

# **Awake Prone Positioning to Reduce Invasive VEntilation in COVID-19 Induced Acute Respiratory failure (APPROVE-CARE)**

### *Study Summary*

The coronavirus disease 2019 (COVID-19) outbreak is a pandemic associated with a pneumonia which can worsen rapidly into respiratory failure known as acute respiratory distress syndrome (ARDS). There is a high rate of mortality in patients with severe respiratory failure requiring mechanical ventilation. Adjunctive therapies constitute an important part of the management of early moderate to severe ARDS. In patients with confirmed moderate-severe ARDs receiving invasive mechanical ventilation, prone position promotes lung homogeneity, improves gas exchange and respiratory mechanics permitting reduction of ventilation intensity, and reducing lung injury. Prone positioning has been demonstrated to save lives and is recommended in evidence-based guidelines for the management of moderate-severe ARDS.

The use of proning outside of mechanically ventilated patients to improve gas exchange and reduce the end for invasive ventilation has not been extensively studied outside of case series. Maintaining self ventilation is associated with increased aeration of dependent lung regions, less need for sedation, improved cardiac filling, and better matching of pulmonary ventilation and perfusion and thus oxygenation.

In this protocol, we outline details for a randomized clinical trial to determine whether placing patients who have hypoxemia related to COVID19 into a prone position can improve oxygenation and reduce the requirement for mechanical ventilation. If effective, this simple intervention could be widely and rapidly implemented, potentially reducing the need for ICU admission and invasive ventilation, and potentially even saving lives.

**1. Study team- Galway**

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**2. Study sponsor**

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### **3. Background and rationale**

#### **a. COVID-19 and Hypoxemia**

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) first appeared in Wuhan China in December 2019. It has since spread and was declared a worldwide pandemic by the World Health Organisation in March 2020.(1) Its main route of infection are respiratory droplets and contact transmission. Many infections will be asymptomatic or mild, but a subset require hospitalization and admission to critical care is associated with a high morbidity and mortality from the disease. Acute respiratory distress syndrome requiring mechanical ventilation is associated with a 40-60% mortality. To date, there are no specific pharmacological therapies currently although many are being trialled.(2)

#### **b. Prone position physiology**

Prone position is a non-pharmacological treatment used in patients with severe ARDS which has proven mortality benefits in this population. (3) Physiological studies have shown differences in ventilation pressures in distinct regions of the chest depending on whether one is in the prone or supine position. While breathing in a supine position, the ventral chest wall is lifted by a driving pressure driven by the difference between pleural pressure and atmospheric pressure ( $P_{\text{pleural}} - P_{\text{atmospheric}}$ ): the diaphragm moves caudally ( $P_{\text{pl}} - P_{\text{abdomen}}$ ), and the dorsal chest wall moves minimally as lying in contact with a rigid surface. In the supine position, there is a reduction in alveolar size from sternum to vertebra in the supine position at the end of the expiration. This phenomenon has also been clearly identified with CT scans (6-9), and leads to a greater expansion of the nondependent regions and lesser expansion of the dependent parenchyma (6-8).

Contrarily while prone, the dorsal chest wall lifts, the diaphragm shifts similarly to supine position, and the ventral chest wall, now in contact with the firm surface of the bed, is impeded from expanding (8). In the prone position the gravitational forces compress the ventral region, but this effect is damped by regional expansion due to shape matching between lung parenchyma and vertebrae. As the lung mass is anatomically greater in dorsal regions (nondependent when prone) than in ventral region (dependent when prone), the increased aeration and recruitment of the dorsal region tends to exceed the decreased aeration and derecruitment of the ventral regions. That generates a more homogenous ventilation across the entire lung(6). Furthermore, when an individual is supine the heart compresses the medial posterior lung parenchyma (10) and the diaphragm compresses the posterior-caudal lung parenchyma, with the abdominal contents displacing the diaphragm cranially (8,10). Compression by either the heart and/or the diaphragm may exaggerate dependent lung collapse in the supine position (9). During prone ventilation, the heart becomes dependent, lying on the sternum, potentially decreasing medial-posterior lung compression (10). In addition, the diaphragm is displaced caudally, decreasing compression of the posterior-caudal lung parenchyma. A further advantage observed in prone position is both an improvement of ventilation/perfusion match and an increase in cardiac output: the latter is thought to be due to the effect of increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction, resulting in increases in right ventricular preload and decreased right ventricular afterload and a decrease in pulmonary vascular resistance (11,12). An important recent study by Guerin et al. showed that prone positioning applied for at least 16 hours per day in patients with ARDS and  $\text{PaO}_2/\text{FiO}_2 < 150$  mmHg significantly reduced 28-day mortality (16% vs 32%).(15) From currently available evidence, prone positioning may be of value even if there is no improvement in gas exchange [10-14].

**c. *Experience with awake prone positioning in self-ventilating patients***

Prone position results in improved ventilation and blood flow ratios. In mechanically ventilated and often paralysed patients, proning requires a high nursing input and patients are at risk for pressure sores related to the position. These issues are less pertinent in patients who are self-ventilating. Proning self-ventilating patients is not commonly carried out as patients with reduced oxygenation generally require assisted ventilation. However, avoidance of mechanical ventilation by improving oxygenation may be importance in COVID19 as outcomes for patients who require mechanical ventilation are poor and resources become limited. We have noted improvement with proning in self ventilating patients at both ward level and in the ICU for patients with confirmed COVID19 and in a patient without COVID19 with ARDS.

**d. *Rationale for treating patients with COVID19 pneumonia with awake prone positioning***

Patients with COVID19 that require invasive mechanical ventilation have a high mortality. We hypothesis that early proning for self-ventilating patients with suspected or confirmed COVID19 who have hypoxemia (spO2 <94%) despite high flow nasal cannula (fiO2 40%) will result in improved oxygenation, reduced work of breathing and a reduced the need for invasive mechanical ventilation.

#### **4. Study Aims and Objective**

##### **a. Research hypothesis**

In patients that are hypoxic secondary to COVID19, the use of prone positioning will result in a reduction in requirement for invasive mechanical ventilation. Key secondary hypothesis include that prone positioning will result reduced requirement for assisted ventilation, in improved oxygenation as measured by either S/F or P/F ratio, reduced work of breathing.

##### **b. Study aim**

The study aims to assess the effect of prone positioning in patients who have hypoxemia related to COVID19 on:

- need for mechanical ventilation
- Improvement in oxygenation as measured by S/F or P/F ratio
- Patient work of breathing as measured by the respiratory distress observation scale
- tolerability of the position as measured by the total number of hours in prone position

##### **c. Study objectives**

###### **Primary objective**

To assess the effect of awake prone positioning on requirement for mechanical ventilation or death in patients with suspected or confirmed COVID 19 infection.

###### **Secondary objective**

To assess the effect of prone positioning on:

- Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
- SpO<sub>2</sub>: FiO<sub>2</sub> ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
- Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)
- Work of breathing assessment

#### **5. Study Details**

##### **a. Study design**

Multi centre open label randomized controlled study in which patients are randomized to awake prone positioning or standard care. This trial is registered with ClinicalTrials.gov (NCT04347941). This trial is part of a prospective meta-trial listed in appendix 1.

##### **b. Study timeline**

Study will begin 5<sup>th</sup> June 2020 and until 28 days following the last enrolled patient

##### **c. End of study**

Study will continue until 28 days after the last enrolled patient or for 6 months until October 2020, depending on levels of enrolment.

## 6. **Study outcome measure**

### a. **Primary outcome measure**

Requirement for invasive mechanical ventilation or death by 28 days post enrolment

### b. **Secondary outcome measure**

- Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
- SpO<sub>2</sub> : FiO<sub>2</sub> ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
- Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)

## 7. **Patient Eligibility**

### a. **Study setting**

A monitored ward or ICU in which patients with confirmed or suspected COVID19 are receiving high flow nasal cannula

### b. **Study population**

Patients who have *suspected or confirmed* COVID19 who have infiltrates on CXR and who have an oxygen requirement of >4L to keep oxygen saturations about 94% using high flow nasal cannula

### c. **Eligibility criteria**

#### **Inclusion criteria**

Suspected or confirmed COVID19 infection  
Bilateral Infiltrates on CXR  
SpO<sub>2</sub> <94% on FiO<sub>2</sub> 40% by high flow nasal cannula  
Able to provide written informed consent

#### **Exclusion criteria**

Age <18  
RR>40  
Uncooperative or likely to be unable to lie on abdomen for 16 hours  
Immediate need for intubation  
SBP<80  
Vomiting or bowel obstruction  
Palliative care  
Multiorgan failure  
Standard contraindications to prone positioning include the presence of an open abdominal wound, unstable pelvic fracture, spinal lesions and instability, pregnancy > 20/40 gestation and brain injury without monitoring of intracranial pressure.

### d. **Co-enrolment guidelines**

Patients will be eligible for inclusion in other studies

## **8. Patient screening, consent and recruitment**

### **a. Patient screening**

All patients admitted to a COVID19 ward, COVID ICU or HDU will be screened for inclusion in the study.

### **b. Informed consent procedure**

As patients will be self-ventilating, written informed consent or witnessed telephone consent to reduce fomite transmission will be obtained for each patient enrolled in the study. A patient information leaflet will be given to all patients screened as eligible. After a period of time to read and consider the information leaflet time will be given for questions, and then if the patient consents to be involved, written consent will be obtained. Due to the risk of fomite result of informed consent will be witnessed and recorded in the patient chart. The original consent form will be disposed of in yellow waste from the patient room, which should be destroyed.

## **9. Assignment of intervention**

Awake prone positioning will be performed before or 1 hour after meal. Call bell will be given to the patient and an oxygen probe will be attached to the patient to monitor spO2 during the procedure. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. Awake prone positioning will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 92-95%. Protocol for sedation and comfort evaluation during PP: No sedation will be used during the PP on ward. The patients are monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP in each day.

### **a. Withdrawal criteria**

- Patients cannot tolerate HFNC or prone position for 30 mins
- Patients experience any side effects during prone position, including vomit, dizzy, hypotension, etc.

### **b. Weaning criteria**

- Patients' PaO2/FIO2 > 300, or SpO2/FIO2 > 340

### **c. Treatment Failure Criteria**

Failure criteria: treatment failure is defined as one of the following criteria:

- Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:
  - Respiratory rate above 40 cycles/min
  - Lack of improvement of signs of respiratory-muscle fatigue
- -Development of copious tracheal secretions
- -Respiratory acidosis with a pH below 7.35
- -SpO2 below 90% at FIO2 ≥ 0.8 for more than 5 min without technical dysfunction



- Hemodynamic instability defined by a SBP below 90 mmHg, MBP below 65 mmHg or requirement for vasopressor;
- Deterioration of neurologic status (with AVPU to pain). For patients who meet the failure criteria in the standard treatment and PP groups, a trial of NIV will be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation. Reasons for intubation will be recorded as well.

#### ***d. Allocation and Randomisation***

Within 6 hr of fulfilling inclusion criteria, a patient will be randomly allocated either to the prone positioning group or the control group (HFNC alone with no prone positioning therapy). Patients will be randomly allocated to either arm of the study at a ratio based on a 1:1 basis using a REDCAP randomisation process. Randomization will be stratified by site using tables of random permutations using the RECAP database for randomization. The random block length is 4, and random numbers are generated by computer.

#### ***e. Blinding***

It is not feasible to blind staff or patients as to the procedure. Study data will be blinded for the purposes of analyses, assigned as group 1 or group2 rather than prone / not prone.

### ***10. Schedule of assessment***

#### ***a. Data collection and management***

Data will be collected using an electronic case report form hosted in UCD. Details of CRF attached in appendix B. No patient identifiers will leave hospital unit and all data sent to CRF at NUI Galway will be pseudoanonymised. A collaborative data sharing agreement with UCD and NUI Galway has been developed. Aggregated data will be shared with investigators of the Awake Prone Positioning in COVID Meta-Trial for interim analysis and Anonymised data without personal identifying features will be sent for final analysis and co-reporting of outcomes.

#### ***b. Data quality***

Data quality will be audited by the CRF at NUI Galway as responsibility of the study sponsor.

### ***11. Statistical Considerations***

#### ***a. Sample size***

From ICNARC data on patients admitted to ICU with COVID19, 60% required advanced respiratory support. From this, we propose a 60% intubation rate in this cohort as defined above and that proning will decrease it to 40%. From this, 97 patients per group for a beta of 0.2 and alpha 0.05, requiring the need to recruit 196 patients. Interim analysis of data will be conducted using aggregated data as part of the Awake Prone Positioning in COVID Meta-Trial.

#### ***b. Analysis population***

Data will be analysed on an intention to treat basis with all data for patients who consented to be involved included in baseline data analysis. Outcome data will be analysed for all patients who were positioned in the prone position for any length of time. A further per protocol analysis will be carried out on all patients who tolerated at least 1 hour of the daytime proning time and at least 2 hours of the night time proning period in any 24 hour period. Patients who were rescue prone will be considered a protocol deviation and will be studied as a group. Definition of the two groups: The

patients who receive the prone positioning are classified as prone positioning group. The patients who receive HFNC alone are classified as HFNC group. Comparisons between the two groups: Quantitative continuous variables are given as either means ( $\pm$ SDs) or medians (with inter-quartile ranges) are compared using the unpaired Student's t test or the Mann-Whitney test. Qualitative or categorical variables are compared with the chi square test or the Fisher's exact test. ANOVA for paired tests to compare the same variables collected at different time points are used. The cumulative probability of remaining on spontaneous breathing are compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. Univariate and multivariate analyses of risk factors for PP failure are performed with logistic regression. All analyses are in intention to treat, and the level of significance is set at 0.05.

**c. *Missing data***

Missing data will be completed using last observation carried forward and the percentage of datasets with full or missing data will be reported.

**12. *Data monitoring***

**a. *Data access and Monitoring arrangement***

The eCRF has an audit trail in place, participating centres only have accounts available for delegated people and specific login accounts are created to only edit for their own site. External monitors can only view data and enter queries, they cannot change data. No directly identifiable data will be stored in the eCRF, e.g. only year of birth and no date of birth will be captured. Audit trail in place (eCRF) compliant with 21 CFR part 11. The database is compliant with the EU Directive on data protection 95/46/EC. eCRF only accessible via site-specific (password-regulated) delegated log-in. (21 CFR part 11 compliance). Also compliant with the EU Directive on data protection 95/46/EC. A Standard contractual clauses for the transfer of personal data from the Community to third countries (controller to controller transfers) has been signed

**13. *Regulation, Ethics and Governance***

**a. *Regulatory and ethics approval***

Study has been approved by Galway University Hospitals Research ethics committee and the National research ethics committee (CA2352, 20-NREC-COV-054).

**b. *Protocol compliance***

A Request for sponsorship from the CRFG at NUI Galway has been sought which will provide the necessary manpower for trial oversight, quality, statistical analysis. Online training on study protocol will be conducted prior to site initiation. Investigators will be available for any data entry queries or clinical concerns.

**c. *Good clinical practice***

All individuals who will participate in conducting this study and have signed a delegation log will require an up to date certificate of good clinical practice.

**d. *Indemnity***

Patients will be covered under the HSE Clinical Indemnity Scheme and by indemnity provided by the National University of Ireland, Galway

#### ***e. Patient confidentiality***

A Data privacy impact assessment has been filed for the study. Patient confidentiality will be maintained by keeping data collected in the study coded. The key will be at the local study site where patient is included. No Personal details or identifying data will be transferred from the site to the sponsor where the data will be analysed. The coded data will be securely entered via the electronic case report form which will be managed by NUI Galway. The need data controlled will be the principal investigator, associate investigators, biostatisticians affiliated with NUI Galway. The site lead will have received training in regard to the requirements under GDPR that relate to health research. A data protection impact assessment has been completed and submitted to the SAOLTA data protection officer.

#### ***f. Data access***

The data will be collected using a paper or digital case report form and the data will be collected in a coded form. The key for the data will be at the local study site in which the patient is included. Data will only be stored on protected and accredited servers. No personal details or identifying data will be transferred from the site to the coordinating centre at NUI Galway where the data will be analysed. The data will be retained for 15 years or as long as local legislation requires. Confidentiality will be maintained by sponsor only having access to coded data and the key only available at the local site. Clinical notes will need to be reviewed by the clinical research team on site. No identifiable data will be collected in the process. Information regarding current clinical presentation and clinical trajectory over the course of hospitalization will be collected Information regarding the patient will be taken out of the record and added to the case report form.

#### ***g. Record retention***

Participants are requested to give consent to store their data for 15 years (without this permission, patient cannot participate). Next, participants are asked whether their coded data can be used for future research in the field of lung infections (data will also be stored 15 years for this purpose, with extra consent as described).

#### ***g. Competing interest***

The principal investigators have no conflict of interest related to this study.

#### ***h. Data safety and Monitoring Board***

Independent Investigators to fulfill data safety and monitoring board the study have been selected. This will be performed by Prof. Andrew Smyth, Galway University Hospitals, Dr. Rabia Hussein, Clinical research facility, UCD. A charter outlining the roles and responsibilities of the DSMB has been created. They will meet on-line after first patient has been enrolled.

### ***14. Dissemination***

Results of both registry and randomised controlled trial will be published in an international journal following peer review. To incentivise participation in the study, centres that recruit a patient will be permitted to have one author on final publication. For each additional 10 patients recruited, a further author from that centre will be added to the authors list.

## References

- 1) Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [supplementary appendix appears online]. *Lancet* 2020;395:497-506
- 2) Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID- 19 in Wuhan, China: a retrospective cohort study [supplementary appendix appears online]. *Lancet*. E-pub Date: [published online ahead of print] March 2020
- 3) Gattinoni et al. "Prone Position in Acute Respiratory Distress Syndrome. Rationale, Indications, and Limits". *Am J Respir Crit Care Med* 2013; 188:11.
- 4) Hubmayr RD. "Perspective on lung injury and recruitment: a skeptical look at the opening and collapse story". *Am J Respir Crit Care Med* 2002;165:1647–1653.
- 5) Pelosi P, D'Andrea L, Vitale G, Pesenti A, Gattinoni L. "Vertical gradient of regional lung inflation in adult respiratory distress syndrome". *Am J Respir Crit Care Med* 1994;149:8–13.
- 6) Gattinoni L, Pelosi P, Vitale G, Pesenti A, D'Andrea L, Mascheroni D. "Body position changes redistribute lung computed-tomographic density in patients with acute respiratory failure". *Anesthesiology* 1991;74:15–23.
- 7) Gattinoni L, D'Andrea L, Pelosi P, Vitale G, Pesenti A, Fumagalli R. "Regional effects and mechanism of positive end-expiratory pressure in early adult respiratory distress syndrome". *JAMA* 1993;269:2122–2127.
- 8) Lai-Fook SJ, Rodarte JR. "Pleural pressure distribution and its relationship to lung volume and interstitial pressure". *J Appl Physiol* 1991;70(3):967.
- 9) RK, Hubmayr RD. "The prone position eliminates compression of the lungs by the heart". *Am J Respir Crit Care Med* 2000;161:1660–1665.
- 10) Agostoni E, Mead J. "Statics of the respiratory system". In: "Handbook of Physiology", Macklem P, Mead J (Eds), American Physiologic Society, Bethesda 1986, p.387.
- 11) 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 Respir Crit Care Med* 1998;158(5 Pt 1):1644.
- 12) Malbouisson LM, Busch CJ, Puybasset L, Lu Q, Cluzel P, Rouby JJ. "Role of the heart in the loss of aeration characterizing lower lobes in acute respiratory distress syndrome. CT Scan ARDS Study Group". *Am J Respir Crit Care Med* 2000;161(6):2005.
- 13) Jozwiak M, Teboul JL, Anguel N, Persichini R, Silva S, Chemla D, Richard C, Monnet X. "Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome". *Am J Respir Crit Care Med*. 2013;188(12):1428.
- 14) Nyrén S, Radell P, Lindahl SG, Mure M, Petersson J, Larsson SA, Jacobsson H, Sánchez-Crespo A. "Lung ventilation and perfusion in prone and supine postures with reference to anesthetized and mechanically ventilated healthy volunteers". *Anesthesiology*. 2010 Mar;112(3):682-7.
- 15) Guerin, C., et al., Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*, 2013. 368(23): p. 2159-68.

16)ElectricalImpedanceTomographyforCardio-PulmonaryMonitoring.PutensenC,HentzeB,MuensterS,MudersT.JClinMed.2019Aug7;8(8):1176.doi:10.3390/jcm8081176.

## Appendix 1

Chicago: Jie Li, Sara Mirza, David Vines, Ahmad A Elshafei, Hangyong He, Tyler Weiss, Jonathan Brayd Scott, Lauren J Harnois, Ramandeep Kaur, Amnah A Alolaiwat

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