=1,2,3, given accumulated data up to that point.

We aim at minimising the expected number of treatment 28-day deaths, for a fixed asymptotic variance – which reflects the power of the test of comparing the benefit of each marker strategy against all others. Thus, we used the allocation proportions proposed by Hu and Zhu[49] . The Bayesian posterior mean estimates of failure rates are plugged in the allocation ratio, minimising the total number of deaths over the trial sample. Let define the optimal allocation probability function ψk proposed by Jeon and Hu, with $\gamma = 2$, the tuning parameter for controlling the degree of randomness.

All this processes are repeated until the sample size has been reached or any stopping rule is fulfilled, at which point the trial is stopped.

For the second randomization, the primary outcome of 28-day mortality across the second randomization arms, will be analysis with a chi-square test, stratified on the results of the first randomization.
Overall, our strategy may augment the statistical power to detect a relevant magnitude of clinical benefit, reduce the number of patients needed and thus the overall duration of the enrolment period.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Analysis of secondary outcomes will be performed at the time of terminal analysis.
All cause-mortality within 90 days will be estimated by the Kaplan-Meier method, compared by the log-rank test across groups. Ventilator-free days, ICU-free, and hospital-free days, will be compared by the nonparametric Wilcoxon rank sum test.
Occurrence of acute cor pulmonale, of barotrauma, or use of any other rescue procedures will be considered in a competing-risks framework, due to competing deaths, with estimation of cumulative incidence function, compared through the Gray's test.
PaO2/FiO2, oxygenation index, SOFA and ventilatory parameters will be analysed by joint mixed models for longitudinal and survival data, that is, a shared parameter model where the longitudinal data and survival models share common random effect(s).
Other cross-sectional data (at the ICU discharge, at H8, at day 14, at one-year), will use landmark analyses, that is restricted to those patients exposed at each time points.

Statistical analyses will be performed on R (https://www.R-project.org/) using the latest available version.

## 12.2 Calculation hypotheses for the number of participants required and the result

The design of the trial, at initiation, has been informed by conducting extensive simulations using standard Monte Carlo methods. These simulations have evaluated the impact of a range of plausible scenarios on the statistical properties of the trial. Simulations have indicated across a range of plausible assumptions of what can be expected, in terms of power to detect an absolute mortality difference ranging between 5-10% for any of the interventions, considering a funded sample size of 1200 patients.

For the **first randomization**, besides early stopping rules in the instances of a lack of efficacy, we have adopted an adaptive accrual design in which after the initial "learning phase", the ratio of patients randomly assigned to the experimental arm versus the control arms may change from 1:1:1 ratio to increase the proportion of patients randomized to the best performing arm.
Through simulations, we evaluated the operating characteristics of our trial design across a range of scenarios corresponding to various reasonable sizes of the treatment effect in each intervention and the treatment-by-subset interaction based on a maximum sample of 1,200 patients[48].

Regarding the **second randomization**, based on the two-sided Z-test with unpooled variance, a sample size of 491 patients in each randomized group achieves 90.01% (80.04%) to detect a difference between the group proportions of 28-day mortality of -8%. The 28-day mortality rate is assumed to be 32%, and 24% in the experimental group. The significance level of the test is 0.05. Thus, we would need to enroll 982 patients.
Based on data from similar trials, we anticipate that 70% of patients will meet inclusion criteria. We thus believe that the total number of patients to be enrolled to allow the detection of statistical differences in both trials will not exceed 1200 patients, expected to be reached over a 3-year recruitment period over 60 participating ICUs. Sample size was computed using PASS 15 software (2017).

The planned enrolment period of the study is 36 months. Considering the adaptive design of the Master Protocol, the actual number of patients needed to test our hypotheses may be different from our initial target of 1200 and 982 patients respectively. Both parts of the study will use a Bayesian statistical design. Bayesian designs provide an alternative, probabilistic interpretation of data particularly well suited to ARDS trials, as recently highlighted in the reanalysis of the Alveolar Recruitment for ARDS Trial[50] .

## 12.3 Anticipated level of statistical significance

The significance level of the test is 0.05.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

***Method for taking into account missing, unused or invalid data***

Missing data will be described for the sample as a whole and by randomization group. The strategy for managing missing data will be determined in consideration of their frequency and nature. In the presence of missing data on the primary endpoint, a multiple imputation by chained equations (MICE) approach will be used on the 28-day mortality. This approach will enable us to assess the robustness of the results, taking into account the various assumptions relating to missing data.

## 12.4 Statistical criteria for termination of the first intervention

• Stop the trial if there is sufficient information on the benefit of intervention (that is, minimal or maximal recruitment). At each interim analysis, the trial can be stopped early for efficacy if the posterior probability of observing at least the minimum expected treatment difference in mortality between interventions in favour of b is higher than a predetermined threshold, computed with equation (1) described below. If this probability exceeds a certain threshold, the trial is stopped early due to demonstrated efficacy in favour of intervention b.

(1) $$(pa - pb > \Delta | ski, , = A, B, C) > v$$

where Δ is the minimal expected treatment difference and v denotes the threshold for stopping decision. The minimal expected treatment difference Δ was set at 0.05, and $v = 0.80$ as recommended by Harrel[51] .

• Detection of subset (R) by treatment (minimal vs maximal recruitment)) interaction for enrichment. If the previous stopping rule is not fulfilled, the interaction between the patient subset (PRT) and the intervention effect is estimated with the measures proposed by Vinnat [52] computed from equations (2), (3). If the posterior probability of these measures exceeding a predefined cutoff η is high enough and clinically relevant, then the trial population is enriched in the subset of interest.

(2) $$\left(\theta_{R=1} / \theta_{R=0} > \eta \middle| \theta_{R=1} \geq \theta_{R=0}, , \right) > \varepsilon$$

(3) $$\left(\theta_{R=0} / \theta_{R=1} > \eta \middle| \theta_{R=0} \geq \theta_{R=1}, , \right) > \varepsilon$$

where η is the threshold for interaction and ε denote the interaction stopping boundary. The threshold for interaction η was set at 1.05, while ε was set at stringent value, that is ε = 0.75, as recommended by Harrel[51].

### *12.4.1 Choice of individuals to be included in the analyses*

All analyses will use intention-to-treat principle, that is, based on the treatment arms allocated by randomization.

### *12.4.2 Subgroup analysis*

Subgroup analysis will be conducted with predefined subgroups of interest. These include patients with pre-randomization $PaO_2/FIO_2$ levels below 100 and below 120, as well as those with varying durations between meeting ARDS severity criteria for study enrollment and the onset of NMBAs administration (less than or more than 48 hours).

Additionally, another subgroup of interest will comprise patients exhibiting a PEEP response at the time of randomization, measured after 20 minutes according to the criteria outlined in section 7.4.

# 13 QUALITY CONTROL AND ASSURANCE



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

**The trials will be conducted within the framework of the promoter standard operating procedures.** The investigating centers participating in the trial and the management of subjects will conform to the Helsinki Declaration and good medical practices in force.

## 13.1 General organisation

The sponsor must ensure the safety and respect of individuals who have agreed to participate in the study. The sponsor must implement a quality assurance system to best monitor the implementation of the study in the investigation centres.

For this purpose, the sponsor shall assign Clinical Research Associates (CRA) whose primary role is to carry out regular follow-up visits at the study locations, after having carried out the initial visits. The purpose of monitoring the study, as defined in Good Clinical Practices (GCP section 5.18.1), is to verify that:

- the rights, safety and protection of the research participants are met
- the data reported are exact, complete and consistent with the source documents
- the study is carried out in accordance with the protocol in force, the GCPs and the statutory and regulatory provisions in force

### *13.1.1 Strategy for centers opening*

The strategy for opening the centres established for this study is determined using the appropriate monitoring plan.

### *13.1.2 Scope of centre monitoring*

In the case of this risk B study, the appropriate monitoring level has been determined based on the complexity, the impact and the budget for the study. Therefore, in agreement with the coordinating investigator, the sponsor has determined the logistical score and impact, resulting in a study monitoring level to be implemented: intermediate level.

## 13.2 Quality control

A Clinical Research Associate (CRA) appointed by the sponsor will be responsible for the good completion of the study, for collecting, documenting, recording and reporting all handwritten data, in accordance with the Standard Operating Procedures applied within the DRCI (Clinical Research and Innovation Department) and in accordance with Good Clinical Practices as well as the statutory and regulatory requirements.

The investigator and the members of the investigator's team agree to make themselves available during regular Quality Control visits carried out by the Clinical Research Associate. During these visits, the following elements will be reviewed depending on the monitoring level:

- written consent
- compliance with the study protocol and with the procedures defined therein
- quality of the data collected in the case report form: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, original copies of laboratory results, etc.)
- management of the products used.

## 13.3 Case report forms

All information required by the protocol must be entered in the case report forms. The data must be collected as and when they are obtained, and clearly recorded in these case report forms. Any missing data must be coded.
Every site will have access to the electronic case report forms via a web-based data collection system. Investigators will be given a document offering guidance on using this tool.
When the investigators complete the case report form via the Internet, the CRA can view the data quickly and remotely. The investigator is responsible for the accuracy, quality and relevance of all


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

the data entered. In addition, the data are immediately verified as they are entered, thanks to consistency checks. To this end, the investigator must validate any changes to the values in the case report form. An audit trail will be kept of all changes. A justification can be added when applicable, as a comment.
A print-out, authenticated (signed and dated) by the investigator, will be requested at the end of the study. The investigator must archive a copy of the authenticated document that was issued to the sponsor.

### 13.4 Management of non-compliances

Any events that occur as a result of non-compliance – by the investigator or any other individual involved in running the study – with the protocol, standard operating procedures, good clinical practices or statutory and regulatory requirements must be recorded in a declaration of non-compliance and sent to the sponsor.
These non-compliances will be managed in accordance with the sponsor's procedures.

### 13.5 Audits/inspections

The investigators agree to consent to the quality assurance audits carried out by the sponsor as well as the inspections carried out by the competent authorities. All data, documents and reports may be subject to regulatory audits and inspections. These audits and inspections cannot be refused on the grounds of medical secrecy.

An audit can be carried out at any time by individuals appointed by the sponsor and independent of those responsible for the research.. The aim of the audits is to ensure the quality of the study, the validity of the results and compliance with the legislation and regulations in force.

The persons who manage and monitor the study agree to comply with the sponsor's requirements and with the competent authority regarding study audits or inspections.

The audit may encompass all stages of the study, from the development of the protocol to the publication of the results, including the storage of the data used or produced as part of the study.

### 13.6 Principal Investigator's commitment to assume responsibility

Before starting the study, each investigator will give the sponsor's representative a copy of his/her updated personal *curriculum vitæ*, signed and dated less than one year, with his/her RPPS number (Répertoire Partagé des Professionnels de Santé, Collective Database of Health Professionals). The CV must include any previous involvement in clinical research and related training.

Each investigator will commit to comply with legislation and to conduct the study in line with GCP, in accordance with the Declaration of Helsinki.

The Principal Investigator at each participating site will sign a commitment of responsibility (standard DRCI document) which will be sent to the sponsor's representative.
The investigators and their staff will sign a delegation of duties form specifying each person's role and will provide their CVs.

## 14 ETHICAL AND LEGAL CONSIDERATIONS

### 14.1 Methods for informing research participants and obtaining their consent

Consent to participate in the studies will be first sought from the patient himself. However, as this study will investigate mechanically ventilated patients under deep sedation at the time they meet the inclusion criteria, the vast majority of patients will not be able to receive the information and to consent to participate in the study. In accordance with Article L1122-1-2 of the Code de Santé Publique, in the case of research involving the human person to be implemented in emergency situations that do not allow the prior consent of the person to be subjected to it, the protocol presented to the opinion of the Committee for the Protection of Persons (CPP) may provide that the consent of this person is not sought and can be addressed to a family member or the trusted


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

person mentioned in article L. 1111-6 under the conditions Section L. 1122-1-1, if present. Thus, consent to the patient's participation in the studies will be sought from a parent or relative.

Patients, their families or the trusted person, will be informed in a full and fair manner, in understandable terms, of the objectives and constraints of the study, the possible risks involved, the necessary surveillance and safety measures, their right to refuse to participate in the studies or the possibility of withdrawing at any time, the duration of their participation, the procedures to be followed, the expected benefits, data confidentiality and insurance coverage. Their consent will be requested for the possible continuation of this research.

All this information will be provided on an information and consent form given to the patient, his or her family or the trusted person. The free, informed and written consent of the patient, his family or trusted person will be obtained by the investigator or a physician representing him/her before final inclusion in the study. A copy of the information and consent form dated and signed by the patient (or a family member if applicable) and the investigator or physician representing the investigator will be provided to the patient (or a family member if applicable). The investigator will keep the original copy of the patient's consent collection form dated and signed. A copy will be placed at the end of the studies in a sealed tamper-proof envelope containing all consent forms, which will be archived by the sponsor. In addition, the investigator will specify in the patient's medical record the patient's participation in the research, the manner in which the patient's consent is collected (or the consent of any other person in the case of section L.1122-2 of the PSC) and how the information is provided for collection. In the absence of initial consent from the patient, investigators inform the patient of his or her participation in the study as soon as possible, and if his or her neurological condition permits. Consent to continue the study will be sought from the patient as soon as he or she is able to give it.

The protocol may ask a derogation from this obligation in the event of an immediate life-threatening emergency, as is the case in our studies. This waiver will therefore be requested to the CPP. The patient, or if necessary, family members or the trusted person will be informed as soon as possible and his (their) consent will be requested for the possible continuation of this research.

In this study, we plan to establish a bio-bank that may help foster discovery of ARDS endotypes that may determine severity or therapeutic responses. Specific consent to participation to this part of the study will be sought. Participants, their families or the trusted person will receive specific information on the purpose of this research as well as on the condition of storage and use of their samples. They will sign a specific consent form to document their willingness to contribute to this part of the study.

## 14.2 Prohibition from participating in another clinical study or exclusion period set after the study

The participants may be included in another interventional study provided that this does not interfere with the primary endpoint and secondary safety objectives of PEPER.
The Participants may be included in another non-interventional study during their participation in the PEPER study.
No exclusion period of participation after the participant has finished this study is defined in the context of this research.

## 14.3 Legal obligations

### *14.3.1 Role of the sponsor*

Assistance Publique Hôpitaux de Paris (AP-HP) is the sponsor of this study and by delegation, the DRCI (Clinical Research and Innovation Department) carries out the study's missions in accordance with Article L.1121-1 of the *Code de la Santé Publique* (French Public Health Code). Assistance Publique - Hôpitaux de Paris reserves the right to halt the study at any time for medical or administrative reasons. In this case, notification will be sent to the investigator.


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### *14.3.2 Request for approval from the CPP (Research Ethics Committee)*

Prior to starting the study, AP-HP, as sponsor, must obtain for this interventional study involving human participants not concerning a health product mentioned in Article L5311-1, approval from the appropriate CPP (Research Ethics Committee), within the scope of its authority and in accordance with in force legislation and regulatory provisions in force.
The study will be registered on the website http://clinicaltrials.gov/

### *14.3.3 Request for authorisation from ANSM*

Proit to starting the study, AP-HP, as sponsor, must obtain authorisation from the ANSM (French Health Products Safety Agency) for the interventional study involving human participants not concerning a health product, within the scope of the ANSM's authority and in accordance with in force legislation and regulatory requirements.

### *14.3.4 Procedures relating to data protection regulations*

The computer file used for this research is implemented in accordance with French (amended "Informatique et Libertés" law governing data protection) and European (General Data Protection Regulation – GDPR) regulations.

Commitment to comply with "Reference Methodology" MR-001 :
This research is governed by the CNIL (French Data Protection Agency) "Reference Methodology for processing personal data used within the scope of health research" (amended MR-001). AP-HP, as sponsor of the research, has signed a declaration of compliance with this "Reference Methodology" adapt based on the internal procedures of the entity managing the data.

### *14.3.5 Amendments to the research*

Any substantial modification to the protocol by the coordinating investigator must be sent to the sponsor for approval. After approval is given, the sponsor must obtain, approval from the CPP (Research Ethics Committee) and authorisation from the ANSM within the scope of their respective authorities, before the amendment can be implemented.
The information note and the consent form can be revised if necessary, in particular in case of a substantial amendment to the study or if adverse reactions occur.

### *14.3.6 Final study report*

The final report for the research involving human participants referred to in Article R1123-67 of the *Code de la Santé Publique* (French Public Health Code) is written and signed by the sponsor and the investigator. A report summary drafted according to the reference plan of the competent authority must be sent to the competent authority within a period of one year following the end of the study, i.e., the end of the participation of the last participant in the study.

### *14.3.7 Archiving*

Specific documents for an interventional study involving human participants not concerning a health product will be archived by the investigator and the sponsor for 25 years after the end of the research.
This indexed archiving includes, in particular:

- A sealed envelope for the investigator containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- A sealed envelope for the sponsor containing a copy of all the information notes and consent forms signed by all individuals at the centre who participated in the study;
- "Study" binders for the investigator and the sponsor, including (non-exhaustive list):


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

- the successive versions of the protocol (identified by the version number and its date), and any appendices
- the ANSM authorisations and CPP (Research Ethics Committee) decisions
- any correspondence
- the enrolment list or register
- the appendices specific to the research
- final study report

− the data collection documents

# 15 FUNDING AND INSURANCE

## 15.1 Funding sources

The study is funded by the PHRC (Hospital Funding for Clinical Research) National 2020 (Ministère de la Santé).

## 15.2 Insurance

Pursuant to Article L.1121-10 of the Code de la Santé Publique (French Public Health Code), insurance policies must guarantee the civil liability of the sponsor and that of any contributor and cover pecuniary consequences of damages arising from the study involving human participants.

For the duration of the study, the Sponsor will take out an insurance policy covering the sponsor's own public liability, as well as the public liability for all the physicians involved in the study. The sponsor will also provide full compensation for any damages caused by the study to the participant enrolled and their beneficiaries, unless the sponsor can prove that the harm is not the fault of the sponsor or any collaborator. Compensation cannot be refused on the grounds of a third-party act or the voluntary withdrawal of the person who initially consented to participate in the study.

Assistance Publique - Hôpitaux de Paris (AP-HP) has taken out insurance with HDI - GLOBAL SE through BIOMEDIC-INSURE for the full study period, which covers its own public liability and that of any collaborator (physician or research staff), in accordance with Article L.1121-10 of the Code de la Santé Publique (French Public Health Code).

# 16 PUBLICATION RULES

The author(s) of any publication relating to this study must include the AP-HP among their affiliations and must name the sponsor AP-HP (DRCI) and the source of funding, if funded by a call for tenders (e.g. national or regional PHRC); a copy of the publication must be sent to the sponsor (see below for rules governing affiliation, and naming of the sponsor and funders).

## 16.1 Mention of AP-HP affiliation for projects sponsored by AP-HP

- If an author has several affiliations, the order in which the institutions are mentioned (AP-HP, University, INSERM, etc.) is unimportant
- However, if the study is funded in the context of an internal AP-HP call for tender, the first affiliation must be "AP-HP"
- Each of these affiliations must be identified by an address and separated by a semicolon (;)
- The AP-HP institution must feature under the acronym "AP-HP" first in the address, specifically followed by: AP-HP, hospital, department, city, postcode, France

## 16.2 Mention of the sponsor AP-HP (DRCI) in the acknowledgements of the text

The publications will mention in the acknowledgements "The sponsors were Assistance Publique – Hôpitaux de Paris (Délégation à la Recherche Clinique et à l'Innovation)" & Assistance Publique des Hôpitaux de Marseille.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### 16.3 Mention of the financial backer in the acknowledgements of the text

If PHRC: “The study was funded by a grant from Programme Hospitalier de Recherche Clinique - PHRC 2020 (French Ministry of Health)”

**This study has been registered on the website http://clinicaltrials.gov/ under number NCT06849570.**

## 17 BIBLIOGRAPHY


1. The ARDS Definition Task Force.. Acute Respiratory Distress Syndrome The Berlin Definition. JAMA : the journal of the American Medical Association 2012;307(23):2526-2533.

2. The ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. New Engl J Medicine [Internet] 2000;342(18):1301-1308.

3. Amato MBP, Meade MO, Slutsky AS, et al. Driving Pressure and Survival in the Acute Respiratory Distress Syndrome. New Engl J Medicine 2015;372(8):747-755.

4. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. Jama 2010;303(9):865-873.

5. Writing Group for the Alveolar Recruitment for ARDS (ART) Investigators, Cavalcanti AB, Suzumura EA, et al. Effect of Lung Recruitment and Titrated Positive End-Expiratory Pressure (PEEP) vs Low PEEP on Mortality in Patients With Acute Respiratory Distress Syndrome: A Randomized Clinical Trial. Jama 2017;318(14):1335-1345.

6. Papazian L, Forel J-M, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. New Engl J Medicine 2010;363(12):1107-1116.

7. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. New Engl J Medicine 2013;368(23):2159-2168.

8. Network NH Lung, and Blood Institute PETAL Clinical Trials, Moss M, Huang DT, et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. New Engl J Med 2019;380(21):1997-2008.

9. Gattinoni L, Caironi P, Chiumello D, et al. Lung recruitment in patients with the acute respiratory distress syndrome. New Engl J Medicine 2006;354(17):1775-1786.

10. Caironi P, Carlesso E, Cressoni M, et al. Lung Recruitability Is Better Estimated According to the Berlin Definition of Acute Respiratory Distress Syndrome at Standard 5 cm H2O Rather Than Higher Positive End-Expiratory Pressure: A Retrospective Cohort Study. Crit Care Med 2015;43(4):781 790.

11. Bellani G, Laffey JG, Pham T, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. Jama 2016;315(8):788-800.

12. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. Nat Rev Dis Primers 2019;5(1):18.





*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

13. Schmidt M, Hajage D, Demoule A, et al. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intens Care Med 2020;1-14.

14. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. New Engl J Medicine 2003;348(8):683-693.

15. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. Am J Resp Crit Care 1998;157(1):294-323.

16. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. Intens Care Med [Internet] 2006;32(1):24-33.

17. Sorbo LD, Tonetti T, Ranieri VM. Alveolar recruitment in acute respiratory distress syndrome: should we open the lung (no matter what) or may accept (part of) the lung closed? Intens Care Med 2019;1–4.

18. Fan E, Sorbo LD, Goligher EC, et al. An Official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: Mechanical Ventilation in Adult Patients with Acute Respiratory Distress Syndrome. Am J Resp Crit Care 2017;195(9):1253-1263.

19. Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. Jama 2018;319(7):698-710.

20. Papazian L, Aubron C, Brochard L, et al. Formal guidelines: management of acute respiratory distress syndrome. Ann Intensive Care 2019;9(1):69.

21. Marini JJ. Evolving concepts for safer ventilation. Crit Care 2019;23(Suppl 1):114.

22. Terragni PP, Rosboch G, Tealdi A, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. Am J Resp Crit Care 2007;175(2):160-166.

23. Bein T, Weber-Carstens S, Goldmann A, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal $CO_2$ removal versus “conventional” protective ventilation (6 ml/kg) in severe ARDS : The prospective randomized Xtravent-study. Intens Care Med 2013;39(5):847-856.

24. Combes A, Fanelli V, Pham T, Ranieri VM, investigators ES of ICMTG and the “Strategy of U-P lung ventilation with ECR for N-O moderate to severe A (SUPERNOVA). Feasibility and safety of extracorporeal CO2 removal to enhance protective ventilation in acute respiratory distress syndrome: the SUPERNOVA study. Intens Care Med 2019;45(5):592-600.

25. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. Jama 2008;299(6):637-645.

26. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. New Engl J Medicine 2004;351(4):327 336.

27. Mercat A, Richard J-CM, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. Jama 2008;299(6):646-655.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

28. Forel J-M, Roch A, Marin V, et al. Neuromuscular blocking agents decrease inflammatory response in patients presenting with acute respiratory distress syndrome. Crit Care Med 2006;34(11):2749-2757.

29. Gainnier M, Roch A, Forel J-M, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. Crit Care Med 2004;32(1):113-119.

30. Papazian L, Hraiech S, Cazenave L, Forel J-M. Neuromuscular blocking agents as part of lung-protective strategy in severe ARDS patients. Anaesth Crit Care Pa 2019;38(4):311–3.

31. Puybasset L, Cluzel P, Chao N, Slutsky AS, Coriat P, Rouby JJ. A computed tomography scan assessment of regional lung volume in acute lung injury. The CT Scan ARDS Study Group. Am J Resp Crit Care 1998;158(5 Pt 1):1644-1655.

32. Marino A, Brioni M, Menga F, et al. Visual anatomical lung CT scan assessment of lung recruitability. Intens Care Med 2013;39(1):66-73.

33. Constantin J-M, Jabaudon M, Lefrant J-Y, et al. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. Lancet Respir Medicine 2019;10(7): 870-880.

34. Dellamonica J, Lerolle N, Sargentini C, et al. PEEP-induced changes in lung volume in acute respiratory distress syndrome. Two methods to estimate alveolar recruitment. Intens Care Med 2011;37(10):1595-1604.

35. Dellamonica J, Lerolle N, Sargentini C, et al. Accuracy and precision of end-expiratory lung-volume measurements by automated nitrogen washout/washin technique in patients with acute respiratory distress syndrome. Crit Care 2011;15(6):R294.

36. Mauri T, Eronia N, Turrini C, et al. Bedside assessment of the effects of positive end-expiratory pressure on lung inflation and recruitment by the helium dilution technique and electrical impedance tomography. Intens Care Med 2016;42(10):1576-1587.

37. Richard J-C, Maggiore SM, Mercat A. Clinical review: bedside assessment of alveolar recruitment. Crit Care 2004;8(3):163-169.

38. Chen L, Sorbo LD, Grieco DL, et al. Potential for Lung Recruitment Estimated by the Recruitment-to-Inflation Ratio in Acute Respiratory Distress Syndrome. Am J Resp Crit Care 2019;201(2):178–87.

39. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. Lancet Respir Medicine 2014;2(8):611-620.

40. Warren MA, Zhao Z, Koyama T, et al. Severity scoring of lung oedema on the chest radiograph is associated with clinical outcomes in ARDS. Thorax 2018;73(9):840-846.

41. Hraiech S, Forel J-M, Guervilly C, et al. How to reduce cisatracurium consumption in ARDS patients: the TOF-ARDS study. Ann Intensive Care 2017;7(1):79.

42. Zhang L-X, Hu F, Cheung SH, Chan WS. Immigrated urn models - asymptotic properties and applications. Ann Statistics 2011;39(1):643-671.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

43. Zhu H. Statistical inference for response adaptive randomization procedures with adjusted optimal allocation proportions. J Biopharm Stat 2017;27(5):732-740.

44. Tymofyeyev Y, Rosenberger WF, Hu F. Implementing optimal allocation in sequential binary response experiments. Journal of the American Statistical Association 2007;102(477):224-234.

45. Angus DC, Berry S, Lewis RJ, et al. The Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) Study: Rationale and Design. Ann Am Thorac Soc 2020;0(ja). 879-891

46. Investigators TWC for the R-C, Angus DC, Derde L, et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. Jama 2020;324(13):1317–29.

47. Investigators R-C, Gordon AC, Mouncey PR, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. New Engl J Med 2021;

48. Vinnat V, Chiche J-D, Demoule A, Chevret S. Simulation study for evaluating an adaptive-randomisation Bayesian hybrid trial design with enrichment. Contemp Clin Trials Commun 2023;33:101-141.

49. Hu F, Zhang L-X. Asymptotic properties of doubly adaptive biased coin designs for multitreatment clinical trials. Ann Stat 2004;32(1):268–301.

50. Zampieri FG, Casey JD, Shankar-Hari M, Harrell FE, Harhay MO. Using Bayesian Methods to Augment the Interpretation of Critical Care Trials. An Overview of Theory and Example Reanalysis of the Alveolar Recruitment for Acute Respiratory Distress Syndrome Trial. Am J Resp Crit Care 2021;203(5):543–52.

51. Harrell F, Lindsell C. Statistical design and analysis plan for sequential parallel-group rct for covid-19 [Internet]. Available from: http://hbiostat.org/proj/covid19/bayesplan.html

52. Vinnat V, Chevret S. Enrichment Bayesian design for randomized clinical trials using categorical biomarkers and a binary outcome. BMC Méd Res Methodol 2022;22(1):54.

# 18 LIST OF ADDENDA

## 18.1 Serious Adverse Events notification form

## 18.2 Pregnancy notification form

## 18.3 Questionnaires or scales



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## *SAPS II score*

| Variables | Score | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 26 | 13 | 12 | 11 | 9 | 7 | 6 | 5 | 4 | 3 | 2 | 0 | 1 | 2 | 3 | 4 | 6 | 7 | 9 | 10 |
| HR (beats/min) | | | | <40 | | | | | | | 40-69 | 70-119 | | | | 120-159 | | ≥160 | | |
| SBP (mmHg) | | <70 | | | | | | 70-99 | | | | 100-199 | | ≥200 | | | | | | |
| Temperature (°C) | | | | | | | | | | | | <39 | | | ≥39 | | | | | |
| $PaO_2/FiO_2$ only if VENT or CPAP | | | | <100 | 100-199 | ≥200 | | | | | | | | | | | | | | |
| Urine output (L/day) | | | | <0.5 | | | | | 0.5-0.999 | | | ≥1 | | | | | | | | |
| Urea (g/L) | | | | | | | | | | | | <0.6 | | | | | 0.6-1.7 | | | >1.8 |
| TLC | | | <1 | | | | | | | | | 1-19.9 | | ≥20 | | | | | | |
| Potassium | | | | | | | | | | <3 | | 3-4.9 | | ≥5 | | | | | | |
| Sodium | | | | | | | | <125 | | | | 125-144 | ≥145 | | | | | | | |
| Bicarbonate | | | | | | | <15 | | | 15-19 | | >20 | | | | | | | | |
| Bilirubin (mg/dl) | | | | | | | | | | | | <40 | | | | 40-59.9 | | | ≥60 | |
| GCS | <6 | 6-8 | | | | 9-10 | | 11-13 | | | | 14-15 | | | | | | | | |

| Age | Score | Chronic disease | Score | Type of admission | Score |
|---|---|---|---|---|---|
| <40 | 0 | Metastatic cancer | 9 | Scheduled surgical | 0 |
| 40-59 | 7 | Hematological malignancy | 10 | Medical | 6 |
| 60-69 | 12 | AIDS | 17 | Emergency surgical | 8 |
| 70-74 | 15 | | | | |
| 75-79 | 16 | | | | |
| >80 | 18 | | | | |
| SAPS II score | 29 | 40 | 52 | 64 | 77 |
| Mortality risk % | 10 | 25 | 50 | 75 | 90 |

GCS: Glasgow coma score; HR: Heart rate; SBP: Systolic blood pressure; $PaO_2$ (mm Hg) arterial oxygen tension; $FiO_2$: Fractional concentration of inspired oxygen; VENT: Ventilator; CPAP: Continuous positive airway pressure; TLC: Total leukocyte count; AIDS: Acquired immunodeficiency syndrome. Probability of death, *P* may be calculated using the following equation: $P=(e^{Logit})/(1+e^{Logit})$; Logit=−7.7631+0.0737 (score)+0.9971 (log [score+1])

## *SOFA score*

**Table 1.** The Sequential Organ Failure Assessment (SOFA) Score*

| | SOFA Score | | | | |
|---|---|---|---|---|---|
| **Variables** | **0** | **1** | **2** | **3** | **4** |
| Respiratory<br>$Pao_2/FIO_2$, mm Hg | >400 | ≤400 | ≤300 | ≤200† | ≤100† |
| Coagulation<br>Platelets $\times 10^3/\mu L$‡ | >150 | ≤150 | ≤100 | ≤50 | ≤20 |
| Liver<br>Bilirubin, mg/dL‡ | <1.2 | 1.2-1.9 | 2.0-5.9 | 6.0-11.9 | >12.0 |
| Cardiovascular<br>Hypotension | No hypotension | Mean arterial pressure <70 mm Hg | Dop ≤5 or dob (any dose)§ | Dop >5, epi ≤0.1, or norepi ≤0.1§ | Dop >15, epi >0.1, or norepi >0.1§ |
| Central nervous system<br>Glasgow Coma Score Scale | 15 | 13-14 | 10-12 | 6-9 | <6 |
| Renal<br>Creatinine, mg/dL<br>or urine output, mL/d‖ | <1.2 | 1.2-1.9 | 2.0-3.4 | 3.5-4.9 or <500 | >5.0 or <200 |

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and $FIO_2$, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
‖To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

*JAMA. 2001;286:1754-1758*



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

***RASS score***

**Richmond Agitation-Sedation Scale (RASS)**

| Score | Term | Description | |
|---|---|---|---|
| +4 | Combative | Overtly combative, violent, immediate danger to staff | |
| +3 | Very agitated | Pulls or removes tube(s) or catheter(s), aggressive | |
| +2 | Agitated | Frequent nonpurposeful movement, fights ventilator | |
| +1 | Restless | Anxious but movements not aggressively vigorous | |
| 0 | Alert and calm | | |
| -1 | Drowsy | Not fully alert but has sustained awakening (eye opening/eye contact) to *voice* (≥10 seconds) | Verbal Stimulation |
| -2 | Light sedation | Briefly awakens to *voice* with eye contact (<10 seconds) | Verbal Stimulation |
| -3 | Moderate sedation | Movement or eye opening to *voice* (but no eye contact) | Verbal Stimulation |
| -4 | Deep sedation | No response to voice but movement or eye opening to *physical* stimulation | Physical Stimulation |
| -5 | Unarousable | No response to *voice* or *physical* stimulation | Physical Stimulation |

***MRC score***

**Tableau. Score MRC (Medical Research Council)**

| Fonctions évaluées (6 à droite et 6 à gauche) | Score attribué à chaque groupe musculaire |
|---|---|
| Antepulsion du bras<br>Flexion de l'avant-bras<br>Extension du poignet<br>Flexion de cuisse<br>Extension de la jambe<br>Flexion dorsale du pied | 0 = absence de contraction visible<br>1 = contraction visible sans mouvement du membre<br>2 = mouvement insuffisant pour vaincre la pesanteur<br>3 = mouvement permettant de vaincre la pesanteur<br>4 = mouvement contre la pesanteur et contre résistance<br>5 = force musculaire normale |

**Légende du Tableau.**
Chaque fonction est cotée de 0 à 5. Le score total va de 0 (tétraplégie complète) à 60 (force musculaire normale).


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

### *CAM-ICU score*

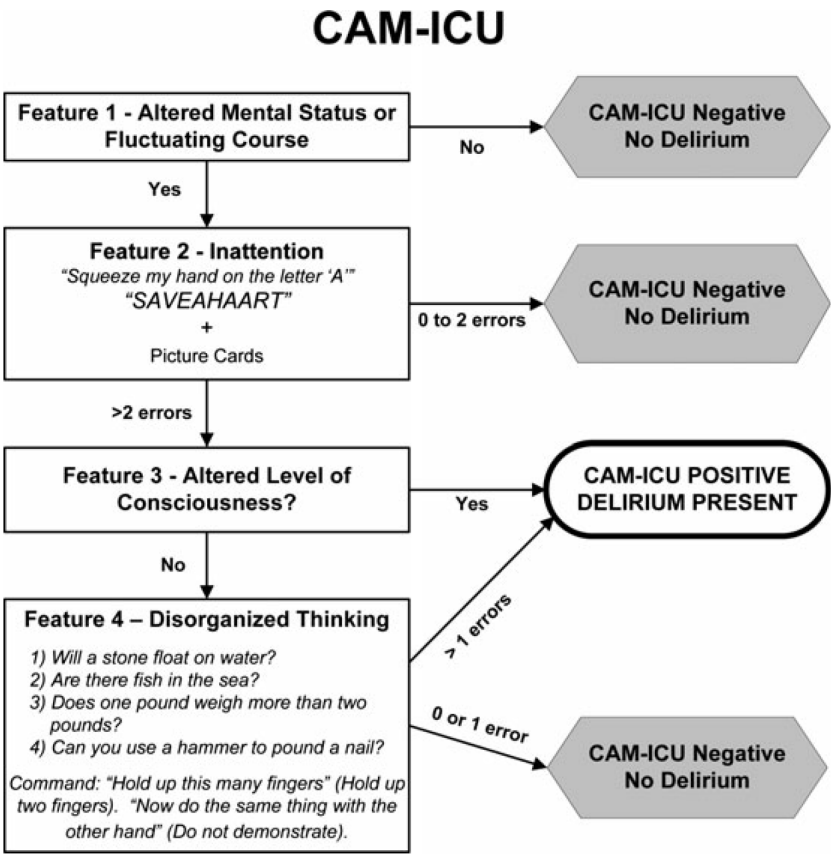



**Figure 1.** CAM-ICU flow sheet. Courtesy of Vanderbilt University, Nashville, TN, 2002. Used with permission. CAM-ICU = Confusion Assessment Method for the Intensive Care Unit.

### *EQ-5D-5L score*

5 dimensions

- Mobility
- Self-care
- Usual activities
- Pain / discomfort
- Anxiety / depression

5 Levels

- No
- Slight
- Moderate
- Severe
- Extreme / unable

3125 (= $5^5$) possible health states



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

Under each heading, please tick the ONE box that best describes your health TODAY

**MOBILITY**

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

**SELF-CARE**

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

**USUAL ACTIVITIES** *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

**PAIN / DISCOMFORT**

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

**ANXIETY / DEPRESSION**

- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

## *IES-R score*

**IES-R version française**

***Nom patient:*** ***Date passation:***

***Instructions***. Voici une liste de difficultés que les gens éprouvent parfois à la suite d'un événement stressant. Veuillez lire chaque item et indiquer à quel point vous avez été bouleversé(e) par chacune de ces difficultés *au cours des 7 derniers jours* en ce qui concerne l'événement :

……

Dans quelle mesure avez-vous été affecté(e) ou bouleversé(e) par ces difficultés ?

| | Pas du tout | Un peu | Moyen-nement | Passa-blement | Extrême-ment |
|---|---|---|---|---|---|
| 1. Tout rappel de l'événement ravivait mes sentiments face à l'événement | 0 | 1 | 2 | 3 | 4 |
| 2. Je me réveillais la nuit | 0 | 1 | 2 | 3 | 4 |
| 3. Différentes choses m'y faisait penser | 0 | 1 | 2 | 3 | 4 |
| 4. Je me sentais irritable et en colère | 0 | 1 | 2 | 3 | 4 |
| 5. Quand j'y repensais ou qu'on me le rappelait, j'évitais de me laisser bouleverser | 0 | 1 | 2 | 3 | 4 |
| 6. Sans le vouloir, j'y repensais | 0 | 1 | 2 | 3 | 4 |
| 7. J'ai eu l'impression que l'événement n'était jamais arrivé ou n'était pas réel | 0 | 1 | 2 | 3 | 4 |
| 8. Je me suis tenu loin de ce qui m'y faisait penser | 0 | 1 | 2 | 3 | 4 |
| 9. Des images de l'événement surgissaient dans ma tête | 0 | 1 | 2 | 3 | 4 |
| 10. J'étais nerveux (nerveuse) et je sursautais facilement | 0 | 1 | 2 | 3 | 4 |
| 11. J'essayais de ne pas y penser | 0 | 1 | 2 | 3 | 4 |
| 12. J'étais conscient(e) d'avoir encore beaucoup d'émotions à propos de l'événement, mais je n'y ai pas fait face | 0 | 1 | 2 | 3 | 4 |
| 13. Mes sentiments à propos de l'événement étaient comme figés | 0 | 1 | 2 | 3 | 4 |
| 14. Je me sentais et je réagissais comme si j'étais encore dans l'événement | 0 | 1 | 2 | 3 | 4 |
| 15. J'avais du mal à m'endormir | 0 | 1 | 2 | 3 | 4 |
| 16. J'ai ressenti des vagues de sentiments intenses à propos de l'événement | 0 | 1 | 2 | 3 | 4 |
| 17. J'ai essayé de l'effacer de ma mémoire | 0 | 1 | 2 | 3 | 4 |
| 18. J'avais du mal à me concentrer | 0 | 1 | 2 | 3 | 4 |
| 19. Ce qui me rappelait l'événement me causait des réactions physiques telles que des sueurs, des difficultés à respirer, des nausées ou des palpitations | 0 | 1 | 2 | 3 | 4 |
| 20. J'ai rêvé à l'événement | 0 | 1 | 2 | 3 | 4 |
| 21. J'étais aux aguets et sur mes gardes | 0 | 1 | 2 | 3 | 4 |
| 22. J'ai essayé de ne pas en parler | 0 | 1 | 2 | 3 | 4 |

**<u>Score</u>**:

- Un score au-dessus de 22 moins d'1 mois après l'événement : indice pour un stress aigü (surveiller)
- Score au dessus de 36 plus d'1 mois après l'événement : indice pour un état de stress post-traumatique (consulter)



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

***T-MoCA score***

| T-MoCA Subtest/ maximum score | Subtest details |
|---|---|
| Visuoexecutive/5* | Trail B test, cube copy, clock drawing |
| Naming/3* | Confrontation naming (lion, hippo, camel) |
| Digit span/2 | Forward (5 digits), backward (3 digits) |
| Attention/1 | Tapping at the letter A in letter list |
| Calculation/3 | Serial 7 subtractions |
| Repetition/2 | Repetition of 2 complex sentences |
| Verbal fluency/1† | ≥11 words beginning with f in 1 minute |
| Abstraction/2 | Similarities eg train and bicycle="transport" |
| Recall/5† | Recall a list of 5 words |
| Orientation/6† | Date, month, year, day, place, city |

Pendlebury ST et al. Stroke. 2013;44:227–9

## 18.4 Recommendations on the monitoring of ventilatory parameters in ARDS patients (before inclusion):

Specifically, screening and assessment of ventilated patients with bilateral infiltrates and a condition known to be associated with ARDS will be performed at least twice daily. During the screening period, investigators will be strongly encouraged to use ventilator settings consistent with standard best practice and to avoid neuromuscular blocking agents (NMBAs) and prone position (PP) use[18,20] . Briefly, assist volume-control ventilation (ACV) mode will be used with $V_T$ will be set at 6 ml/kg, computed using the predicted body weight determined as follows: PBW = X + 0.91 (height in cm – 152.4), with X = 50 for males and 45.5 for females. Inspiratory flow will be 50 to 70 L/min and end-inspiratory pause duration 0 to 0.5s. All ventilators used in study will correct the measurements of $V_T$ for gas compression. For patients ventilated using modes allowing spontaneous ventilation, pressures and volumes will be set to obtain a $V_T$ =6mL/kg for controlled breaths and/or a target of 6mL/kg for spontaneous breaths.

Respiratory rate will be kept at no more than 35/min and adjusted to achieve $PaCO_2$ values such that arterial pH is between 7.25 and 7.45. When pH remains lower than 7.25 despite a breathing rate of 35/min, $V_T$ will be increased stepwise to 8 ml/kg by 1 ml/kg steps until pH is ³7.15, provided $PaCO_2$ is kept ≥38 mm Hg and PPLAT<32 $cmH_2O$, if needed by decreasing the PEEP level to 5 $cmH_2O$. Detailed management strategies of respiratory acidosis are described in the Investigator's manual.

PEEP will be set according to ARMA lung protective algorithm (see below) taking into account total PEEP (the sum of applied PEEP & intrinsic PEEP)2. In patients who are completely relaxed or on neuromuscular blockade, total PEEP will be measured using the end-expiration occlusion method. Estimation of total PEEP when muscle activity precludes the use of this method is described in the Investigator's manual.

Oxygenation targets and $FiO_2$. $FiO_2$ (0.21 to 1) will be set to achieve the following oxygenation targets: 90% ≤ $SpO_2$ ≤96% or 65 mmHg ≤ $PaO_2$ ≤90 mmHg. When $PaO_2$ measurements are available, they will take priority over $SpO_2$.

At least twice daily, arterial blood gas (ABG) will be obtained to calculate the $PaO_2/FiO_2$ ratio, assess patient's eligibility and classify the severity of ARDS according to the ARDS Berlin definition Taskforce1. For all patients with $PaO_2/FiO_2$ ratio <200 mmHg, informed consent will be obtained


*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019

for enrolment in both parts of the study. Patients with consent will then be randomized and undergo a PRT (see below) prior to activation of the allocated study ventilation strategy. For patients with $PaO_2/FiO_2$ ratio ≥200 mmHg, ventilation will be resumed using the same ventilatory settings. All patients meeting the ARDS criteria and who are hospitalized during the study in participating centers will be recorded anonymously. As soon as patients will be randomized, only assist volume-control ventilation (ACV) will be allowed, with volumes set at 6 mL/kg PBW, until weaning criteria are met. Patients on ACV will be monitored with adequate alarms settings to ensure an effective delivery of $V_T$ of 6 mL/kg PBW. If needed, sedation will be started or adapted at the discretion of the attending physician to ensure adequate patient-ventilator synchrony during low $V_T$ ventilation.



*This document is the property of DRCI/AP-HP. All reproduction is strictly prohibited.*
Version no. 4.0 dated 31/05/2019