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Supplementary appendix 1

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Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: A randomized, controlled, multinational, open-label meta-trial

Supplementary appendix

1.1 Authors' contribution

SE, JL and ET designed the meta-trial project.
MIE, YP, SE, JL, DV, SM, BM, JGL, DC, IP and OR designed and conducted the individual trials. All authors significantly contributed to the conduct of the meta-trial, attending monthly web meetings. ET conducted data analysis.
IP, BM, JL, YP, SE, ET, MIE, and OR drafted the manuscript.
All authors reviewed the manuscript for important intellectual content, and approved the final manuscript.
SE, JL, MIE, YP, IP, BM and OR equally contributed to the overall project described in this article.

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We also thank the member of data safety monitoring board, Andrew Smyth (National University of Ireland, Galway, Ireland) for his oversight in the Irish trial.

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Table S1. Inclusion and exclusion criteria in each trial

	Mexico	USA and Canada	Ireland	France and Spain
Inclusion criteria	1) Adult patients (18 y) with RT-PCR-confirmed Covid-19 and respiratory distress (regardless of Berlin criteria for ARDS). 2) Requirement of a F_iO_2 ≥30% through high-flow nasal cannula (HFNC) to maintain a capillary S_pO_2 ≥90%. 3) Written informed consent	1) Covid-19 pneumonia based on the center for disease control guidelines 2) Presence of acute hypoxemic respiratory failure; 3) Acute onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms; 4) Bilateral opacities on chest x-ray or computer tomographic scanner not fully explained by effusions, lobar or lung collapse, or nodules; 5) Cardiac failure not the primary cause of acute respiratory failure 6) Written informed consent 7) P_aO_2 / F_iO_2 ratio <200 mmHg or S_pO_2 / F_iO_2 < 240 with HFNC at 50 L/min and SpO_2 maintained at 92-95%	1) Suspected or confirmed Covid-19 infection 2) Bilateral Infiltrates on chest X-ray S_pO_2 <94% on F_iO_2 40% by either venturi facemask or high flow nasal cannula 3) Respiratory rate<40 breath/min 4) Written informed consent	1) Adult patient suffering from Covid-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. 2) Patient treated by nasal high flow therapy 3) Moderate or severe ARDS: bilateral radiological opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxemia with worsening within the 7 previous days, not entirely explained by left ventricular failure; P_aO_2 / F_iO_2 ratio <300 mmHg (or equivalent S_pO_2 / F_iO_2). 4) Written informed consent in France, oral consent in Spain

Exclusion criteria	1) Age <18 y 2) Pregnancy 3)Patients with immediate need of mechanical ventilation (altered mental status, signs of respiratory fatigue) 4) Any vasopressor requirement to maintain a median arterial pressure ≥65 mmHg 5) Contraindications for APP: recent abdominal or thoracic surgery/trauma, facial/pelvic/spine fractures, untreated pneumothorax) 6) Do not resuscitate or do not intubate order 7) Refusal or disability (uncooperative) of the patient to enroll in the study	1) Patients with a consistent SpO_2<80% when evaluated with a FiO_2 of 0·6, or signs of respiratory fatigue (respiratory rate > 40/min, $PaCO_2$> 50mmHg / pH<7·30, and obvious accessory respiratory muscle use); 2) Immediate need for intubation (PaO_2/FiO_2< 50 mmHg or SpO_2/FiO_2 <90, unable to protect airway or mental status change); 3) Hemodynamic instability (sustained systolic blood pressure <90mmHg, sustained mean blood pressure below 65 mmHg or requirement for vasopressor); 4) Unable to collaborate with HFNC/APP with agitation or refusal of HFNC/APP. 5) Chest trauma or any contraindication for APP 6) Pneumothorax 7) Age < 18 years 8) Pregnant 9) Body mass index > 40 kg/m^2 10) Unable to communicate 11) Patient self-proned for more than 1 hr 12) Patient with moderate or severe ILD 13) Patient with stage IV lung cancer 14) Patient requiring long term oxygen therapy	1) Age <18 2)Uncooperative or likely to be unable to lie on abdomen for 16 hours 3) Vomiting or bowel obstruction 4) Palliative care 5) Multiorgan failure 6)Standard contraindications to APP including 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.	1) Indication for immediate tracheal intubation 2) Significant acute progressive circulatory insufficiency 3) Impaired consciousness, confusion, restlessness 4) Body mass index> 40 kg / m2 5) Chest trauma or other contraindication to APP 6) Pneumothorax 7) Vulnerable person: safeguard of justice, curatorship or tutorship known at inclusion 8) Pregnant or lactating woman

HFNC denotes high-flow nasal cannula, APP awake prone positioning, SpO_2 denotes peripheral blood oxygen saturation, PaO_2, partial pressure of oxygen, FiO_2 Fraction of inspired oxygen.

Table S2. Standard management in each trial

Mexico	USA and Canada	Ireland	France and Spain
HFNC will be initiated at 40 L/min at 37ºC according to patient comfort and tolerance (Vapotherm, Precision Flow. Exeter, New Hampshire), with F_iO_2 titrated to a capillary S_pO_2 of 92% to 95%. HFNC will be withdrawn when F_iO_2 is ≤40%. Staff intensivists will continuously monitor vital signs and adherence to protocol on a 24/7 basis.	HFNC will be initiated at 50 L/min (AIRVO2 or Optiflow, Fisher & Paykel Health care Limited., Auckland, New Zealand) with temperature set at 37°C. Nasal cannula size will be determined by the patient's nostril size (≤ 50%). FiO_2 will be adjusted to maintain SpO_2 at 92% to 95%. Flow and temperature will be adjusted based on patient's comfort and clinical response	Control patients will receive full standard care.	HFNC adapted for an S_pO_2 of 90-95%. Except in case of poor tolerance by the patient a minimum gas flow rate of 50 L/min will be set initially. Weaning of the HFNC will first be performed reducing F_iO_2 down to 0·4 before reducing the gas flow rate. In clinically stable patients with a F_iO_2 less than or equal to 0·4 and a gas flow rate less than or equal to 30 L/min, an attempt will be made to switch to standard oxygen therapy at 4-6 L/min.

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen.

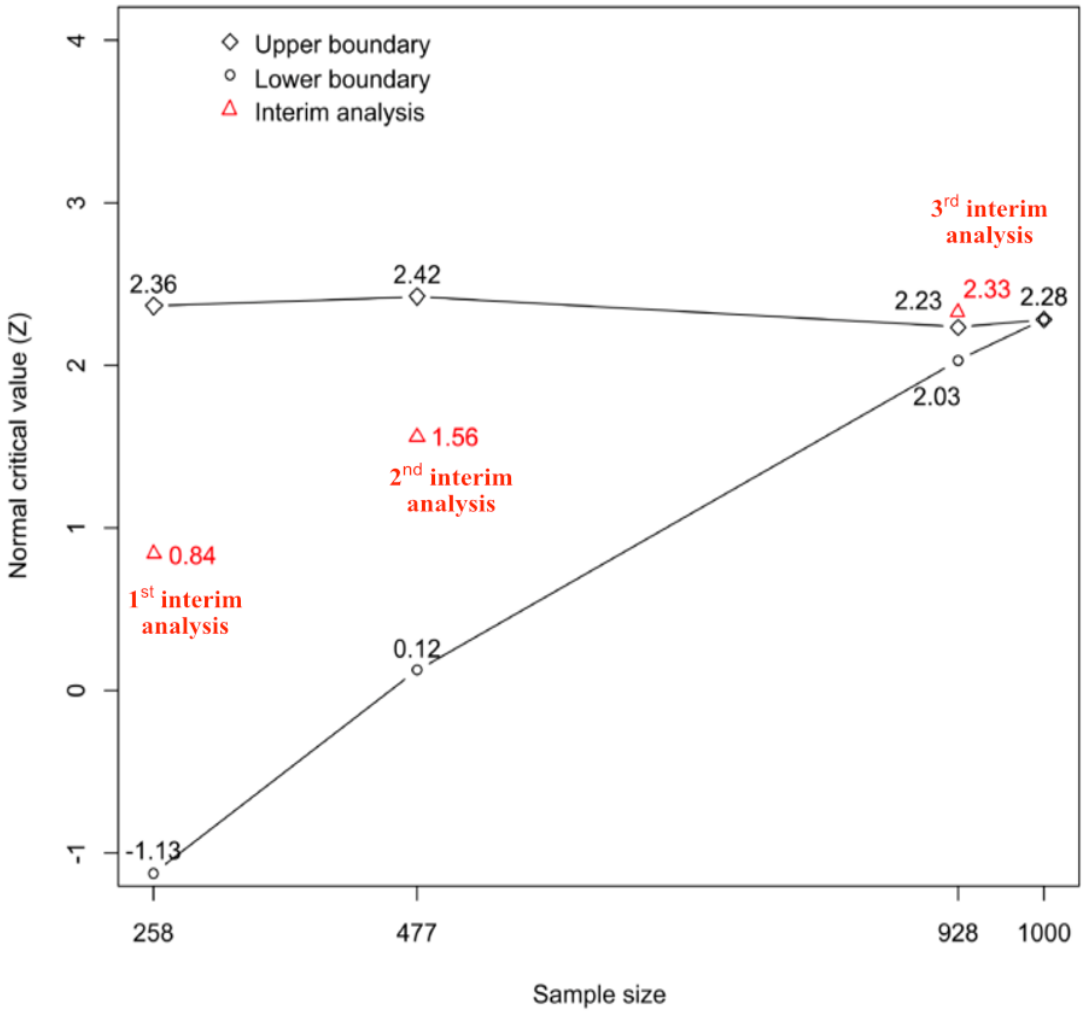

Figure S1. Z statistic for the three interim analyses

The changing pace of the pandemic dynamics made planning and executions of interim analysis very challenging. The meta-trial experienced a sudden surge of inclusions in the last months of 2020 while preparing the second interim analysis (planned at 400 patients). By the time the results were available in December (which recommended to continue recruitment), 800 patients had already been included, thus the steering committee decided not to perform the third interim analysis (planned at 600 patients) and move directly to the fourth interim analysis (800 patients). In the short time required to make this decision, 928 patients had been included in the interim analysis which ended up with the decision to stop recruitment. At the time of recruitment interruption, 1126 patients had been included.

Table S3. Repeated confidence intervals of the primary outcome

Analysis	Awake prone positioning	Standard care	Difference of proportions	Confidence interval
1	35% (46/131)	40% (51/127)	-5·0%	[-19·3%;9·4%]
2	35% (84/238)	42 % (101/239)	-7·0%	[-17·8%;4·0%]
3	40% (184/463)	47% (220/465)	-7·6%	[-14·9%;-0·2%]
4	39·5% (223/564)	46·1% (257/557)	-6·6%	[-13·2%;0%]

As multiple looks at the data affects the construction of confidence intervals just as it affects significance levels of hypothesis tests the sequence of confidence intervals, using the Miettinen and Nurminen method https://pubmed.ncbi.nlm.nih.gov/4023479/ on the nominal alpha-level of the upper bound, corresponding to the interim and final analyses. Using this method assures a confidence level of 95% for the 4 confidence intervals simultaneously.

Table S4. American trial

Variable	MD	Standard care (n = 110)	MD	APP (n = 112)
Age, mean ± sd	0	62·5 ± 13·3	0	62·2 ± 12·5
Female sex — no. (%)	0	42 (38%)	0	40 (36%)
Body mass index, mean ± sd †	0	30·5 ± 5·3	0	30·0 ± 5·1
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		0·8 [0·3;1·8]		0·8 [0·3;1·8]
Respiratory rate at enrolment, mean ± sd	0	26·1 ± 7·4	0	25·3 ± 6·1
Mean arterial pressure at enrolment, mean ± sd	4	91·7 ± 11·1	7	91·2 ± 13·0
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	156·0 ± 40·6	0	152·0 ± 37·8
Coexisting illness— no. (%) ‡				
Chronic heart disease — no. (%)	0	41 (37%)	0	25 (22%)
Chronic lung disease — no. (%)	0	21 (19%)	0	11 (10%)
Chronic kidney disease — no. (%)	0	8 (7%)	0	11 (10%)
Severe liver disease — no. (%)	0	2 (2%)	0	1 (1%)
Diabetes mellitus (type I and II) — no. (%)	0	51 (46%)	0	49 (44%)
Obesity — no. (%)	0	61 (56%)	0	59 (53%)
Active malignancy — no. (%)	0	6 (6%)	0	8 (7%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	88 (80%)	0	80 (71%)
Do-not-intubate — no. (%)	0	15 (14%)	0	7 (6%)
Highest treating location — no. (%)				
General ward	0	14 (13%)	0	20 (18%)
Intermediate care unit	0	0 (0%)	0	1 (1%)
Intensive care unit	0	96 (87%)	0	91 (81%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

Table S5. Canadian trial

Variable	MD	Standard care (n = 6)	MD	APP (n = 7)
Age, mean ± sd	0	68·3 ± 20·5	0	65·1 ± 15·6
Female sex — no. (%)	0	2 (33%)	0	4 (57%)
Body mass index, mean ± sd †	2	30·7 ± 6·5	1	27·4 ± 3·6
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		0·2 [0; 0·4]		0·0 [0; 0·2]
Respiratory rate at enrolment, mean ± sd	0	28·2 ± 2·2	0	29·0 ± 1·9
Mean arterial pressure at enrolment, mean ± sd	0	88·2 ± 10·0	0	89·9 ± 8·0
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	166·8 ± 86·5	0	169·3 ± 68·1
Coexisting illness— no. (%) ‡				
Chronic heart disease — no. (%)	0	3 (50%)	0	3 (43%)
Chronic lung disease — no. (%)	0	1 (17%)	0	2 (29%)
Chronic kidney disease — no. (%)	0	2 (33%)	0	0 (0%)
Severe liver disease — no. (%)	0	0 (0%)	0	0 (0%)
Diabetes mellitus (type I and II) — no. (%)	0	2 (33%)	0	5 (71%)
Obesity — no. (%)	2	2 (50%)	1	1 (17%)
Active malignancy — no. (%)	0	0 (0%)	0	0 (0%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	4 (67%)	0	6 (86%)
Do-not-intubate — no. (%)	0	3 (50%)	0	3 (43%)
Highest treating location — no. (%)				
General ward	0	3 (50%)	0	2 (29%)
Intermediate care unit	0	0 (0%)	0	3 (43%)
Intensive care unit	0	3 (50%)	0	2 (29%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

Table S6. French trial

Variable	MD	Standard care (n = 202)	MD	APP (n = 200)
Age, mean ± sd	1	62·9 ± 11·5	0	64·2 ± 10·2
Female sex — no. (%)	0	51 (25%)	0	49 (25%)
Body mass index, mean ± sd †	0	28·9 ± 4·4	1	28·7 ± 4·1
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		1·0 [1·0; 3·0]		2·0 [1·0; 3·0]
Respiratory rate at enrolment, mean ± sd	0	23·8 ± 5·5	1	24·2 ± 5·2
Mean arterial pressure at enrolment, mean ± sd	2	90·2 ± 13·0	0	91·6 ± 13·4
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	155·8 ± 44·6	0	155·2 ± 48·3
Coexisting illness— no. (%‡				
Chronic heart disease — no. (%)	0	11 (5%)	0	22 (11%)
Chronic lung disease — no. (%)	0	28 (14%)	0	28 (14%)
Chronic kidney disease — no. (%)	0	5 (3%)	0	7 (4%)
Severe liver disease — no. (%)	0	1 (1%)	0	3 (2%)
Diabetes mellitus (type I and II) — no. (%)	0	50 (25%)	0	50 (25%)
Obesity — no. (%)	0	74 (37%)	1	61 (31%)
Active malignancy — no. (%)	0	22 (11%)	0	33 (17%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	193 (96%)	0	199 (100%)
Do-not-intubate — no. (%)	0	6 (3%)	0	9 (5%)
Highest treating location — no. (%)				
General ward	0	0 (0%)	0	0 (0%)
Intermediate care unit	0	0 (0%)	0	0 (0%)
Intensive care unit	0	202 (100%)	0	200 (100%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

Table S7. Irish trial

Variable	MD	Standard care (n = 12)	MD	APP (n = 12)
Age, mean ± sd	0	59·3 ± 16·0	0	62·8 ± 11·0
Female sex — no. (%)	0	5 (42%)	0	3 (25%)
Body mass index, mean ± sd †	0	34·2 ± 7·9	0	32·2 ± 7·1
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		1·0 [1·0; 1·8]		1·0 [1·0; 2·5]
Respiratory rate at enrolment, mean ± sd	0	25·8 ± 6·3	0	23·8 ± 4·6
Mean arterial pressure at enrolment, mean ± sd	0	90·2 ± 11·7	0	94·9 ± 9·3
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	178·3 ± 52·7	0	193·9 ± 45·5
Coexisting illness— no. (%)‡				
Chronic heart disease — no. (%)	0	4 (33%)	0	7 (58%)
Chronic lung disease — no. (%)	0	4 (33%)	0	2 (17%)
Chronic kidney disease — no. (%)	0	0 (0%)	0	0 (0%)
Severe liver disease — no. (%)	0	0 (0%)	0	0 (0%)
Diabetes mellitus (type I and II) — no. (%)	0	0 (0%)	0	3 (25%)
Obesity — no. (%)	0	8 (67%)	0	6 (50%)
Active malignancy — no. (%)	0	1 (8%)	0	1 (8%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	11 (92%)	0	12 (100%)
Do-not-intubate — no. (%)	0	0 (0%)	0	2 (17%)
Highest treating location — no. (%)				
General ward	0	0 (0%)	0	0 (0%)
Intermediate care unit	0	4 (33%)	0	8 (67%)
Intensive care unit	0	8 (67%)	0	4 (33%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

Table S8. Mexican trial

Variable	MD	Standard care (n = 214)	MD	APP (n = 216)
Age, mean ± sd	0	58·2 ± 15·8	0	58·6 ± 15·8
Female sex — no. (%)	0	88 (41%)	0	84 (39%)
Body mass index, mean ± sd †	0	30·0 ± 3·8	0	30·3 ± 4·6
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		0·6 [0·4; 1·0]		0·7 [0·4; 1·0]
Respiratory rate at enrolment, mean ± sd	0	25·3 ± 4·2	0	25·0 ± 4·3
Mean arterial pressure at enrolment, mean ± sd	0	82·6 ± 7·4	0	82·7 ± 7·3
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	135·5 ± 37·9	0	134·7 ± 38·7
Coexisting illness— no. (%)‡				
Chronic heart disease — no. (%)	0	67 (31%)	0	62 (29%)
Chronic lung disease — no. (%)	0	10 (5%)	0	18 (8%)
Chronic kidney disease — no. (%)	0	19 (9%)	0	24 (11%)
Severe liver disease — no. (%)	0	3 (1%)	0	4 (2%)
Diabetes mellitus (type I and II) — no. (%)	0	68 (32%)	0	64 (30%)
Obesity — no. (%)	0	81 (38%)	0	86 (40%)
Active malignancy — no. (%)	0	2 (1%)	0	3 (1%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	184 (86%)	0	182 (84%)
Do-not-intubate — no. (%)	0	20 (9%)	0	23 (11%)
Highest treating location — no. (%)				
General ward	0	0 (0%)	0	0 (0%)
Intermediate care unit	0	162 (76%)	0	172 (80%)
Intensive care unit	0	52 (24%)	0	44 (20%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

Table S9. Spanish trial

Variable	MD	Standard care (n = 13)	MD	APP (n = 17)
Age, mean ± sd	0	52·4 ± 11·5	0	58·1 ± 9·9
Female sex — no. (%)	0	3 (23%)	0	4 (24%)
Body mass index, mean ± sd †	0	28·9 ± 4·9	0	30·1 ± 3·2
Number of days from admission in hospital to enrolment in study, med [Q1 ; Q3]		1·0 [0; 4·0]		2·0 [1·0;4·0]
Respiratory rate at enrolment, mean ± sd	0	20·8 ± 3·8	0	21·4 ± 4·9
Mean arterial pressure at enrolment, mean ± sd	0	85·4 ± 14·2	0	93·2 ± 17·9
SpO_2:F_iO_2 ratio at enrolment, mean ± sd	0	155·8 ± 30·7	0	162·9 ± 22·8
Coexisting illness— no. (%)‡				
Chronic heart disease — no. (%)	0	1 (8%)	0	1 (6%)
Chronic lung disease — no. (%)	0	0 (0%)	0	2 (12%)
Chronic kidney disease — no. (%)	0	1 (8%)	0	3 (18%)
Severe liver disease — no. (%)	0	0 (0%)	0	0 (0%)
Diabetes mellitus (type I and II) — no. (%)	0	2 (15%)	0	5 (29%)
Obesity — no. (%)	0	5 (39%)	0	8 (47%)
Active malignancy — no. (%)	0	0 (0%)	0	0 (0%)
Use of glucocorticoids for treatment of Covid-19 — no. (%)	0	12 (92%)	0	15 (88%)
Do-not-intubate — no. (%)	0	0 (0%)	0	0 (0%)
Highest treating location — no. (%)				
General ward	0	0 (0%)	0	0 (0%)
Intermediate care unit	0	0 (0%)	0	0 (0%)
Intensive care unit	0	13 (100%)	0	17 (100%)

SpO_2 denotes peripheral blood oxygen saturation, FiO_2 Fraction of inspired oxygen, MD missing data.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Coexisting illnesses were defined as follows: chronic heart disease — heart failure or coronary artery disease or hypertension; chronic lung disease — obstructive or restrictive lung disease; chronic kidney disease — estimated glomerular filtration rate < 60 mL/min/1·73 m^2 prior to hospital admission; severe liver disease —cirrhosis and/or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score≥10; obesity — body-mass index ≥30 kg/m^2.

3.4 Daily duration of time spent in prone positioning in individual trials

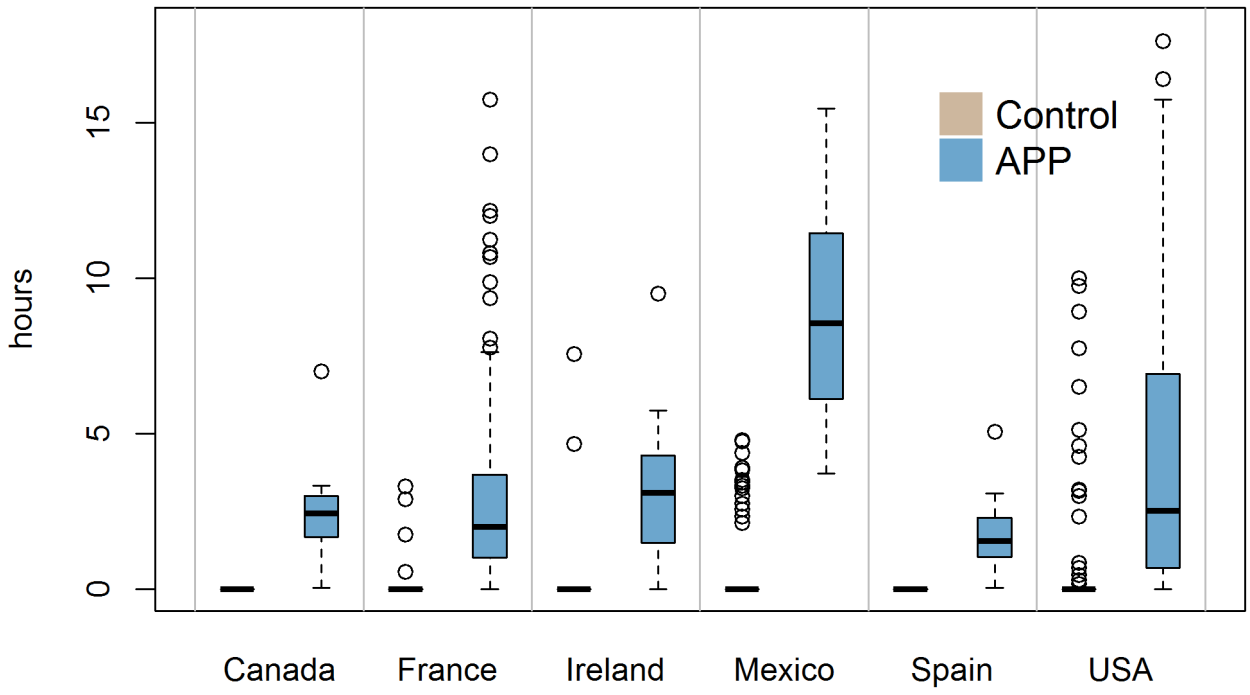

Figure S2: Boxplots durations of prone positioning (in hours per day from Day 0 to Day 14) in both groups

Group	Country	min	max	Mean ± sd	Median[Q1;Q3]
APP	Canada	0·0	7·0	2·7 ± 2·2	2·4 [1·7; 3·0]
APP	France	0·0	15·8	2·9 ± 2·9	2·0 [1·0; 3·7]
APP	Ireland	0·0	9·5	3·3 ± 2·7	3·1 [2·1; 3·9]
APP	Mexico	3·7	15·5	9·0 ± 3·2	8·6 [6·1; 11·4]
APP	Spain	0·0	5·1	1·7 ± 1·2	1·6 [1·1; 2·3]
APP	USA	0·0	19·2	4·4 ± 4·7	2·5 [0·7; 6·9]
APP	Meta-trial	0·0	19·2	5·6 ± 4·4	5·0 [1·6; 8·8]
Standard care	Canada	0·0	0·0	0 ± 0	0 [0;0]
Standard care	France	0·0	3·3	0 ± 0·3	0 [0;0]
Standard care	Ireland	0·0	7·6	1·0 ± 2·5	0 [0;0]
Standard care	Mexico	0·0	4·8	0·3 ± 1·0	0 [0;0]
Standard care	Spain	0·0	0·0	0 ± 0	0 [0;0]
Standard care	USA	0·0	10·0	0·7 ± 2·0	0 [0;0]
Standard care	Meta-trial	0·0	10·0	0·3 ± 1·2	0 [0;0]

APP, awake prone positioning

Table S10: Description of the durations of prone positioning (in hours per day from Day 0 to Day 14) in individual trials

3.5 Investigation of heterogeneity between trials

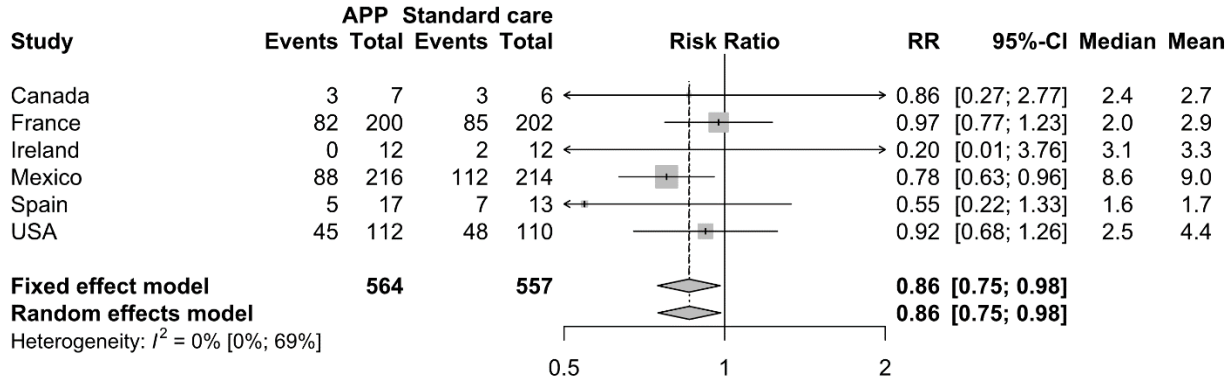

Figure S3: Forest plot with mixed effects linear model with group as a fixed effect and country as a random effect on intubation or death (primary outcome) at Day 28. Median and mean durations of prone positioning sessions in hours

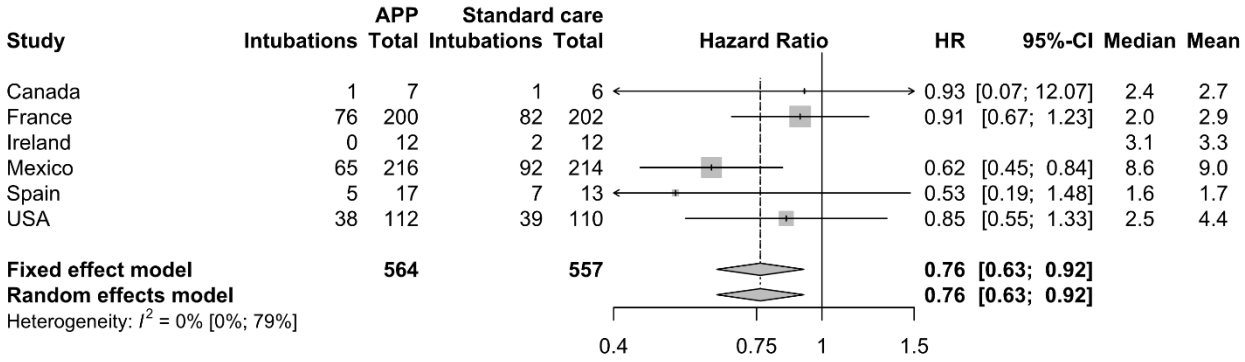

Figure S4: Forest plot with mixed effects linear model with group as a fixed effect and country as a random effect on intubation at Day 28. Median and mean durations of prone positioning sessions in hours

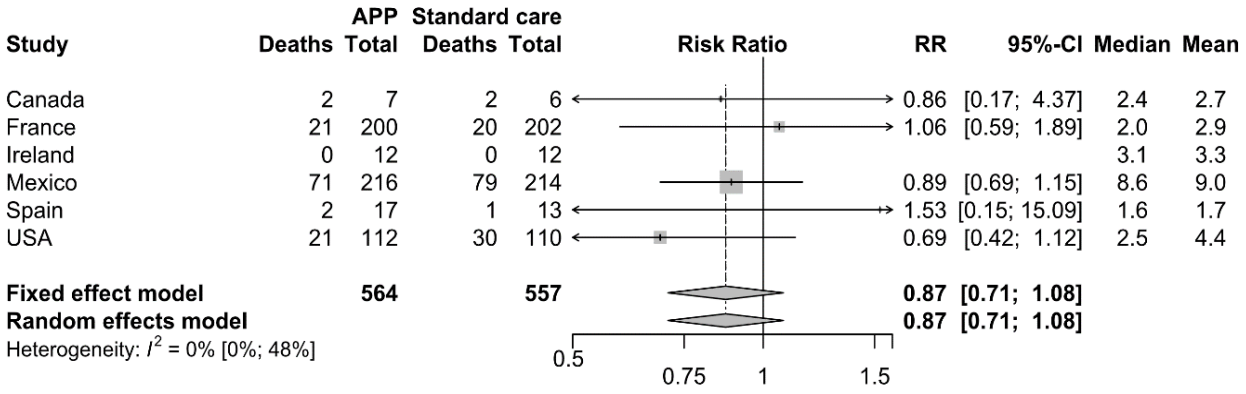

Figure S5: Forest plot with mixed effects linear model with group as a fixed effect and country as a random effect on death at Day 28. Median and mean durations of prone positioning sessions in hours

3.6 Interaction between subgroups according to severity (SpO_2/F_1O_2 < 190 vs ≥ 190)

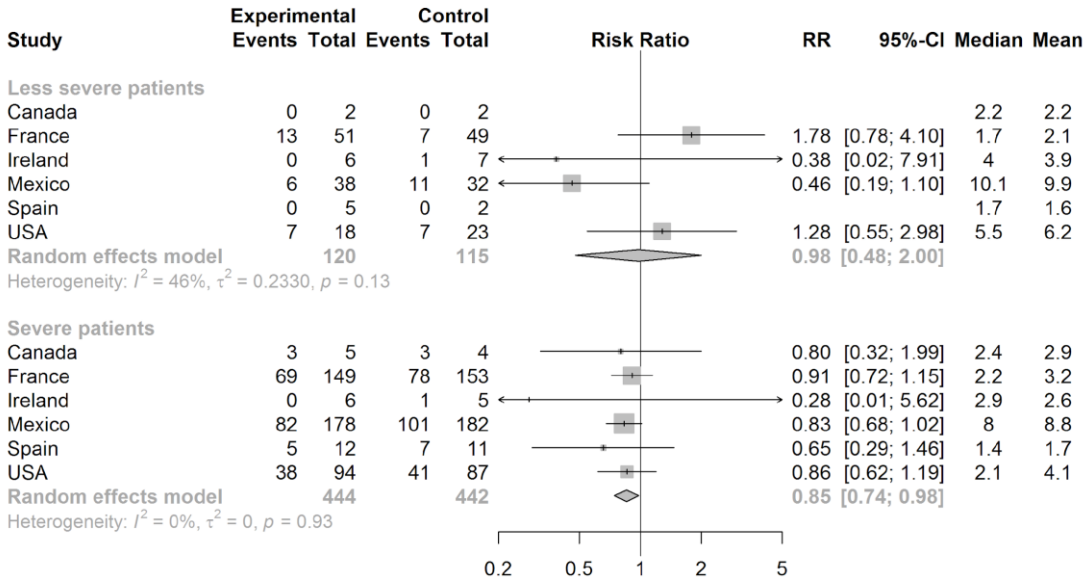

Figure S6: Subgroup analysis of the primary outcome according to the severity at enrollment. Interaction test p=0·62. Median and mean durations of prone positioning sessions in hours

3.7 Per-protocol analysis

Patients in the standard care group who remained in APP for more than 1 hour during any one of the first 14 days whilst on HFNC, and patients in the APP group who stayed in APP less than 1 hour daily on average while on HFNC during the first 14 days, were excluded from the per-protocol population as defined a priori.

Results:

The per-protocol analysis was carried out, after excluding 64 patients of the standard care group who underwent off-protocol APP and 83 patients from the APP group who didn't stay in APP for a minimum of 1 hour daily when eligible as defined prospectively. In the per-protocol population, the primary outcome occurred in 195 of 481 (41%) patients in the APP group and in 221 out of 493 (45%) patients in the standard care group (relative risk 0·90, 95% CI 0·77 to 1·04).

Interpretation:

Beyond lack of power, as the adherence to the protocol may have been influenced by the course of the disease (rescue APP among the most severe patients), the APP and standard care groups of the pre-defined per-protocol population were probably no longer comparable, which precludes meaningful interpretation of this analysis.