National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[G] Evidence review for awake prone positioning

NICE guideline NG191

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Guideline version (Final)

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Objective

This evidence review aimed to determine the effectiveness of body positioning in awake non-intubated people in hospital with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see Appendix A for more information). The review question for this evidence review is:

What is the effectiveness of body positioning in awake patients with COVID-19 in preventing intubation or death?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The review protocol specified that patients should be awake and non-intubated with higher oxygen requirements. Details of whether patients were described as awake and reported levels of respiratory support have been extracted where available and included in Table 1. Reported details of standard care have also been included in Table 1.

Reported adverse events were summed and meta-analysed as a single adverse events category (see Appendix F for full details of specific types and frequencies of adverse events).

Data with zero events in both treatment groups were not meta-analysed but have been included in the evidence tables (see Appendix F for full details).

Data from the studies by Kharat et al. 2021 and Taylor et al. 2021 were adjusted to account for their cluster RCT study design. We adjusted the outcomes of these 2 cluster RCTs for clustering by using the intra-cluster correlation coefficient (ICC) and number of clusters in each arm.

Baseline characteristics and outcomes were reported for 2 sets of analyses by Taylor et al. 2021 (by treatment allocation and by attempt to prone). Only data from analyses by treatment allocation were included in this evidence review (to allow comparison based on randomisation).

Included studies

The searches for the effectiveness evidence were run on 05 01 2022. The following databases were searched: Central Register of Controlled Trials (Wiley), Embase (Ovid) MEDLINE ALL (Ovid), EMcare (Ovid) and the World Health Organisation Covid-19 database. Full search strategies for each database are provided in Appendix B. Pre-prints were searched via EPPI-Reviewer v5.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The search identified 392 references. These references were screened using their titles and abstracts and 42 full text references were obtained and assessed for relevance against the criteria in the PICO.

35 studies were excluded. Details of excluded studies are in Appendix E.

Seven studies were included in this evidence review. These included 1 meta-trial of 6 RCTs (Ehrmann et al. 2021), 2 cluster RCTs (Kharat et al. 2021, Taylor et al. 2021), 3 individually randomised RCTs (Fralick et al. 2021, Jayakumar et al. 2021, Rosén et al. 2021) and 1 post hoc analysis (Kaur et al. 2021) of 1 of the RCTs included in the meta-trial by Ehrmann et al. 2021.

Two trials (Fralick et al. 2021 and Rosen et al. 2021) were stopped early due to futility.

Two studies did not explicitly state that included people were awake (Fralick et al. 2021; Kharat et al. 2021), although description of the interventions implied that people were able to move.

A summary of the included studies is shown in Table 1.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Ehrmann et al. 2021 2 April 2020 to 26 January 2021 Canada, France, Ireland, Mexico, USA, Spain NB: 1 post hoc analysis study (Kaur et al. 2021) relating to 1 of the RCTs covered by the meta-trial by Ehrmann et al. has also been included in this evidence review. Full details are presented in appendix F.	Multinational collaborative meta-trial (prospective individual participant data meta-analysis of 6 RCTs: NCT04325906, NCT04347941, NCT04358939, NCT04395144, NCT04391140, and NCT04477655) Full publication	Acute hypoxaemic respiratory failure (defined as need for respiratory support with high-flow nasal cannula (HFNC) and ratio of peripheral arterial oxygen saturation (SpO2) to fraction of inspired oxygen (FiO2) [SpO2:FiO2] of 315 or less (equivalent to ratio of partial pressure of arterial oxygen [PaO2] to FiO2 [PaO2:FiO2] ≤300 mm Hg) Eligible patients required respiratory support with high-flow nasal cannula (HFNC). HFNC initiated at maximally tolerated flow setting, and FiO2 titrated to	Adults requiring respiratory support with HFNC for acute hypoxaemic respiratory failure due to COVID-19 (99% confirmed COVID-19 in each group) Mean age (SD) years: intervention 61.5 (13.3), comparator 60.7 (14.0) % male: intervention 67% comparator 66% Key comorbidities: chronic lung disease intervention 11%, comparator 12% Respiratory support: intervention NR, comparator NR Location at enrolment Intensive care unit intervention n= 336 (60%), control n=339 (61%) Intermediate care unit intervention n= 197 (35%), control n= 189 (34%) Emergency department intervention n= 5 (1%), control n= 5 (1%) General ward intervention n= 26 (5%), control n=24 (4%) Key exclusions: people unable or refusing to provide informed consent, haemodynamically unstable, severely obese with BMI over 40 kg/m², pregnant, or	Awake prone positioning (N=564) Patients instructed and assisted to lie in prone position for as long as possible and as frequently as possible each day. Median daily duration of awake prone positioning (until day 14) = 5·0 hours (IQR 1·6–8·8) (varying between trials with median daily awake prone positioning duration of 1·6 hours in Spain to 8·6 h in Mexico) Glucocorticoids for treatment of COVID-19 n= 494 (88%) 28 day follow up	Standard care (N=557) Standard care with HFNC. Awake prone positioning as rescue intervention discouraged and recorded as protocol violation. Glucocorticoids for treatment of COVID-19 n= 492 (88%)	Mortality Intubation Use of NIV Time to intubation Time to death Length of hospital stay Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		maintain SpO2 90% to 95%. Use of non-invasive (NIV) not included in the trial protocol but recorded prospectively.	contraindicated to awake prone positioning			
Fralick et al. 2021 May 2020 to May 2021 Canada and USA	Pragmatic RCT (COVID-PRONE, NCT04383613) Preprint	Hypoxic but not critically ill. Eligible people had need for supplemental oxygen (up to 50% fraction of inspired oxygen [FiO2])	Hypoxic but not critically ill patients hospitalised with confirmed or suspected COVID-19 (N=248 in intention to treat [ITT] analysis) (98% had PCR-confirmed COVID-19) Median age (inter-quartile range [IQR]) years: intervention 59.5 (45 to 68), comparator 54 (44 to 62) % female: intervention 34.9%, comparator 36.9% Key comorbidities: COPD or asthma Intervention 9.5%, comparator 12.3%; current smoker: intervention 0%, comparator 5.7% Respiratory support: nasal prong intervention 87.3%, comparator 91.8%; HFNC intervention 4%, comparator 1.6%; face mask intervention 6.3%, comparator 5.7% Respiratory measures: median (IQR) oxygen saturation	Prone positioning (N=126) Patients recommended to adopt a prone position four times per day (up to 2 hours per session) and encouraged to sleep in prone position overnight. Recommended for up to 7 days in hospital, until hospital discharge, or until the patient no longer required supplemental oxygen (whichever came first). Self-reported time spent in prone position assessed from time of randomisation to 72 hours, and from 72 hours until day 7. Patients followed until first of: death, hospital discharge or 30 days.	Standard care (no instruction to prone position) (N=122) Median total time in prone position to first 72 hours was 0 hours [IQR 0,2] in control group. After accounting for hospital discharge within the first 72 hours, approximately 0 hours per day in the control arm in the first 72 hours. From 72 hours to 7 days median 0 (IQR 0, 0) Dexamethasone n= 119 (97.5%), remdesivir n= 48 (39.3%), tocilizumab n= 2 (1.6%)	In-hospital death Mechanical ventilation Time to discharge from hospital Serious adverse events composite Aspiration pneumonia Venous thromboembolism Other (unspecified)

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			intervention 94 (93 to 95), comparator 94 (93 to 96); median (IQR) FiO2: intervention 32 (28 to 36), comparator 32 (28 to 36); median (IQR) S/F ratio intervention 303 (261 to 336), comparator 305 (267 to 339) Key exclusions: prone positioning contraindicated (e.g. recent abdominal surgery), or impractical (e.g. in people with dementia, severe delirium), or mechanical intubation indicated at time of randomisation according to treating physician. NB: did not explicitly state pregnant women or children excluded	Median total time in prone position to first 72 hours was 6 hours [IQR 1.5,12.8] in intervention group. After accounting for hospital discharge within the first 72 hours, approximately 2.5 hours per day in the prone arm in the first 72 hours. From 72 hours to 7 days median 0 (IQR 0, 12) Dexamethasone n= 117 (92.9%), remdesivir n= 56 (44.4%), tocilizumab n= 0 (0%) Patients followed until first of: death, hospital discharge or 30 days		
Jayakumar et al. 2021 Study dates not reported (NR) India	Multicentre pragmatic RCT Clinical trials registry of India (Ref. No. CTRI/2020/12/029702) Full publication	Non-intubated with acute hypoxic respiratory failure secondary to COVID-19 pneumonia requiring 4 or more litres of supplemental oxygen to maintain	60 non-intubated awake adults admitted to intensive care unit in 3 hospitals with PCR-confirmed COVID-19 Mean age (SD) years: intervention 54.8 (11.1), comparator 57.3 (12.1) % male: intervention 83%, comparator 83%	Awake prone positioning (N=30) People encouraged by bedside nurses to lie prone for at least 6 hours a day (cumulative), supported by use of standard pillows and C-pillow where required.	Standard care (N=30) Patients able to change position according to their comfort (supine, semi-sitting, sitting or lateral). Patients permitted to lie prone based on comfort if they wished (but proning not actively	ICU mortality NIV Total number of patients intubated ICU length of stay Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		saturation of 92% and above or if ABG was available, PaO2/FiO2 ratio between 100 and 300 mmHg (mild to moderate ARDS) with PaCO2 less than 45 mmHg were included. Patients with AHRF and hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine also considered for inclusion. Both groups received oxygen via nasal prongs, face mask, non-rebreather mask, high flow nasal cannula (HFNC) or NIV according to clinician discretion	Respiratory comorbidities (asthma, pulmonary fibrosis): intervention 7%, comparator 10% Initial device, face mask: intervention 63%, comparator 63% Initial device, non-rebreather mask: intervention 23%, comparator 37% Initial device, HFNC: intervention 3%, comparator 0% Initial device, NIV: intervention 7%, comparator 0 Initial device, nasal prongs: intervention 3%, comparator 0% Initial FiO2 mean (SD): intervention 48.2 (18.6), comparator 50.2 (20.8) Initial P/F ratio (mean (SD): intervention 201.4 (118.8), comparator 185.6 (126.1) Key exclusions: people below 18 years of age, pregnant women, people requiring immediate intubation, or with contraindications to prone positioning (spinal instability secondary to severe rheumatoid arthritis, life threatening cardiac arrhythmias)	Proning sessions recorded only lasted more than 30 minutes (for both groups). Protocol followed for 7 days or until escalation of respiratory support to the next level or patient improvement to discharge or death (whichever first). Adherence to protocol (primary outcome) was 43% among the patients in the prone group (13 patients completed an average of 6 hours a day or more proned). 70% of patients in intervention group could lie prone for 4 hours a day. For intervention group, median maximum duration was 2 hours. Steroids n= 30 (100%), remdesivir n= 22 (73%), tocilizumab n= 6 (20%), heparin/low molecular weight heparin n= 30 (100%)	encouraged by treating team in this arm). 47% (14 out of 30) were completely supine. 53% spent some hours proned (but none above 6 hours). Steroids n= 30 (100%), remdesivir n= 23 (77%), tocilizumab n= 5 (17%), heparin/low molecular weight heparin n= 30 (100%)	

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Kharat et al. 2021 6 April 2020 to 29 May 2020 Switzerland	Cluster RCT (ward level randomisation) Swiss National Clinical Trial portal (SNCTP000003718) Full publication	Patients were admitted to ward on low-flow oxygen therapy (1 to 6 L·min−1) via nasal cannula to reach SpO2 level of 90–92%.	Adults (n=27) admitted to medical ward with confirmed COVID-19 pneumonia on low-flow oxygen therapy (1 to 6 L·min−1) via nasal cannula to reach SpO2 level of 90–92%. Mean age (SD) years: intervention 54 (14), comparator 60 (11) % male: intervention 60%, comparator 65% % with COPD: intervention 0%, comparator 0% Baseline median (IQR) oxygen flow on nasal cannula 2.5 (2.0–3.0) L·min−1 Key exclusions: People initially treated in ICU or high-dependency unit and recovering from ARDS, people with oxygen needs >6 L·min−1 via nasal cannula or >40% inspiratory oxygen fraction (FiO2) using a Venturi mask to reach SpO2 level of 90–92%, pregnant women, terminally ill people, those unable to self-prone.	Self proning plus standard care (N=10 patients) Estimated self-prone time 295 ± 216 min Azithromycin n= 1 (10%), hydroxychloroquine n= 6 (60%), lopinavir/ritonavir n= 5 (50%) Baseline median (IQR) oxygen flow on nasal cannula 2.0 (1.0– 3.0) L·min−1 Intervention and assessments of endpoints limited to 24 hours	Standard care (N=17 patients) Standard care comprised: 1) oxygen titration with nasal cannula according to institutional recommendations to reach SpO2 values between 90% and 94%. At least 6 routine nurse rounds per 24 hours to monitor oxygen requirements and adapt oxygen flow to target 2) empirical antibiotics for community-acquired pneumonia 3) hydroxychloroquine and lopinavir/ritonavir as proposed by institutional guidelines 4) restrictive fluid strategy. Estimated prone time 7 ± 29 min (due to single patient spending estimated	Adverse effects (defined by neck pain, position-related discomfort and gastro-oesophageal reflux)

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
					time of 120 min in position) Azithromycin n= 1 (6%), hydroxychloroquine n=13 (77%), lopinavir/ritonavir n=10 (59%)	
Rosén et al. 2021 7 October 2020 to 7 February 2021 Sweden	Multicentre RCT (PROFLO, ISRCTN54917435) Full publication	Adults with moderate to severe hypoxemic respiratory failure and high-flow nasal oxygen or non-invasive ventilation for respiratory support and PaO2/FiO2 ratio ≤20 kPa or corresponding values of SpO2 and FiO2 for more than one hour. Respiratory support: HFNO intervention 86%, comparator 74%	Adults with moderate to severe hypoxemic respiratory failure admitted to hospital with PCR-confirmed COVID-19 and high-flow nasal oxygen or non-invasive ventilation for respiratory support and PaO2/FiO2 ratio ≤20 kPa Median age (IQR) years: intervention 66 (53 to 74), comparator 65 (55 to 70) % male: intervention 64%, comparator 82% Enrolment outside ICU intervention 53%, comparator 51% Key comorbidities: lung disease Intervention 11%, comparator 26%; asthma intervention 3%, comparator 13%; COPD intervention 6%, comparator 10%; fibrosis intervention 3%, comparator 0%	Awake prone positioning protocol targeting 16 hours per day (N=36) Prone and semi-prone positioning was allowed. Flat supine positioning discouraged. People advised to take semi-recumbent or lateral position between proning sessions. Median prone duration was 9.0 h per day [IQR 4.4–10.6] in prone group (P=0.014) Total protocol duration, days = 4.2 (IQR 1.7 - 5.7) Daily prone time day 1–3, hours 8.5 (IQR 5.2–12.2) 30 day follow up	Standard care (N=39) Awake prone positioning not encouraged but could be prescribed by the attending clinician at their discretion. Standard care delivered in both groups according to clinical practice in participating hospitals. Intravenous sedation allowed but not protocolised. Decision to intubate made at the discretion of attending clinician but followed local guidelines. Positioning after intubation not protocolised (but PP usual practice for mechanically	Primary outcome: intubation within 30 days after enrolment Use of NIV Time from enrolment to NIV for patients included with HFNO Time from enrolment to IMV Ventilator-free days (for all patients) ICU admission Hospital length of stay ICU length of stay

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
			Respiratory support: HFNO intervention 86%, comparator 74% Key exclusions: Oxygen supplementation device other than HFNO or NIV, inability to prone or semi-prone, immediate need for endotracheal intubation, severe hemodynamic instability, previous intubation for COVID-19 pneumonia, pregnancy, terminal illness with less than one year life expectancy, do-not-intubate order; inability to understand oral or written study information.		ventilated patients with COVID-19 with moderate to severe ARDS at participating centres). Median prone duration was 3.4 h per day [IQR 1.8–8.4] in control group Total protocol duration, days 4.9 (IQR 2.3–8.1) Daily prone time day 1–3, hours 2.6 (IQR 0.3–8.1)	30 day mortality Adverse events: Pressure sores Vomiting during proning Central or arterial line dislodgement Cardiac arrest within 30 days
Taylor et al. 2021 1 June 2020 to 31 August 2020 USA	Cluster pilot RCT (mixed methods) Full publication	Eligible patients were on room air oxygen saturation below 93% or new oxygen requirement of 3 L per minute or above without need for mechanical ventilation. Oxygen saturation at baseline, median (IQR): intervention 92 (89 to 94), comparator 93 (91 to 95)	Awake non-intubated hypoxic adults admitted to hospital with COVID-19. People had positive SARS-CoV-2 test or suspected COVID-19 pneumonia and i) room air oxygen saturation below 93% or ii) new oxygen requirement of 3 L per minute or above without need for mechanical ventilation. At time of eligibility, 23 (53%) had positive test result for SARS-CoV-2 and 20 (47%) had suspected COVID-19. Eight (19%) subsequently tested negative for SARS-CoV-2 (usual care [n = 2] vs. prone [n = 6]).	Awake prone positioning strategy (N=28). 10 of these attempted to prone, 17 did not attempt to prone. Hospitalised people with COVID-19 guided to adopt prone position when hypoxia thresholds met. Prone position applied depended on tolerance and adherence. Patients reported that they could only lie prone for between 10 and 120 minutes per day.	Standard care (N=13). 10 did not attempt to prone. 3 attempted to prone. Standard care determined by clinical assessments and need. Expected to be routine practice for hospitalised people with COVID-19-related hypoxia and should be similar for both groups. Prone positioning neither encouraged nor disallowed in standard care group.	ICU admission required within 48 hours ICU admission required during hospitalisation Intubation Hospital length of stay Hospital mortality Serious adverse events Adverse events:

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		Oxygen support at baseline: room air intervention 0%, comparator 8%; <4 L nasal cannula intervention 56%, comparator 54%; 4-6 L nasal cannula intervention 41%, comparator 23%; medium flow nasal cannula intervention 0%, comparator 15%; humidified HFNC intervention 0%, comparator 0%; bilevel positive airway pressure intervention 4%, comparator 0%	Median (IQR) age (SD) years: intervention 56 (45 to 66), comparator 60 (54 to 63) % female: intervention 37%, comparator 23% Key comorbidities: chronic lung disease Intervention 22%, comparator 23%; smoking history= never intervention 70%, comparator 54%; smoking history 1-5 cigarette pack-years intervention 11%, comparator 8%; smoking history 6 or more cigarette pack-years intervention 11%, comparator 38% Key exclusions: People with contraindications to prone positioning (e.g. unable to self-turn, spinal instability, facial or pelvic fractures, open chest or abdomen, altered mental status, anticipated difficult airway, signs of respiratory fatigue, or receiving end-of-life care)	Corticosteroids n= 19 (70%), remdesivir n= 10 (37%), Convalescent plasma n= 1 (4%) Quantitative data collected at time of eligibility, 48 hours, and hospital discharge	Corticosteroids n= 9 (69%), remdesivir n= 5 (38%), Convalescent plasma n=2 (15%)	Anterior pressure wound Loss of intravenous catheter Emergent intubation outside of ICU

The duration of time that people spent in the awake prone position varied between the included trials. Details are presented in Table 2 below.

Table 2. Awake prone positioning in included studies

Study	Intervention duration	Adherence details	Proning undertaken	Notes
Ehrmann et al. 2021	Patients in the awake prone positioning group were instructed and assisted to lie in the prone position for as long and as frequently as possible each day.	In the standard care group, one patient out of ten underwent awake prone positioning. These protocol violations could have led to an underestimation of the efficacy of awake prone positioning in the intention-to-treat population.	In the intervention group, the median daily duration of awake prone positioning (recorded until day 14) was 5.0 h per day	
Fralick et al. 2021	There was no expected duration of proning.	A measure of adherence was not provided.	Of the patients randomised to prone positioning, the median total time spent in prone position up to the first 72 hours was 6 hours [IQR 1.5,12.8] and 0 hours [IQR 0,2] in the control arm. After accounting for hospital discharge within the first 72 hours, on a per day basis this equated to approximately 2.5 hours per day in the	Investigators noted that non-adherence was high.

			prone arm compared to 0 hours per day in the control arm in the first 72 hours.	
Jayakumar et al. 2021	Patients were encouraged by bedside nurses to lie prone for a minimum of 6 hours in a day.	The primary outcome of adherence to protocol was 43% among the patients in the prone group (13 patients completed an average of at least 6 hours a day in prone position).	70% of the patients in the prone group were able to lie prone for 4 hours a day. The median maximum duration per session in the prone group was 2 hours. In the control group, 53% spent some hours proned (but none above 6 hours).	
Kaur et al. 2021	Patients were instructed to maintain prone positioning as long as tolerated.	13 were excluded due to being self-proned for less than one hour = non-adherence rate of 9.4%	The early awake prone positioning (APP) group spent a median of 5.07 h/day and the late group spent a median of 3 h/day in the prone position.	
Kharat et al. 2021	Self-proning for 12 h per day as an addition to usual care for 24 h. It was suggested that patients use their mobile phone 'timer' function to alternate body position every 4 h. Nurses regularly visited patients to encourage them to change their bed position during their rounds.	Not reported	Estimated self-prone time was 295±216 min in the self-prone group and 7±29 min in the control group (due to a single patient who spent an estimated time of 120 min in the position).	Aim was 12 hours of proning but an average of 4.5 hours was achieved.

Rosen 2021	A protocol targeting at least 16 h APP per day was initiated.	Not reported.	Median of 9 hours per day in intervention group. Median of 3.4 hours per day in control group.	Despite not measuring adherence, the investigators stated that non-adherence was high.
Taylor 2021	Patients were encouraged to sustain the prone position as long as possible but were allowed to return to the supine position as necessary.	63% non-adherence in the intervention arm.	Only 10/27 in intervention arm attempted proning. 3/13 in usual care attempted proning.	23% of participants in the usual care arm attempted the prone position within 48 hours compared to 37% in the intervention arm.

See appendix F for full evidence tables.

Results

What is the effectiveness of body positioning in awake patients with COVID-19 in preventing intubation or death?

Awake prone positioning reduced the need for intubation and increased time to intubation in people in hospital with COVID-19 compared with standard care. No other benefits in outcomes from awake prone positioning were observed compared with standard care.

What is the evidence informing this conclusion?

Evidence comes from 1 meta-trial of 6 RCTs (Ehrmann et al. 2021), 2 cluster RCTs (Kharat et al., 2021; Taylor et al. 2021), 3 individually randomised RCTs (Fralick et al. 2021; Jayakumar et al. 2021; Rosen et al. 2021) and 1 post hoc analysis of an RCT included in the meta-trial (Kaur et al. 2021).

The numbers of people included in the trials ranged from 27 (Kharat et al. 2021) to 1,121 (Ehrmann et al. 2021).

The trials were conducted in hospitals, with 1 study based in intensive care (Jayakumar et al. 2021). In the Ehrmann et al. trial only 5% of people were in general wards at enrolment (with 95% in ICU/intermediate care/emergency department). Just under half (47%) of people were based in ICU in the study by Rosen et al. (2021).

No studies were UK-based. Studies were based in Canada, France, Ireland, Mexico, USA, Spain (Ehrmann et al. 2021), Canada and USA (Fralick et al. 2021), India (Jayakumar et al. 2021), Switzerland (Kharat et al. 2021), Sweden (Rosen et al. 2021), and the USA (Taylor et al. 2021).

All studies compared prone positioning with standard care.

Publication status

One study was only available as a preprint (Fralick et al., 2021 (COVID-PRONE), posted to medRxiv on November 8 2021) and therefore has not been peer-reviewed.

Study characteristics

The average age of people included in the trials ranged from 54 years (Kharat et al. 2021, intervention group) to 66 years (Rosen et al. 2021, intervention group). People included in the trials were mostly males. Children and pregnant women were excluded (with the exception of Fralick et al. 2021 that did not explicitly state that children were excluded and Fralick et al. 2021 and Taylor et al. 2021, where it was not reported whether pregnant women were excluded).

The amount of time people were able to be in the awake prone position varied between and within the included studies.

The types of oxygen support used also varied between the included studies.

What are the main results?

There was a significant reduction in the number of people requiring intubation and increase in the time to intubation for people who were in the awake prone positioning group compared with standard care.

No significant differences were seen in people who were in the awake prone position compared with standard care in mortality, time to death, intubation within 30 days after enrolment, time from enrolment to invasive mechanical ventilation, ventilator-free days, mechanical ventilation (intubation or bilevel positive airway pressure), use of non-invasive ventilation, time from enrolment to non-invasive ventilation, hospital length of stay, ICU admission, ICU length of stay, or all types of adverse events combined.

A post hoc analysis (Kaur et al. 2021) of 1 of the RCTs included in the meta-trial by Ehrmann et al. 2021 indicated that early awake prone positioning (within 24 hours of high flow nasal cannula initiation) reduced mortality but not intubation or other outcomes compared with later awake prone positioning.

Our confidence in the results

All studies were rated at high risk of bias. The certainty of evidence ranged from low to very low. All outcomes were downgraded for risk of bias. Most studies were downgraded at least once for imprecision.

Evidence to decision

Benefits and harms

The panel discussed the evidence from the 7 included studies on awake prone positioning in non-intubated people in hospital with COVID-19 and higher oxygen requirements.

They agreed that the available studies showed that awake prone positioning reduced intubation rates and increased the median time to intubation compared with standard care but that there were no benefits in the other outcomes studied.

The evidence did not show increased harms overall from awake prone positioning compared with standard care. However, the panel noted that there was a lack of patient-reported outcome measures in the trials.

The panel were aware that longer duration of prone positioning sessions may result in clinical benefits.

The panel noted that no studies were from the UK and that available details on ethnicity were limited in the trials. The low adherence and variability in the duration of proning sessions within and between trials were also commented upon. The reported details available in the trials for standard care, for example body positioning, and on patient preferences were limited. The panel were aware that the largest available trial (Ehrmann et al. 2021) was in people mostly in intensive care, intermediate care, or the emergency department who were receiving high-flow nasal oxygen. The panel considered it uncertain whether the findings from the evidence would be generalisable to a general ward setting.

The panel agreed that more research is needed to guide treatment and made a research recommendation for trials done in the UK with a focus on patient-reported outcomes.

Certainty of the evidence

The panel noted that the certainty of evidence was low to very low for all outcomes. Reasons for downgrading evidence included risk of bias (with all studies rated at high risk of bias for reasons that included a lack of blinding and issues with protocol adherence) and imprecision (with outcomes rated as having serious imprecision when the confidence interval crossed the line of no effect and outcomes further downgraded as having very serious imprecision when fewer than 300 people contributed to the outcome).

The study by Fralick et al (2021) was only available as a preprint and so had not been peer reviewed.

Values and preferences

The panel noted that the available evidence showed benefits from awake prone positioning in reducing intubation rates. It is likely that this outcome would be of similar importance to patients.

Resources

Some people may need support from healthcare professionals to move in and out of a prone position. It was noted that early prone positioning and longer duration of prone positioning sessions may be beneficial but that there should be appropriate observation and monitoring for safety during prone positioning. The panel commented that the need for healthcare professionals to provide additional support for prone positioning could divert them away from other clinical activities. It was also noted that some people who self prone may not respond and others may deteriorate and so usual resources, including access to escalation (for example, to higher levels of respiratory support including urgent intubation) should be available for people who are considered for escalation.

The panel also noted that some people may find it physically uncomfortable to be in a prone position (for example, people with recent abdominal wounds) and may require additional pillows to be available to provide support. Some people may prefer an alternative position such as lateral (side) lying or sitting out in a chair.

Cost effectiveness was not assessed as part of this evidence review.

Equity

All trials were in adults (except for the trial by Fralick et al. 2021 that did not state whether children were eligible). Although there are no sufficient data on awake prone positioning in children with COVID-19, it was noted that there is evidence of benefit in other causes of acute respiratory distress syndrome.

Pregnant women were excluded in the trials (except for 2 trials [Fralick et al. 2021 and Taylor et al. 2021] where it was not reported whether pregnant women were excluded). The recommendation includes a link to information on body positioning provided by the Royal College of Obstetricians and Gynaecologists.

Some people may not be able to physically move into and out of a prone position by themselves especially when ill. This could include people with mobility issues, chronic disabilities, learning disabilities, attention deficit disorder, people who are very underweight or morbidly obese (BMI > 40), or people with cognitive impairment. If proning was considered suitable, these people would require the availability of healthcare professionals to support them in moving in and out of a prone position.

The panel did not raise any additional concerns.

Acceptability

The panel commented that the ability of people with COVID-19 to move into and out of a prone position is likely to vary. They discussed that prone positioning may not be suitable for some people and some may prefer alternative body positioning, for example right and left side lying or being seated in a chair. The panel noted the issues with adherence to prone positioning in the trials and that there was some evidence of mild position-related discomfort from awake prone positioning.

The panel also commented on the need for published trials to include patient-reported outcomes (such as anxiety and breathlessness) and included this in a research recommendation

Feasibility

The panel noted that how well people can tolerate prone positioning and how long they can be in a prone position can vary. Some people may require the availability of additional support from healthcare professionals to move into and out of a prone position. Some may find it uncomfortable to remain in a prone position for an extended length of time. Different physical modalities of non-invasive respiratory support and the position of intravenous cannulae or other lines may also affect comfort, adverse events, and the ability to be in a prone position.

Appendices

Appendix A: PICO table

Population	People in hospital with suspected or confirmed COVID-19 who are awake and non-intubated with higher oxygen requirements (including people on a reservoir mask or simple facemask at a high flow rate and people on non-invasive respiratory support).
Intervention	Body positioning, including: • Awake prone positioning • Left / right lateral positioning • "Rodin's thinker" pose
Comparators	• Usual care • A different specified position
Outcomes	• Mortality • Intubation • Time to non-invasive respiratory support • Length of hospital stay • Admission to ICU • Complications (for example: pneumothorax, pneumomediastinum, delirium, intolerance of positioning or haemodynamic instability) • Composites such as ventilator-free days or organ support-free days • Duration of non-invasive respiratory support • Patient reported outcomes including pain, discomfort, breathlessness, anxiety, impact on sleep
Subgroups	• Type of supplementary respiratory support (for example: nasal cannula, face mask) • Mean prone duration • People on general wards, and those with do-not-intubate goals of care • Frailty • Obesity • Pregnant women
Study design	The following study design types for this question are preferred. Where these studies are not identified, other study designs (including prospective and retrospective observational studies) will be considered: • RCTs • Systematic reviews of RCTs and observational studies

Appendix B: Literature search strategy/Data source

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.

NICE (15 October 2020) Developing NICE guidelines: the manual. Process and methods [PMG20]. Appendix L: Interim process and methods for guidelines developed in response to health and social care emergencies
A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 5th January 2022. This search report is compliant with the requirements of PRISMA-S.
The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist. .
The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results daily. Individual topic searches were conducted within EPPI Reviewer to get round the limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.
Limits to exclude letters, comments, editorials, case reports and animal studies were applied in adherence to standard NICE practice and the review protocol.
The search was limited from 2020 to date as defined in the review protocol.
The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters

- Covid-19 filter

The development of NICE's main database search strategy for COVID-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

- RCT filters:
    - McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.
      Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

    - McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

      Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. Journal of the Medical Library Association, 94(1), 41-47.

- Systematic reviews filters:
    - Lee, E. et al. (2012) An optimal search filter for retrieving systematic reviews and meta-analyses. *BMC Medical Research Methodology,* 12(1), 51.

      In MEDLINE, the standard NICE modifications were used: pubmed.tw added; systematic review.pt added from MeSH update 2019.

      In Embase, the standard NICE modifications were used: pubmed.tw added to line medline.tw.

Main search – Databases

Database	Date searched	Database platform	Segment	No. of results

MEDLINE ALL	05/01/2022	Ovid	Ovid MEDLINE(R) ALL <1946 to January 04, 2022>	81
Embase	05/01/2022	Ovid	Embase <1974 to 2022 January 04>	136
EMcare	05/01/2022	Ovid	Ovid Emcare 1995 to 2021 Week 52	49
Cochrane – CENTRAL	05/01/2022	Wiley	*Cochrane* Central Register of Controlled Trials Issue 12 of 12, December 2021	30
MedRxiv/BioRxiv/Europe PMC/NIH Portfolio Preprints [EPPI review]	05/01/2022	N/A	last modified 05/01/2022	41
WHO Covid-19 Database	05/01/2022	N/A	N/A	92

Search strategy history

Database name: MEDLINE ALL

1 SARS-CoV-2/ or COVID-19/ (130925)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw,kf. (4580)
3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab,kw,kf. (73163)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw,kf. (223095)
5 or/1-4 (229250)
6 exp Posture/ (77298)
7 Patient Positioning/ (7455)
8 Wakefulness/ (19219)
9 ((position* or pose*) adj3 (body or bodies or lateral* or prone* or awake* or sit or sitting or seated or tripod or supine or fac* down or ventral or recumbent)).ti,ab. (39950)
10 proning.ti,ab. (202)
11 (rodin* adj2 (thinker or pose* or position*)).ti,ab. (5)
12 or/6-11 (127203)
13 5 and 12 (864)
14 randomized controlled trial.pt. (554806)
15 randomi?ed.mp. (977644)
16 placebo.mp. (231783)
17 or/14-16 (1039571)
18 (MEDLINE or pubmed).tw. (261208)
19 systematic review.tw. (208883)
20 systematic review.pt. (180902)
21 meta-analysis.pt. (149880)

22 intervention*.ti. (173304)
23 or/18-22 (565966)
24 17 or 23 (1453721)
25 13 and 24 (91)
26 limit 25 to yr="2020 -Current" (91)
27 (26 and english.lg.) not (letter or historical article or comment or editorial or news or case reports).pt. not (Animals/ not humans/) (81)

Database name: Embase

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (186022)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (4178)
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (64981)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (226290)
5 or/1-4 (242545)
6 exp body position/ (116465)
7 patient positioning/ (21670)
8 wakefulness/ (36073)
9 ((position* or pose*) adj3 (body or bodies or lateral* or prone* or awake* or sit or sitting or seated or tripod or supine or fac* down or ventral or recumbent)).ti,ab. (59094)
10 proning.ti,ab. (466)
11 (rodin* adj2 (thinker or pose* or position*)).ti,ab. (6)
12 or/6-11 (200972)
13 5 and 12 (2072)
14 random:.tw. (1738844)
15 placebo:.mp. (486799)
16 double-blind:.tw. (226296)
17 or/14-16 (2003904)
18 (MEDLINE or pubmed).tw. (325400)
19 exp systematic review/ or systematic review.tw. (391179)
20 meta-analysis/ (233551)
21 intervention*.ti. (228989)
22 or/18-21 (794013)
23 17 or 22 (2550045)
24 13 and 23 (186)
25 limit 24 to yr="2020 -Current" (182)
26 (25 and english.lg.) not (letter or editorial or conference).pt. (136)

Database name: EMcare

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ (54692)
2 (corona* adj1 (virus* or viral*)).ti,ab,kw. (972)
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab,kw. (14279)
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab,kw. (72926)
5 or/1-4 (77411)
6 exp body position/ (50690)
7 patient positioning/ (9528)

8 wakefulness/ (8041)
9 ((position* or pose*) adj3 (body or bodies or lateral* or prone* or awake* or sit or sitting or seated or tripod or supine or fac* down or ventral or recumbent)).ti,ab. (16204)
10 proning.ti,ab. (114)
11 (rodin* adj2 (thinker or pose* or position*)).ti,ab. (2)
12 or/6-11 (72915)
13 5 and 12 (681)
14 random:.tw. (513232)
15 placebo:.mp. (121429)
16 double-blind:.tw. (53965)
17 or/14-16 (573018)
18 (MEDLINE or pubmed).tw. (123479)
19 exp systematic review/ or systematic review.tw. (160366)
20 meta-analysis/ (72431)
21 intervention*.ti. (104220)
22 or/18-21 (313612)
23 17 or 22 (792390)
24 13 and 23 (53)
25 limit 24 to yr="2020 -Current" (52)
26 (25 and english.lg.) not (letter or editorial or conference).pt. (49)

Database name: Central Register of Controlled Trials

#1 MeSH descriptor: [SARS-CoV-2] this term only 627
#2 MeSH descriptor: [COVID-19] this term only 1042
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 292
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 614
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or covid19 or covid-19 or covid):ti,ab,kw 9401
#6 {OR #1-#5} 9453
#7 MeSH descriptor: [Posture] explode all trees 4441
#8 MeSH descriptor: [Patient Positioning] this term only 556
#9 MeSH descriptor: [Wakefulness] this term only 1037
#10 ((position* or pose*) near/3 (body or bodies or lateral* or prone* or awake* or sit or sitting or seated or tripod or supine or fac* down or ventral or recumbent)):ti,ab 9863
#11 proning:ti,ab 40
#12 (rodin* near/2 (thinker or pose* or position*)):ti,ab 0
#13 {OR #7-#12} 14332
#14 #6 and #13 with Publication Year from 2020 to 2021, in Trials 147
#15 "conference":pt or (clinicaltrials or trialsearch):so 582582
#16 #14 not #15 30

Database name: Pre-prints - medRxiv and bioRxiv/ Europe PMC/NIH Portfolio

These were searched via EPPI reviewer v5 using filters Title and Abstract HAS ALL and AND Title and Abstract HAS ANY.
Search terms combined terms Position, pose, body, bodies, lateral, prone, awake, sit, sitting, seated, tripod, supine, ventral ,recumbent, proning, Rodin

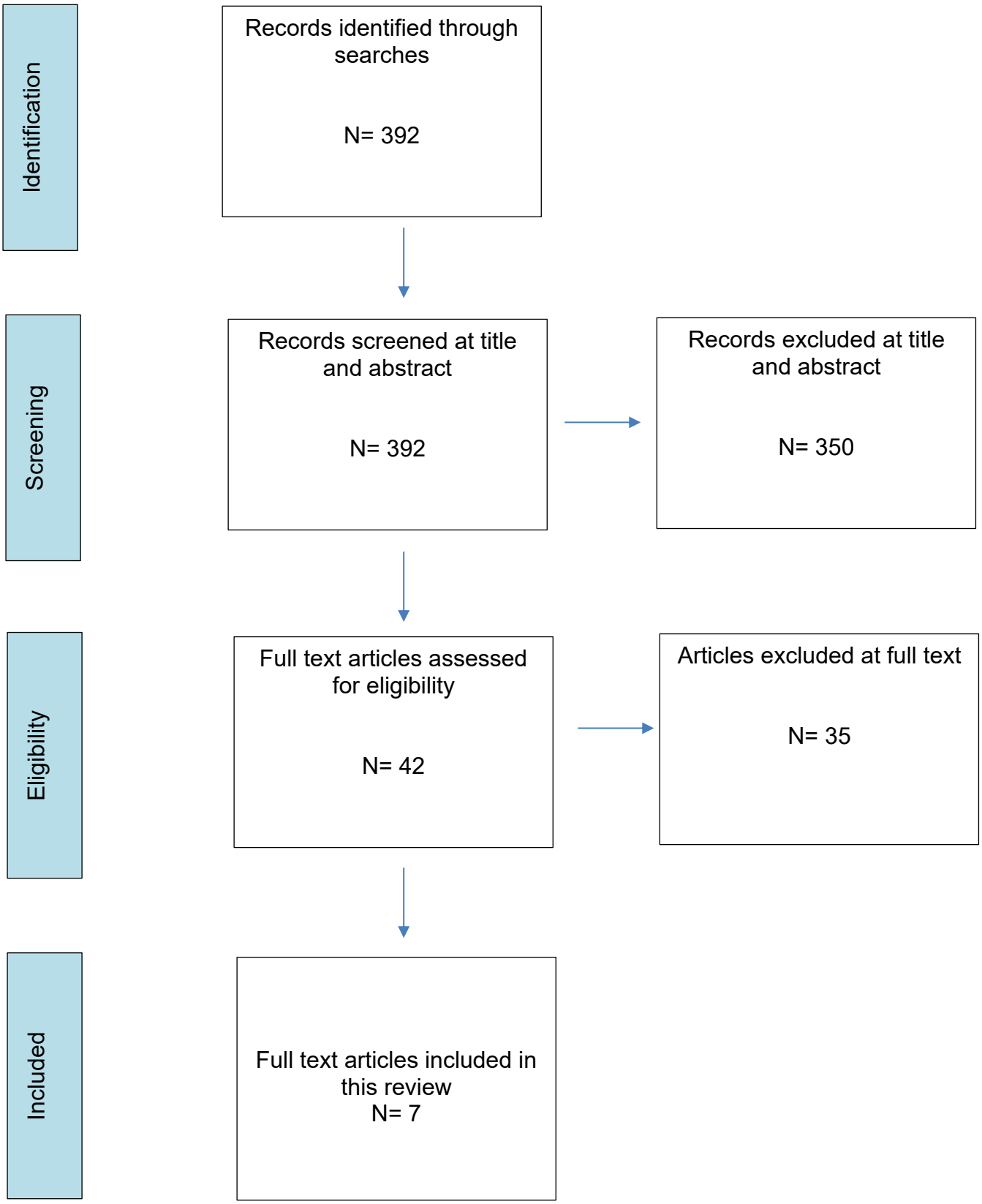
Database name: World Health Organisation Covid-19 database

tw:((tw:((position OR pose))) AND (tw:((body OR bodies OR lateral OR prone OR awake OR sit OR sitting OR seated OR tripod OR supine OR ventral OR recumbent)))) AND type:("article" OR "preprint" OR "non-conventional") AND type_of_study:("clinical_trials" OR "systematic_reviews" OR "policy_brief") AND (year_cluster:[2020 TO 2022])

tw:(proning) AND type:("article" OR "preprint") AND type_of_study:("clinical_trials" OR "systematic_reviews" OR "policy_brief") AND (year_cluster:[2020 TO 2022])

(tw:((thinker or pose* or position*))) AND (tw:(rodin)) – 1 result (not downloaded because picked up in results because Rodin one of authors, not RCT/SR/controlled studies)

Appendix C: PRISMA diagram



Appendix D: Included studies

Ehrmann, Stephan, Li, Jie, Ibarra-Estrada, Miguel et al. (2021) Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. The Lancet. Respiratory medicine

Fralick, Mike, Colacci, Michael, Munshi, Laveena et al. Prone positioning of patients with moderate hypoxia due to COVID-19: A multicenter pragmatic randomized trial. medrxiv preprint

Jayakumar, Devachandran, Ramachandran Dnb, Pratheema, Rabindrarajan Dnb, Ebenezer et al. (2021) Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection-A Multicenter Feasibility Randomized Controlled Trial. Journal of intensive care medicine: 8850666211014480

Kaur, Ramandeep, Vines, David L, Mirza, Sara et al. (2021) Early versus late awake prone positioning in non-intubated patients with COVID-19. Critical care (London, England) 25(1): 340

Kharat, Aileen, Dupuis-Lozeron, Elise, Cantero, Chloe et al. (2021) Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. ERJ open research 7(1)

Rosen, Jacob, von Oelreich, Erik, Fors, Diddi et al. (2021) Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. Critical care (London, England) 25(1): 209

Taylor, Stephanie Parks, Bundy, Henry, Smith, William M et al. (2020) Awake-Prone Positioning Strategy for Non-Intubated Hypoxic Patients with COVID-19: A Pilot Trial with Embedded Implementation Evaluation. Annals of the American Thoracic Society

Appendix E: Excluded studies at full text screening

Study	Code [Reason]
Adeola, Janet O, Patel, Shivani, Gone, Evelyne N et al. (2021) A Quick Review on the Multisystem Effects of Prone Position in Acute Respiratory Distress Syndrome (ARDS) Including COVID-19. Clinical medicine insights. Circulatory, respiratory and pulmonary medicine 15: 11795484211028526	- Review article but not a systematic review
Aditianingsih, Dita, Sugiarto, Adhrie, Manggala Sidharta, Kusuma et al. Prone Versus Supine Position in Intubated COVID-19 Patients With ARDS: A Systematic Review and Meta-Analysis.	- More recent systematic review included that covers the same topic
Aditianingsih, Dita, Sugiarto, Adhrie, Manggala Sidharta, Kusuma et al. (2021) Prone Versus Supine Position in Intubated COVID-19 Patients With ARDS: A Systematic Review and Meta-Analysis .	- More recent systematic review included that covers the same topic
Allicock, Karen A., Coyne, Danielle, Garton, Anna N. et al. (2021) Awake Self-Prone Positioning: Implementation During the COVID-19 Pandemic. Critical care nurse 41(5): 23-33	- Not a relevant study design
Awad, M. T., Ghazaleh, S., Khader, Y. et al. (2021) Efficacy of early prone position on non-intubated COVID-19 patients with respiratory failure-a systemic review and meta-analysis. American Journal of Respiratory and Critical Care Medicine 203(9)	- Conference abstract
Beran, Azizullah, Mhanna, Mohammed, Srour, Omar et al. (2021) Effect of Prone Positioning on Clinical Outcomes of Non-Intubated Subjects with COVID-19: A Comparative Systematic Review and Meta-Analysis. Respiratory care	- More recent systematic review included that covers the same topic
Cantero, Chloe, Kharat, Aileen, Lador, Frederic et al. (2021) Self-proning in covid-19 patients on low-flow oxygen therapy: A cluster randomised controlled trial. ERJ Open Research 7(1): 00692-2020	- Duplicate reference *Duplicate of included RCT (Kharat et al. 2021)*
Carpio-Orantes, L. D., González-Segovia, O., Mojica-Ríos, F. et al. (2021) Severe pneumonia due to COVID-19 cured with conscious proning and tocilizumab. A report of a case and review of the pharmacological therapeutic evidence. Medicina Interna de Mexico 34(4): 585-595	- Not a relevant study design (RCTs included)
Chad, Thomas and Sampson, Caroline (2020) Prone positioning in conscious patients on medical wards: A review of the evidence and its	- Not a relevant study design

Study	Code [Reason]
relevance to patients with COVID-19 infection. Clin Med (Lond) 20(4): e97-e103	
Chua, E. X., Wong, Z. Z., Hasan, M. S. et al. (2021) Effect of prone versus supine ventilation in intubated COVID-19 patients: A systematic review and meta-analysis. Anesthesia and Analgesia 133(3suppl2): 1927-1927	- Not eligible study population (intubated)
Dong, Wei, Gong, Yiping, Feng, Juan et al. Early Awake Prone and Lateral Position in Non-intubated Severe and Critical Patients with COVID-19 in Wuhan: A Respective Cohort Study. medrxiv preprint	- Not a relevant study design (RCTs included)
Ferrando, Carlos, Mellado-Artigas, Ricard, Gea, Alfredo et al. (2020) Awake prone positioning does not reduce the risk of intubation in COVID-19 treated with high-flow nasal oxygen therapy: a multicenter, adjusted cohort study. Crit Care 24(1): 597-597	- Not a relevant study design (RCTs included)
Geloso, A., Santa Cruz, R., Gonzalez, L. et al. (2021) Analytic review and meta-analysis of awake prone positioning in patients with Covid-19. Medicina Intensiva	- Not a relevant study design
Izdebski, Adam, Thoral, Patrick, Lalisang, Robbert et al. A pragmatic approach to estimating average treatment effects from EHR data: the effect of prone positioning on mechanically ventilated COVID-19 patients.	- Not a relevant study design *Not RCT*
Jayakumar, Devachandran Ramachandran Pratheema Rabindrarajan Ebenezer Tirupakuzhi Vijayaraghavan Bharath Kumar Ramakrishnan Nagarajan Venkataraman Ramesh (2021) Standard care vs. awake prone position in adult non-intubated patients with acute hypoxaemic respiratory failure secondary to COVID-19 infection ? A multi-centre feasibility randomized controlled trial.	- Duplicate reference *Pre-print of a study that has now fully published.*
Jayakumar, Devachandran, Ramachandran, Pratheema, Rabindrarajan, Ebenezer et al. Awake prone position in adult nonintubated patients with acute hypoxaemic respiratory failure secondary to COVID-19:A multi-centre feasibility randomized controlled trial. medrxiv preprint	- Duplicate reference *Preprint of included final publication*
Johnson, SA, Horton, DJ, Fuller, MJ et al. (2021) Patient-directed prone positioning in awake patients with COVID-19 requiring hospitalization (PAPR). Annals of the american thoracic society 18(8): 1423-1426	- Not a relevant study design *Letter to editor. Outcomes either not eligible or already covered by other included RCTs.*

Study	Code [Reason]
Karpov, A., Mitra, A.R., Crowe, S. et al. (2020) Prone Position after Liberation from Prolonged Mechanical Ventilation in COVID-19 Respiratory Failure. Critical Care Research and Practice 2020: 6688120	- Study does not contain a relevant intervention
Kluge, Stefan, Malin, Jakob J., Fichtner, Falk et al. (2021) Recommendations on the In-Hospital Treatment of Patients With COVID-19. Deutsches Arzteblatt international	- Not a relevant study design
Kollias, Anastasios, Kyriakoulis, Konstantinos G, Rapti, Vasiliki et al. (2022) Prone Positioning in Patients With COVID-19: Analysis of Multicenter Registry Data and Meta-analysis of Aggregate Data. In vivo (Athens, Greece) 36(1): 361-370	- Not a relevant study design (RCTs included)
Menga, Luca S, Berardi, Cecilia, Ruggiero, Ersilia et al. (2022) Noninvasive respiratory support for acute respiratory failure due to COVID-19. Current opinion in critical care 28(1): 25-50	- Review article but not a systematic review
Otáhal, Michal, Mlček, Mikuláš, Borges, João Batista et al. Prone Positioning May Increase Lung Overdistension in COVID-19-Induced ARDS.	- Not a relevant study design
Page David, B, Vijaykumar, Kadambari, Russell Derek, W et al. (2021) Prolonged Prone Positioning for COVID-19-induced Acute Respiratory Distress Syndrome: : A Randomized Pilot Study. Annals of the American Thoracic Society	- Not an eligible study population *Eligible people in this study were endotracheally intubated. No data reported for non-intubated people.*
Pavlov, Ivan, He, Hangyong, McNicholas, Bairbre et al. (2021) Awake prone positioning in non-intubated patients with acute hypoxemic respiratory failure due to COVID-19: A systematic review of proportional outcomes comparing observational studies with and without awake prone positioning in the setting of COVID-19. Respiratory care	- More recent systematic review included that covers the same topic
Pb, Sryma, Mittal, Saurabh, Madan, Karan et al. (2021) Awake prone positioning in non-intubated patients for the management of hypoxemia in COVID-19: A systematic review and meta-analysis. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 91(2)	- More recent systematic review included that covers the same topic
Poon, Wynne Hsing, Ling, Ryan Ruiyang, Yang, Isabelle Xiaorui et al. (2021) Prone positioning during venovenous extracorporeal membrane oxygenation for acute respiratory distress	- More recent systematic review included that covers the same topic

Study	Code [Reason]
syndrome: a systematic review and meta-analysis. Critical Care 25(1): 292	
Pooni, Rajan S. (2020) Research in brief: Prone positioning in COVID-19: What's the evidence. Clin Med (Lond) 20(4): 369-369	- Not a relevant study design
Richards, Hayden, Robins-Browne, Karen, O'Brien, Troy et al. (2021) Clinical benefits of prone positioning in the treatment of non-intubated patients with acute hypoxic respiratory failure: a rapid systematic review. Emergency medicine journal : EMJ	- More recent systematic review included that covers the same topic
Ripoll-Gallardo, Alba, Grillenzoni, Luca, Bollon, Jordy et al. (2020) Prone Positioning in Non-Intubated Patients With COVID-19 Outside of the Intensive Care Unit: More Evidence Needed. Disaster Med Public Health Prep 14(4): e22-e24	- Not a relevant study design
Seckel, Maureen A. (2021) Awake Self-Prone Positioning and the Evidence. Crit Care Nurse 41(4): 76-79	- Not a relevant study design
Sodhi, Kanwalpreet and Chanchalani, Gunjan (2020) Awake Proning: Current Evidence and Practical Considerations. Indian J Crit Care Med 24(12): 1236-1241	- Not a relevant study design
Solverson, Kevin; Weatherald, Jason; Parhar, Ken Kuljit S. (2020) Tolerability and safety of awake prone positioning COVID-19 patients with severe hypoxemic respiratory failure. Canadian journal of anaesthesia = Journal canadien d'anesthesie	- Not a relevant study design
Somagutta, M. R., Pormento, M. K. L., Khan, M. A. et al. (2021) Awake self prone positioning outcomes in nonintubated COVID-19 patients. Critical Care Medicine 49(1suppl1): 118-118	- Not a relevant study design
Vollenberg, Richard, Matern, Philipp, Nowacki, Tobias et al. (2021) Prone Position in Mechanically Ventilated COVID-19 Patients: A Multicenter Study. Journal of clinical medicine 10(5)	- Not a relevant study design *Not RCT* - Not an eligible study population *Included patients were mechanically ventilated.*
Vollman, K. (2020) Implementing Prone Positioning in Your Unit: What Do You Need to Know?. CONNECT 14(3): 130-140	- Not a relevant study design

Appendix F: Evidence tables

Evidence tables

Ehrmann, 2021

Bibliographic Reference	Ehrmann, Stephan; Li, Jie; Ibarra-Estrada, Miguel; Perez, Yonatan; Pavlov, Ivan; McNicholas, Bairbre; Roca, Oriol; Mirza, Sara; Vines, David; Garcia-Salcido, Roxana; Aguirre-Avalos, Guadalupe; Trump Matthew, W; Nay, Mai-Anh; Dellamonica, Jean; Nseir, Saad; Mogri, Idrees; Cosgrave, David; Jayaraman, Dev; Masclans Joan, R; Laffey John, G; Tavernier, Elsa; Awake Prone Positioning, Meta-Trial; Group; Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial.; The Lancet. Respiratory medicine; 2021

Study details

Study design	Meta-trial
Trial registration (if reported)	6 RCTs: NCT04325906, NCT04347941, NCT04358939, NCT04395144, NCT04391140, and NCT04477655
Study start date	02-Apr-2020
Study end date	26-Jan-2021
Aim of the study	To assess efficacy of awake prone positioning to prevent intubation or death in patients with severe COVID-19
Country/ Geographical location	Canada, France, Ireland, Mexico, USA, Spain
Study setting	Hospitals Location at enrolment Intensive care unit intervention n= 336 (60%), control n=339 (61%) Intermediate care unit intervention n= 197 (35%), control n= 189 (34%) Emergency department intervention n= 5 (1%), control n= 5 (1%) General ward intervention n= 26 (5%), control n=24 (4%)
Population description	Adults requiring respiratory support with high-flow nasal cannula for acute hypoxaemic respiratory failure due to COVID-19. 99% confirmed COVID-19 in each group.

Inclusion criteria	Adults (>18 years old) with acute hypoxaemic respiratory failure due to proven (or highly clinically suspected, pending microbiological confirmation) COVID-19 pneumonia. Acute hypoxaemic respiratory failure defined as need for respiratory support with high-flow nasal cannula and ratio of peripheral arterial oxygen saturation (SpO2) to fraction of inspired oxygen (FiO2) [SpO2:FiO2] of 315 or less (equivalent to ratio of partial pressure of arterial oxygen [PaO2] to FiO2 [PaO2:FiO2] ≤300 mm Hg).
Exclusion criteria	People unable or refusing to provide informed consent, haemodynamically unstable, severely obese with BMI over 40 kg/m², pregnant, or contraindicated to awake prone positioning
Intervention/test/approach	Awake prone positioning (N=564) Patients instructed and assisted to lie in prone position for as long as possible and as frequently as possible each day. Duration of proning recorded by bedside nurses. HFNC initiated at maximally tolerated flow setting, and FiO2 titrated to maintain SpO2 90% to 95%. Use of NIV not included in the trial protocol but recorded prospectively. Awake prone positioning ceased upon weaning of HFNC (due to improved oxygenation defined in each trial), discharge from hospital, intubation, or death. Median daily duration of awake prone positioning (until day 14) = 5·0 hours (IQR 1·6–8·8) (varying between trials with median daily awake prone positioning duration of 1·6 hours in Spain to 8·6 h in Mexico) Glucocorticoids for treatment of COVID-19 n= 494 (88%)
Comparator (where applicable)	Standard care (N=557) Standard care with high-flow nasal cannula. Awake prone positioning as rescue intervention discouraged and recorded as protocol violation. Glucocorticoids for treatment of COVID-19 n= 492 (88%)
Methods for population selection/allocation	Randomisation using 1:1 computer-generated variable block size sequence. Allocation concealment at randomisation was ensured by an online randomisation system or with on-site opaque sealed envelopes, depending on the trial

Methods of data analysis	All analyses performed at individual patient level. All outcomes further analysed in subgroups determined a priori: severe (SpO2:FiO2 <190, equivalent to PaO2:FiO2 <150 mmHg22 at enrolment) versus less severe (SpO2:FiO2 ≥190, equivalent to PaO2:FiO2 ≥150 mmHg22 at enrolment) hypoxaemia.

Study arms

Prone (N = 564)

Standard care (N = 557)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 564)	Standard care (N = 557)
Age Mean (SD)	61.5 (13.3)	60.7 (14)
Gender % female No of events	n = 184 ; % = 33	n = 191 ; % = 34
% Male No of events	n = 380 ; % = 67	n = 366 ; % = 66
Ethnicity No of events	n = NR ; % = NR	n = NR ; % = NR
BMI kg/m2 Mean (SD)	29.7 (4.6)	29.7 (4.6)
Respiratory rate (breaths per min) Mean (SD)	24.7 (5.1)	24.9 (5.6)
Mean arterial pressure (mm Hg) Mean (SD)	88.2 (12.1)	87.4 (11.4)
SpO2:FiO2 Mean (SD)	147.9 (43.9)	148.6 (43.1)

Characteristic	Prone (N = 564)	Standard care (N = 557)
Mexico No of events	n = 216 ; % = 38	n = 214 ; % = 38
France No of events	n = 200 ; % = 35	n = 202 ; % = 36
USA No of events	n = 112 ; % = 20	n = 110 ; % = 20
Spain No of events	n = 17 ; % = 3	n = 13 ; % = 2
Ireland No of events	n = 12 ; % = 2	n = 12 ; % = 2
Canada No of events	n = 7 ; % = 1	n = 6 ; % = 1
Chronic heart disease Heart failure or coronary artery disease or hypertension No of events	n = 120 ; % = 21	n = 127 ; % = 23
Chronic lung disease Obstructive or restrictive lung disease No of events	n = 63 ; % = 11	n = 64 ; % = 12
Chronic kidney disease Estimated glomerular filtration rate <60 mL/min per 1·73 m² before hospital admission No of events	n = 45 ; % = 8	n = 35 ; % = 6
Severe liver disease Cirrhosis or portal hypertension with history of variceal bleeding, or liver disease with Child-Pugh score 10 or above No of events	n = 8 ; % = 1	n = 6 ; % = 1
Obesity No of events	n = 221 ; % = 39	n = 231 ; % = 42
Active malignancy No of events	n = 45 ; % = 8	n = 31 ; % = 6
Diabetes No of events	n = 176 ; % = 31	n = 173 ; % = 31

Characteristic	Prone (N = 564)	Standard care (N = 557)
Do not intubate order No of events	n = 44 ; % = 8	n = 44 ; % = 8

Outcomes

Treatment failure

Outcome	Prone, N = 564	Standard care, N = 557
Treatment failure at day 28 (intubation or death) No of events	n = 223 ; % = 40	n = 257 ; % = 46

Intubation

Outcome	Prone, N = 564	Standard care, N = 557
Intubation rate at day 28 No of events	n = 185 ; % = 33	n = 223 ; % = 40

Mortality

Outcome	Prone, , N = 564	Standard care, , N = 557
Mortality at day 28 (all patients) No of events	n = 117 ; % = 21	n = 132 ; % = 24

Mortality

Outcome	Prone vs Standard care
Mortality at day 28 (all patients) Relative risk/95% CI	0.87 (0.71 to 1.07)

Time to event analysis (median days)

Outcome	Prone, , N = 564	Standard care, , N = 557
Intubation Median (IQR)	2.3 (1.3 to 5)	2 (1 to 3.8)
Death Median (IQR)	12 (9 to 17)	14 (9.8 to 19)

Time to event analysis

Outcome	Prone vs Standard care
Intubation Hazard ratio/95% CI	0.75 (0.62 to 0.91)
Death Hazard ratio/95% CI	0.87 (0.68 to 1.11)

Hospital length of stay

Outcome	Prone, , N = 564	Standard care, , N = 557
Hospital length of stay (days) Mean (SD)	16.4 (10.5)	16.5 (9.7)

Adverse events

Outcome	Prone, , N = 564	Standard care, , N = 557
Skin breakdown No of events	n = 8 ; % = 1	n = 10 ; % = 2
Vomiting No of events	n = 15 ; % = 3	n = 18 ; % = 3
Central or arterial line dislodgement No of events	n = 26 ; % = 5	n = 17 ; % = 3
Cardiac arrest at any time No cardiac arrest occurred in prone position and no cardiac arrest during manoeuvres to move patients prone or supine. No of events	n = 3 ; % = 1	n = 1 ; % = 0

Use of non-invasive ventilation

Outcome	Prone, , N = 564	Standard care, , N = 557
Use of non-invasive ventilation No of events	n = 94 ; % = 17	n = 110 ; % = 20

Fralick et al.

Bibliographic Reference	Fralick, Mike; Colacci, Michael; Munshi, Laveena; Venus, Kevin; Fidler, Lee; Hussein, Haseena; Britto, Karen; Fowler, Rob; Costa, Bruno; da;

Dhalla, Irfan; Yaffe, Richard; Dunbar-Yaffe; Day, Laura; Branfield; MacMillan, Thomas; Zipursky, Jonathan; Carpenter, Travis; Tang, Terence; Cooke, Amanda; Hensel, Rachel; Bregger, Melissa; Gordon, Alexis; Worndl, Erin; Go, Stephanie; Mandelzweig, Keren; Castellucci, Lana; Tamming, Daniel; Razak, Fahad; Verma, Amol; Investigators, COVID; PRONE; Prone positioning of patients with moderate hypoxia due to COVID-19: A multicenter pragmatic randomized trial; medrxiv preprint

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04383613 (COVID-PRONE)
Study start date	May-2020
Study end date	May-2021
Aim of the study	To assess effectiveness of prone positioning for reduction of death or respiratory failure in non-critically ill patients hospitalised with COVID-19
Country/ Geographical location	Canada and USA (15 hospitals)
Study setting	Hospital
Population description	Hypoxic but not critically ill patients hospitalised with confirmed or suspected COVID-19 (N=248 in ITT analysis). 98% had PCR-confirmed COVID-19.
Inclusion criteria	People with laboratory-confirmed or clinically highly suspected diagnosis of COVID-19, need for supplemental oxygen (up to 50% fraction of inspired oxygen [FiO2]), and able to independently prone with verbal instruction
Exclusion criteria	Excluded if prone positioning contraindicated (e.g. recent abdominal surgery), or impractical (e.g. in people with dementia, severe delirium), or mechanical intubation indicated at time of randomisation according to treating physician
Intervention/test/approach	Prone positioning (N=126) Patients recommended to adopt a prone position four times per day (up to 2 hours per session) and encouraged to sleep in prone position overnight. Recommended for up to 7 days in hospital, until hospital discharge, or until the patient no longer required supplemental oxygen (whichever came first). Self-reported time spent in prone position assessed from time of randomisation to 72 hours, and from 72 hours until day 7. Patients followed until first of: death, hospital discharge or 30 days. Median total time in prone position to first 72 hours was 6 hours [IQR 1.5,12.8] in intervention group. After accounting for hospital discharge within the first 72 hours, approximately 2.5

	hours per day in the prone arm in the first 72 hours. From 72 hours to 7 days median 0 (IQR 0, 12) Dexamethasone n= 117 (92.9%), remdesivir n= 56 (44.4%), tocilizumab n= 0 (0%)
Comparator (where applicable)	Standard care (no instruction to prone position) (N=122) Median total time in prone position to first 72 hours was 0 hours [IQR 0,2] in control group. After accounting for hospital discharge within the first 72 hours, approximately 0 hours per day in the control arm in the first 72 hours. From 72 hours to 7 days median 0 (IQR 0, 0) Dexamethasone n= 119 (97.5%), remdesivir n= 48 (39.3%), tocilizumab n= 2 (1.6%)
Methods for population selection/allocation	Randomisation within 48 hours of hospitalisation. Median time from hospital admission until randomisation = 1 day. Randomised in 1:1 ratio (stratified by site) to prone position or standard care. Used web-based system On May 10, 2021, stopped clinical trial due to futility.
Methods of data analysis	Primary outcome controlled for age and sex in multivariable logistic regression model. Planned a priori subgroup analyses of the primary outcome: (1) severity of hypoxaemia at randomisation based on arterial blood gas, (2) age, (3) chest radiograph findings and (4) amount of supplemental oxygen at baseline prior to randomisation. Unable to perform the planned subgroup analysis based on severity of hypoxemia at randomisation as few patients had an arterial blood gas assessed or the analysis based on chest radiograph findings as almost all patients had abnormal chest x-ray. Time-to-hospital discharge was analysed using a Cox proportional hazards model that adjusted for age and sex. Post-hoc analysis to determine if longer time spent prone was associated with improved outcomes
Study limitations (Author)	Poor adherence to time spent prone. Expected event rate was lower than anticipated because the study was planned prior to effective treatments being available (e.g., dexamethasone, remdesivir, tocilizumab)
Other details	Trial stopped early due to futility for pre-specified primary outcome

Study arms

Prone (N = 126)

Control (N = 122)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 126)	Control (N = 122)
Age Median (IQR)	59.5 (45 to 68)	54 (44 to 62)
Gender % female No of events	n = 44 ; % = 34.9	n = 45 ; % = 36.9
Ethnicity No of events	n = NR ; % = NR	n = NR ; % = NR
Diabetes No of events	n = 36 ; % = 28.6	n = 31 ; % = 25.4
Hypertension No of events	n = 56 ; % = 44.4	n = 42 ; % = 34.4
Current smoker No of events	n = 0 ; % = 0	n = 7 ; % = 5.7
COPD or asthma No of events	n = 12 ; % = 9.5	n = 15 ; % = 12.3
Heart failure No of events	n = 4 ; % = 3.2	n = 2 ; % = 1.6
Lymphocyte count Median (IQR)	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.2)
Creatinine (umol/L) Median (IQR)	79 (66 to 97)	78 (65 to 94)

Characteristic	Prone (N = 126)	Control (N = 122)
Systolic BP (mm Hg) Median (IQR)	124 (116 to 135)	121 (112 to 130)
Oxygen saturation (%) Median (IQR)	94 (93 to 95)	94 (93 to 96)
FiO2 (%) Median (IQR)	32 (28 to 36)	32 (28 to 36)
S/F ratio Median (IQR)	303 (261 to 336)	305 (267 to 339)
Nasal prong No of events	n = 110 ; % = 87.3	n = 112 ; % = 91.8
high flow nasal cannula No of events	n = 5 ; % = 4	n = 2 ; % = 1.6
face mask No of events	n = 8 ; % = 6.3	n = 7 ; % = 5.7
Full code No of events	n = 113 ; % = 89.7	n = 116 ; % = 95.1
Do not resuscitate No of events	n = 5 ; % = 4	n = 0 ; % = 0
Other (unspecified) No of events	n = 7 ; % = 5.6	n = 6 ; % = 4.9

Outcomes

Mortality

Outcome	Prone, , N = 126	Control, , N = 122
Mortality No of events	n = 1 ; % = 0.8	n = 1 ; % = 0.8

Respiratory outcomes

Outcome	Prone, , N = 126	Control, , N = 122
Mechanical ventilation No of events	n = 6 ; % = 4.8	n = 5 ; % = 4.1

Discharge

Outcome	Prone, , N = 126	Control, , N = 122
Days to discharge Median (IQR)	5 (3 to 9)	4 (3 to 8)

Days to discharge

Outcome	Prone vs Control, , N2 = 126, N1 = 122
Days to discharge Hazard ratio/95% CI	0.91 (0.69 to 1.2)

Serious adverse events

Outcome	Prone, , N = 126	Control, , N = 122
Serious adverse events composite No of events	n = 5 ; % = 4	n = 3 ; % = 2.5
Aspiration pneumonia No of events	n = 2 ; % = 1.6	n = 1 ; % = 0.8
Venous thromboembolism No of events	n = 3 ; % = 2.4	n = 2 ; % = 1.6
Other (unspecified) No of events	n = 0 ; % = 0	n = 0 ; % = 0

Jayakumar, 2021

Bibliographic Reference	Jayakumar, Devachandran; Ramachandran Dnb, Pratheema; Rabindrarajan Dnb, Ebenezer; Vijayaraghavan Md, Bharath Kumar Tirupakuzhi; Ramakrishnan Ab, Nagarajan; Venkataraman Ab, Ramesh; Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection-A Multicenter Feasibility Randomized Controlled Trial.; Journal of intensive care medicine; 2021; 8850666211014480

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	Clinical trials registry of India (Ref. No. CTRI/2020/12/029702)

Aim of the study	To assess the use of prone positioning in non-intubated patients with COVID-19 pneumonia requiring supplemental oxygen
Country/ Geographical location	Chennai, India
Study setting	3 hospitals. Patients with PCR-confirmed COVID-19 pneumonia managed in designated locations in hospital. People requiring more than 4 litres/min of oxygen managed in areas capable of providing intensive care. People admitted to intensive care unit were screened for trial eligibility.
Population description	Non-intubated awake adults admitted to intensive care unit with acute hypoxic respiratory failure secondary to COVID-19 pneumonia requiring 4 or more litres of supplemental oxygen to maintain saturation of 92% and above.
Inclusion criteria	Patients 18 years of age and above requiring 4 or more litres per minute of supplemental oxygen to maintain SpO2 92% and above or if ABG was available, PaO2/FiO2 ratio between 100 and 300 mmHg (mild to moderate ARDS) with PaCO2 less than 45 mmHg were included. Patients with AHRF and hemodynamic shock requiring <0.1mcg/kg/min of norepinephrine also considered for inclusion.
Exclusion criteria	Patients below 18 years of age, pregnant women, patients with hemodynamic shock needing norepinephrine 0.1 mcg/ kg/min and above, GCS <15, patients requiring immediate intubation, patients with contraindications to prone positioning (spinal instability secondary to severe rheumatoid arthritis, life threatening cardiac arrhythmias)
Intervention/test/approach	Awake proning (patients encouraged by bedside nurses to lie prone for at least 6 hours a day (cumulative). Proning on NIV supported by use of standard pillows and C-pillow where required. Both groups received oxygen via nasal prongs, face mask, non-rebreather mask, high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) according to clinician discretion. Additional pillows provided for comfort. Proning sessions considered significant and recorded only lasted more than 30 minutes (for both groups). Protocol followed for 7 days or until escalation of respiratory support to the next level or patient improvement to discharge or death (whichever was first). 70% of patients in intervention group could lie prone for 4 hours a day. For intervention group, median maximum duration was 2 hours.

	Steroids n= 30 (100%), remdesivir n= 22 (73%), tocilizumab n= 6 (20%), heparin/low molecular weight heparin n= 30 (100%)
Comparator (where applicable)	Standard care. Patients able to change position according to their comfort (supine, semi-sitting, sitting or lateral). Patients permitted to lie prone based on comfort if they wished (but proning not actively encouraged by treating team in this arm). Both groups received oxygen via nasal prongs, face mask, non-rebreather mask, high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) according to clinician discretion. Oxygen flow and fraction of inspired oxygen (FiO2) titrated to maintain a saturation of 92% and above in both arms. Decisions to escalate respiratory support from initial device to a device higher and decision to intubate left to treating team. Patients on HFNC could be placed on noninvasive ventilation or intubated and mechanically ventilated. Patients on NRBM could be placed on HFNC, NIV or intubated. In supine group, 47% (14 out of 30) were completely supine. 53% spent some hours proned (but none above 6 hours). Steroids n= 30 (100%), remdesivir n= 23 (77%), tocilizumab n= 5 (17%), heparin/low molecular weight heparin n= 30 (100%)
Methods for population selection/allocation	Patients randomised in blocks of 4 using computerised random number generator. Allocation concealed using sealed opaque envelopes. Sites not aware of block sizes.
Attrition/loss to follow-up	None
Study limitations (Reviewer)	Neither participants nor the treating clinicians were blinded (due to type of intervention). The authors wrote: It was a feasibility study; therefore, the results are not powered to change practice. Second, it was not practically possible to collect the oxygenation data for every prone session; therefore, the protocol mandated a blood gas after 2 hours and twice daily blood gases thereafter to compute P/F ratios. This might not have accurately captured the improvement in oxygenation immediately after prone positioning. Third, only 43% could adhere to the protocol which required 6 hours of cumulative prone positioning in the prone group. Several factors like change in nursing ratios, the overwhelming clinical burden, the need for isolation and cohorting which restricts access to trial personnel could have contributed to this low adherence, but it is important to note that 73% (22 out of 30) managed 4 or more hours of prone position a day. Whether the use of positional aids or mattresses will facilitate prolonged prone positioning is unknown and yet to be evaluated. Fourth, 53% (16 out of 30) in the supine group spent some hours in the prone position. Although this is a significant cross over, none of the patients

	exceeded 6 hours of prone positioning amounting to protocol violation. Fifth, the patients selected had mild to moderate illness severity and this explains the low mortality rate overall in both the groups. Sixth, onset of illness was not a criterion for inclusion. Some of these patients might have had illnesses for longer periods than others. This might have affected the overall efficacy of the intervention.
Other details	Adherence to protocol (primary outcome) was 43% among the patients in the prone group (13 patients completed an average of 6 hours a day or more proned).

Study arms

Prone (N = 30)

Standard care (N = 30)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 30)	Standard care (N = 30)
Age (years) Mean (SD)	54.8 (11.1)	57.3 (12.1)
Gender Number of males No of events	n = 25 ; % = 83	n = 25 ; % = 83
Ethnicity No of events	n = NR	n = NR
BMI Mean (SD)	28.2 (5.7)	25.8 (2.6)
APACHE II score Mean (SD)	9.5 (3.6)	8.6 (3.1)
Diabetes No of events	n = 13 ; % = 43	n = 19 ; % = 63

Characteristic	Prone (N = 30)	Standard care (N = 30)
Hypertension No of events	n = 13 ; % = 43	n = 9 ; % = 30
Respiratory comorbidities (asthma, pulmonary fibrosis) No of events	n = 2 ; % = 7	n = 3 ; % = 10
Initial device: face mask No of events	n = 19 ; % = 63	n = 19 ; % = 63
Initial device: non-rebreather mask No of events	n = 7 ; % = 23	n = 11 ; % = 37
Initial device: high-flow nasal cannula No of events	n = 1 ; % = 3	n = 0 ; % = 0
Initial device: non-invasive ventilation No of events	n = 2 ; % = 7	n = 0 ; % = 0
Nasal prongs No of events	n = 1 ; % = 3	n = 0 ; % = 0
Initial FiO2 Mean (SD)	48.2 (18.6)	50.2 (20.8)
Initial P/F ratio Mean (SD)	201.4 (118.8)	185.6 (126.1)

Outcomes

Respiratory support

Outcome	Prone, , N = 30	Standard care, , N = 30
NIV No of events	n = 5	n = 1
Total number of patients intubated No of events	n = 4	n = 4

Respiratory escalation - Polarity - Lower values are better
Total number of patients intubated - Polarity - Lower values are better

Adverse events

Outcome	Prone, , N = 30	Standard care, , N = 30
Adverse events (unspecified) No of events	n = 0	n = 0
Adverse events (unspecified) P value	P=0.34	*empty data*

Adverse events (unspecified) - Polarity - Lower values are better

ICU length of stay

Outcome	Prone, , N = 30	Standard care, , N = 30
ICU length of stay Mean (SD)	11.53 (6.92)	9.97 (5.69)

ICU length of stay - Polarity - Lower values are better

Mortality

Outcome	Prone, , N = 30	Standard care, , N = 30
Mortality No of events	n = 3	n = 2
Mortality P value	P=1	*empty data*

Mortality - Polarity - Lower values are better

Kaur, 2021

Bibliographic Reference	Kaur, Ramandeep; Vines, David L; Mirza, Sara; Elshafei, Ahmad; Jackson, Julie A; Harnois, Lauren J; Weiss, Tyler; Scott, J Brady; Trump, Matthew W; Mogri, Idrees; Cerda, Flor; Alolaiwat, Amnah A; Miller, Amanda R; Klein, Andrew M; Oetting, Trevor W; Morris, Lindsey; Heckart, Scott; Capouch, Lindsay; He, Hangyong; Li, Jie; Early versus late awake prone positioning in non-intubated patients with COVID-19.; Critical care (London, England); 2021; vol. 25 (no. 1); 340

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	Post hoc analysis of data from 1 RCT (ClinicalTrials.gov NCT04325906) included in the meta-trial by Ehrmann et al. 2021
Study start date	02-Apr-2020
Study end date	26-Jan-2021

Aim of the study	To compare outcomes of COVID-19 patients who received early versus late APP
Country/ Geographical location	This post hoc analysis used the American RCT dataset
Population description	Adults with acute hypoxemic respiratory failure secondary to COVID-19 and ratio of saturation of pulse oximetry (SpO2) to the fraction of inspired oxygen (FiO2) <24 who had received awake prone positioning for at least one hour (N=125)
Inclusion criteria	Adults with acute hypoxemic respiratory failure secondary to COVID-19 who had received awake prone positioning for at least one hour
Intervention/test/approach	Early prone positioning defined as awake prone positioning initiated within 24 hours of high-flow nasal cannula start (N=92) Prone positioning under clinician supervision and patients instructed to maintain prone position for as long as tolerable. Median time from HFNC initiation to APP = 2.25 (0.8–12.82) hours. Median time to start APP from hospital admission = 18 hours Total APP hours in first three days, median (IQR) = 16 (5.4–51.5) Median (IQR) APP duration was 5.07 (2.0–9.05) hours per day. All received respiratory support via HFNC initiated at 50 L/min with FiO2 titrated to maintain SpO2 90 to 95%. HFNC stopped when the weaning criteria of FiO2 at 0.4 and flow at 40 L/min met. HFNC duration, days median (IQR) = 5 (2.2–9) Antiviral therapy n=65 (70.7 %) Steroid use n= 64 (69.6%)
Comparator (where applicable)	Late awake prone positioning (N=33)

	Median time from HFNC initiation to APP = 36.35 (30.2–75.23) hours (p<0.0001). Median time to start APP from hospital admission = 60 hours (p<0.001) Total APP hours in first three days, median (IQR) = 5 (2.5–17.5) (p=0.004) Median (IQR) APP duration was 3.0 (1.09–5.64) hours per day (p<0.0001). All received respiratory support via HFNC initiated at 50 L/min with FiO2 titrated to maintain SpO2 90 to 95%. HFNC stopped when the weaning criteria of FiO2 at 0.4 and flow at 40 L/min met. HFNC duration, days median (IQR) = 6 (3.2–10.5), P=0.18 Antiviral therapy n= 19 (57.6 %), P=0.12 Steroid use n= 29 (87.9%), P=0.039
Methods of data analysis	Patients who received APP for minimum of one hour included, irrespective of originally assigned group (APP or standard care). Subjects excluded if information on APP was missing
Other details	Older age (OR 1.12 [95% CI 1.0–1.95], p=0.001), intubation (OR 10.65 [95% CI 2.77–40.91], p=0.001), longer time to initiate APP (OR 1.02 [95% CI 1.0–1.04], p=0.047) and hydrocortisone use (OR 6.2 [95% CI 1.23–31.1], p=0.027) associated with increased mortality.

Study arms

Early prone (N = 92)

Late prone (N = 33)

Characteristics

Arm-level characteristics

Characteristic	Early prone (N = 92)	Late prone (N = 33)
Age Mean (SD)	61.1 (12.3)	64.9 (10.4)

Characteristic	Early prone (N = 92)	Late prone (N = 33)
Gender % male No of events	n = 56 ; % = 61	n = 23 ; % = 67
Hispanic/Latino No of events	n = 59 ; % = 64.1	n = 11 ; % = 33.3
Caucasian No of events	n = 22 ; % = 23.9	n = 15 ; % = 45.5
African American No of events	n = 5 ; % = 5.4	n = 2 ; % = 6.1
Asian No of events	n = 2 ; % = 2.2	n = 2 ; % = 6.1
Unknown No of events	n = 1 ; % = 1.1	n = 2 ; % = 6.1
Other (unspecified) No of events	n = 3 ; % = 3.3	n = 1 ; % = 3
Diabetes mellitus No of events	n = 17 ; % = 51.5	n = 37 ; % = 40.2
Chronic lung disease No of events	n = 10 ; % = 11	n = 7 ; % = 21
Cardiovascular disease No of events	n = 18 ; % = 19.6	n = 11 ; % = 33.3
Chronic renal disease No of events	n = 10 ; % = 10.9	n = 1 ; % = 3
Chronic liver disease No of events	n = 1 ; % = 1.1	n = 0 ; % = 0
Immunocompromised condition No of events	n = 11 ; % = 12	n = 5 ; % = 15
Neurologic disease No of events	n = 4 ; % = 4.3	n = 1 ; % = 3
Other (unspecified)	n = 23 ; % = 25	n = 2 ; % = 6.1

Characteristic	Early prone (N = 92)	Late prone (N = 33)
No of events		
Current smoker No of events	n = 4 ; % = 4.3	n = 0 ; % = 0
Former smoker No of events	n = 23 ; % = 25	n = 15 ; % = 45.5
Never No of events	n = 57 ; % = 62	n = 16 ; % = 48.5
Not available No of events	n = 8 ; % = 8.7	n = 2 ; % = 6
SOFA score on admission Median (IQR)	3 (2 to 4.75)	3 (3 to 4.5)
Assigned to APP group No of events	n = 88 ; % = 96	n = 13 ; % = 39
SpO2/FiO2 ratio on enrolment Median (IQR)	135 (116.2 to 166.5)	155 (131.6 to 188.5)

Outcomes

Mortality

Outcome	Early prone, , N = 92	Late prone, , N = 33
28 Day mortality No of events	n = 24 ; % = 26	n = 15 ; % = 45
28 Day mortality P value	NA	0.039
Death without intubation No of events	n = 7 ; % = 7.6	n = 6 ; % = 18.2
Death without intubation P value	NA	0.088

Length of stay

Outcome	Early prone, , N = 92	Late prone, , N = 33
Hospital length of stay (days) P value	NA	0.66
Hospital length of stay (days) Median (IQR)	13.97 (9.64 to 24.9)	12.53 (9 to 20.9)
ICU length of stay (days) P value	NA	*P=0.55*
ICU length of stay (days) Median (IQR)	7.91 (4.25 to 21)	8 (3.38 to 16.9)

Respiratory outcomes

Outcome	Early prone, N = 92	Late prone, N = 33
IMV use No of events	n = 34 ; % = 37	n = 14 ; % = 42.4
IMV use P value	NA	0.58
Time from HFNC start to intubation (days) P value	NA	0.65
Time from HFNC start to intubation (days) Median (IQR)	5.13 (1.89 to 10.85)	5.27 (3.2 to 9.56)
Time from APP start to intubation (days) P value	NA	0.37
Time from APP start to intubation (days) Median (IQR)	4.73 (1.85 to 10.6)	3.12 (1.31 to 8.23)
NIV use No of events	n = 23 ; % = 25	n = 5 ; % = 15.2
NIV use Custom value	NA	0.24

Inhaled vasodilator use

Outcome	Early prone, , N = 92	Late prone, , N = 33
Inhaled vasodilator use No of events	n = 26 ; % = 28.3	n = 9 ; % = 27.3
Inhaled vasodilator use P value	NA	0.28

Kharat, 2021

Bibliographic Reference	Kharat, Aileen; Dupuis-Lozeron, Elise; Cantero, Chloe; Marti, Christophe; Grosgurin, Olivier; Lolachi, Sanaz; Lador, Frederic; Plojoux, Jerome; Janssens, Jean-Paul; Soccal, Paola M; Adler, Dan; Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial.; ERJ open research; 2021; vol. 7 (no. 1)

Study details

Study design	Cluster randomised controlled trial
Trial registration (if reported)	Swiss National Clinical Trial portal (SNCTP000003718)
Study start date	06-Apr-2020
Study end date	29-May-2020
Country/ Geographical location	Geneva, Switzerland
Study setting	Medical hospital wards
Population description	People with confirmed COVID-19 pneumonia admitted to ward on low-flow oxygen therapy (N=27)
Inclusion criteria	People aged 18 years and above admitted to a medical ward with COVID-19 pneumonia on low-flow oxygen therapy (1 to 6 L·min−1) via nasal cannula to reach SpO2 level of 90–92%.
Exclusion criteria	People initially treated in ICU or high-dependency unit and recovering from ARDS, people with oxygen needs >6 L·min−1 via nasal cannula or >40% inspiratory oxygen fraction (FiO2) using a Venturi mask to reach SpO2 level of 90–92%, pregnant women, terminally ill people, those unable to self-prone.
Intervention/test/approach	Self-proning for maximum of 12 hours per day (N=10) plus standard care Intern and resident from division of lung diseases promoted self-proning for 12 h per day as addition to usual care for 24 h.

	Study investigators gave initial demonstration and then explanatory brochure including photographs of prone position, with suggestion to use mobile phone timer function to alternate body position every 4 hours. Regular encouragement from nurses to change bed position during rounds. Vital signs recorded after 24 hours with brief patient survey on tolerance and estimated time of proning. Time spend in prone position was self-reported by patients in a diary. Estimated prone time 295 ± 216 min Azithromycin n= 1 (10%), hydroxychloroquine n= 6 (60%), lopinavir/ritonavir n= 5 (50%)
Comparator (where applicable)	Standard care (N=17) Standard care comprised: 1) oxygen titration with nasal cannula according to institutional recommendations to reach SpO2 values between 90% and 94%. At least 6 routine nurse rounds per 24 hours to monitor oxygen requirements and adapt oxygen flow to target 2) empirical antibiotics for community-acquired pneumonia 3) hydroxychloroquine and lopinavir/ritonavir as proposed by institutional guidelines 4) restrictive fluid strategy. Estimated prone time 7 ± 29 min (due to single patient spending estimated time of 120 min in position) Azithromycin n= 1 (6%), hydroxychloroquine n=13 (77%), lopinavir/ritonavir n=10 (59%)
Methods for population selection/allocation	Single-centre cluster RCT. Randomisation unit was medical ward in division of internal medicine of hospital. 6 clusters selected and computer-generated randomisation assigned each medical ward randomly (1:1 ratio) to either intervention or standard care. After April 2020 most COVID-19 wards closed due to effective containment. 4 additional patients individually randomised by computer-generated programme in wards remaining open. Enrolment closed as no further eligible patients were admitted to the ward for COVID-19 pneumonia (despite not having met sample size calculation) (enrolment of 76 patients required in sample size calculation so underpowered).

	3 wards randomised to invitation to self-prone. 3 wards randomised to standard care. Unblinded. Patients screened by daily review of ward admissions.

Study arms

Prone (N = 10)

Standard care (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 10)	Standard care (N = 17)
Age (years) Mean (SD)	54 (14)	60 (11)
Gender Male No of events	n = 6 ; % = 60	n = 11 ; % = 65
Ethnicity No of events	n = NR ; % = NR	n = NR ; % = NR
BMI (kg/m2) Mean (SD)	29.7 (5.3)	27.3 (4.2)
Hypertension No of events	n = 3 ; % = 30	n = 9 ; % = 53
Diabetes No of events	n = 2 ; % = 20	n = 3 ; % = 18
Chronic kidney disease No of events	n = 0 ; % = 0	n = 1 ; % = 6
Self-reported heart disease No of events	n = 0 ; % = 0	n = 0 ; % = 0
COPD No of events	n = 0 ; % = 0	n = 0 ; % = 0

Characteristic	Prone (N = 10)	Standard care (N = 17)
Time onset of symptoms until inclusion (days) Mean (SD)	10.6 (5.1)	10.5 (5.3)

Outcomes

Adverse events

Outcome	Prone, , N = 10	Standard care, , N = 17
Adverse events Reported events were all mild position-related discomfort No of events	n = 6 ; % = 60	n = 0 ; % = 0

Adverse events - Polarity - Lower values are better

Rosen, 2021

Bibliographic Reference	Rosen, Jacob; von Oelreich, Erik; Fors, Diddi; Jonsson Fagerlund, Malin; Taxbro, Knut; Skorup, Paul; Eby, Ludvig; Campoccia Jalde, Francesca; Johansson, Niclas; Bergstrom, Gustav; Frykholm, Peter; PROFLO Study, Group; Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial.; Critical care (London, England); 2021; vol. 25 (no. 1); 209

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	ISRCTN54917435 (PROFLO study)
Study start date	07-Oct-2020
Study end date	07-Feb-2021
Aim of the study	To assess if prone positioning and standard care reduces the rate of endotracheal intubation compared to standard care alone among COVID-19 patients with hypoxemic respiratory failure
Country/ Geographical location	Sweden
Study setting	3 hospitals
Population description	Adults with moderate to severe hypoxemic respiratory failure admitted to hospital with confirmed COVID-19 and high-flow nasal oxygen or non-invasive ventilation for respiratory support and PaO2/FiO2 ratio ≤20 kPa (N=79 randomised)

Inclusion criteria	Adults (≥18 years old) with PCR-confirmed COVID-19 and hypoxemic respiratory failure, HFNO or NIV for respiratory support and PaO2/FiO2-ratio≤20 kPa or corresponding values of SpO2 and FiO2 for more than one hour
Exclusion criteria	Oxygen supplementation device other than HFNO or NIV, inability to prone or semi-prone, immediate need for endotracheal intubation, severe hemodynamic instability, previous intubation for COVID-19 pneumonia, pregnancy, terminal illness with less than one year life expectancy, do-not-intubate order; inability to understand oral or written study information
Intervention/test/approach	Awake prone positioning (APP) protocol targeting 16 h prone positioning per day (N=36) Prone and semi-prone positioning was allowed. Flat supine positioning discouraged. People advised to take semi-recumbent or lateral position between proning sessions. Protocol discontinuation criteria: intubation, death or clinical improvement defined as use of standard nasal cannula or open face mask with an oxygen flow rate of ≤5 L min−1 for 12 h. Attending clinicians could withdraw patient if considered APP unsafe Median prone duration was 9.0 h per day [IQR 4.4–10.6] in prone group (P=0.014) Total protocol duration, days = 4.2 (IQR 1.7 - 5.7) Daily prone time day 1–3, hours 8.5 (IQR 5.2–12.2)
Comparator (where applicable)	Standard care (N=39) APP not encouraged but could be prescribed by the attending clinician at their discretion. Standard care delivered in both groups according to clinical practice in participating hospitals. Intravenous sedation allowed but not protocolised. Decision to intubate made at the discretion of attending clinician but followed local guidelines. Positioning after intubation not protocolised (but PP usual practice for mechanically ventilated patients with COVID-19 with moderate to severe ARDS at participating centres). Median prone duration was 3.4 h per day [IQR 1.8–8.4] in control group Total protocol duration, days 4.9 (IQR 2.3–8.1)

	Daily prone time day 1–3, hours 2.6 (IQR 0.3–8.1)
Methods for population selection/allocation	Randomisation with ratio of 1:1 and block size of eight via a centralized web-based system. Trial was stopped early due to futility
Attrition/loss to follow-up	No patients lost to follow up
Other details	Exploratory analysis based on duration of APP shorter than 3 hours (N=26) versus longer than 9 hours (n=26) irrespective of allocation were compared. No significant difference in proportion of patients intubated in unadjusted analysis (HR 1.14, 95%CI 0.44 to 2.96, P=0.79) or analysis adjusted for age and PaO2/Fio2 at enrolment (HR 0.79, 95%CI 0.29 to 2.18, P=0.65). The trial was halted early resulting in limited statistical power to detect differences between groups. In particular, analyses of subgroups that may benefit from APP and analyses of secondary outcomes with few events may have been hampered and the results should therefore be interpreted with caution. included patients with moderate to severe respiratory failure and there was a liberal use of NIV in both groups early after enrolment

Study arms

Prone (N = 36)

Standard care (N = 39)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 36)	Standard care (N = 39)
Age Median (IQR)	66 (53 to 74)	65 (55 to 70)
Gender % male No of events	n = 23 ; % = 64	n = 32 ; % = 82
Ethnicity No of events	n = NR ; % = NR	n = NR ; % = NR
BMI	28 (25 to 30)	29 (27 to 33)

Characteristic	Prone (N = 36)	Standard care (N = 39)
Median (IQR)		
Obesity (BMI 30 kg/m2 or above) No of events	n = 8 ; % = 23	n = 12 ; % = 32
Hypertension No of events	n = 17	n = 21 ; % = 55
Ischaemic cardiac disease No of events	n = 6 ; % = 17	n = 5 ; % = 13
Congestive heart failure No of events	n = 2 ; % = 6	n = 6 ; % = 15
Lung disease No of events	n = 4 ; % = 11	n = 10 ; % = 26
Asthma No of events	n = 1 ; % = 3	n = 5 ; % = 13
COPD No of events	n = 2 ; % = 6	n = 4 ; % = 10
Fibrosis No of events	n = 1 ; % = 3	n = 0 ; % = 0
Sarcoidosis No of events	n = 0 ; % = 0	n = 1 ; % = 3
Diabetes mellitus No of events	n = 14 ; % = 39	n = 11 ; % = 28
Renal disease No of events	n = 3 ; % = 8	n = 2 ; % = 5
Active cancer No of events	n = 4 ; % = 11	n = 1 ; % = 3
Liver disease No of events	n = 0 ; % = 0	n = 1 ; % = 3
Enrolment outside ICU No of events	n = 19 ; % = 53	n = 20 ; % = 51
HFNO	n = 31 ; % = 86	n = 29 ; % = 74

Characteristic	Prone (N = 36)	Standard care (N = 39)
No of events		
Flow rate (HFNO) Median (IQR)	50 (40 to 50)	50 (40 to 50)
Positive End Expiratory Pressure Median (IQR)	7 (6 to 10)	8 (6 to 8)
FiO2 Median (IQR)	0.6 (0.55 to 0.7)	0.6 (0.55 to 0.7)
SpO2 Median (IQR)	93 (91 to 94)	94 (92 to 95)
PaO2 Median (IQR)	8.8 (7.7 to 9.7)	9.2 (8.2 to 10)
Respiratory rate Median (IQR)	24 (21 to 29)	26 (23 to 32)
PaO2/FiO2 ratio Median (IQR)	15.4 (11.5 to 17.4)	15.4 (12.5 to 17.3)
SpO2/FiO2 ratio Median (IQR)	151 (131 to 174)	157 (136 to 175)
Systolic blood pressure Median (IQR)	130 (120 to 140)	157 (136 to 175)
Diastolic blood pressure Median (IQR)	69 (62 to 75)	70 (60 to 80)

Outcomes

Intubation

Outcome	Prone, , N = 36	Standard care, , N = 39
Intubation within 30 days after enrolment No of events	n = 12 ; % = 33	n = 13 ; % = 33

Intubation

Outcome	Prone vs Standard care
Intubation within 30 days after enrolment P value	0.99
Intubation within 30 days after enrolment Hazard ratio/95% CI	1.01 (0.46 to 2.21)
Subanalysis of patients with Pao2/Fio2 ratio 15 kPa or less (unadjusted analysis) P value	0.90
Subanalysis of patients with Pao2/Fio2 ratio 15 kPa or less (unadjusted analysis) Hazard ratio/95% CI	0.94 (0.35 to 2.5)
Subanalysis of patients with Pao2/Fio2 ratio 15 kPa or less (adjusted for age) P value	0.49
Subanalysis of patients with Pao2/Fio2 ratio 15 kPa or less (adjusted for age) Hazard ratio/95% CI	0.51 (0.25 to 1.89)

Mortality

Outcome	Prone, , N = 36	Standard care, , N = 39
30 day mortality No of events	n = 6 ; % = 17	n = 3 ; % = 8
30 day mortality P value	NA	0.3

Ventilator free days (all patients)

Outcome	Prone, , N = 36	Standard care, , N = 39
Ventilator free days (all patients) defined as days free from invasive mechanical ventilation from enrolment until day 30. Patients who died were registered as 0 VFD P value	NA	0.69
Ventilator free days (all patients) defined as days free from invasive mechanical ventilation from	30 (12 to 30)	30 (11 to 30)

Outcome	Prone, , N = 36	Standard care, , N = 39
enrolment until day 30. Patients who died were registered as 0 VFD Median (IQR)		

Respiratory and other clinical outcomes

Outcome	Prone, , N = 36	Standard care, , N = 39
Enrolment to IMV (days) P value	NA	0.59
Enrolment to IMV (days) Median (IQR)	2 (1 to 5)	2 (1 to 6)
Use of NIV No of events	n = 21 ; % = 58	n = 27 ; % = 69
Use of NIV P value	NA	0.33
Enrolment to NIV (days) P value	NA	0.63
Enrolment to NIV (days) Median (IQR)	0.23 (0.05 to 1.2)	0.25 (0.1 to 1.1)

Hospitalisation outcomes

Outcome	Prone, , N = 36	Standard care, , N = 39
Admitted to ICU No of events	n = 27 ; % = 75	n = 27 ; % = 69
Admitted to ICU P value	NA	0.58
ICU length of stay (days) P value	NA	0.25
ICU length of stay (days) Median (IQR)	5 (4 to 13)	11 (3 to 22)

Outcome	Prone, , N = 36	Standard care, , N = 39
Hospital length of stay (days) P value	NA	0.44
Hospital length of stay (days) Median (IQR)	16 (11 to 22)	18 (11 to 30)

Adverse events

Outcome	Prone, , N = 36	Standard care, , N = 39
Pressure sores No of events	n = 2 ; % = 6	n = 9 ; % = 23
Pressure sores P value	NA	0.032
Vomiting during proning No of events	n = 1 ; % = 3	n = 0 ; % = 0
Central or arterial line dislodgement No of events	n = 0 ; % = 0	n = 0 ; % = 0
Cardiac arrest within 30 days No of events	n = 2 ; % = 6	n = 1 ; % = 3
Cardiac arrest within 30 days P value	NA	0.51

Taylor, 2020

Bibliographic Reference	Taylor, Stephanie Parks; Bundy, Henry; Smith, William M; Skavroneck, Sara; Taylor, Brice; Kowalkowski, Marc A; Awake-Prone Positioning Strategy for Non-Intubated Hypoxic Patients with COVID-19: A Pilot Trial with Embedded Implementation Evaluation.; Annals of the American Thoracic Society; 2020

Study details

Study design	Cluster randomised controlled trial
Study start date	01-Jun-2020
Study end date	31-Aug-2020
Aim of the study	Hospital

Country/ Geographical location	USA
Study setting	Hospital
Population description	Awake non-intubated hypoxic adults admitted to hospital with COVID-19 (N=40).
Inclusion criteria	People with positive SARS-CoV-2 test or suspected COVID-19 pneumonia and i) room air oxygen saturation below 93% or ii) new oxygen requirement of 3 L per minute or above without need for mechanical ventilation. At time of eligibility, 23 (53%) had positive test result for SARS-CoV-2 and 20 (47%) had suspected COVID-19. Eight (19%) subsequently tested negative for SARS-CoV-2 (usual care [n = 2] vs. prone [n = 6]).
Exclusion criteria	People with contraindications to prone positioning (e.g. unable to self-turn, spinal instability, facial or pelvic fractures, open chest or abdomen, altered mental status, anticipated difficult airway, signs of respiratory fatigue, or receiving end-of-life care)
Intervention/test/approach	Awake prone positioning strategy (N=28 [NB 1 patient excluded as left against medical advice]). 10 of these attempted to prone, 17 did not attempt to prone. Hospitalised people with COVID-19 guided to adopt prone position when hypoxia thresholds met. Prone position applied depended on tolerance and adherence. Protocol combined i) prone positioning education and explanation of risks and benefits to patients by bedside clinicians, ii) routine status monitoring, and iii) attention to improvement of comfort as required. Patients were encouraged to prone for as long as possible (allowed to move to supine position as required). 1-hour educational training on strategy and trial processes for medical teams allocated to intervention group before patient enrolment. Teams randomised to intervention to commence prone positioning from time of eligibility and sustained for at least 48 hours or until intubation, intensive care unit transfer, hospital discharge, or death. Patients reported that they could only lie prone for between 10 and 120 minutes per day. Corticosteroids n= 19 (70%), remdesivir n= 10 (37%), convalescent plasma n= 1 (4%)

Comparator (where applicable)	Standard care (N=13). 10 did not attempt to prone. 3 attempted to prone. Standard care determined by clinical assessments and need. Expected to be routine practice for hospitalised people with COVID-19-related hypoxia and should be similar for both groups. Prone positioning neither encouraged nor disallowed in standard care group. Corticosteroids n= 9 (69%), remdesivir n= 5 (38%), convalescent plasma n=2 (15%)
Methods for population selection/allocation	5 inpatient medical service teams randomised (using computer-generated random numbers) to two treatment arms: i) usual care (current standard management of hypoxia and COVID-19 (2 clusters); or ii) the Awake Prone Positioning Strategy (APPS) plus usual care (3 clusters).
Study limitations (Author)	Limitation of cluster-level randomisation was diffusion of prone positioning into the control group
Other details	Those did not attempt prone position more frequently were male, Black, with chronic lung disease or heart failure, and 6 or more pack-years' smoking history versus those who did attempt prone position.

Study arms

Prone (N = 28)

Standard care (N = 13)

Characteristics

Arm-level characteristics

Characteristic	Prone (N = 28)	Standard care (N = 13)
Age Median (IQR)	56 (45 to 66)	60 (54 to 63)
Gender (% Female) No of events	n = 10 ; % = 37	n = 3 ; % = 23
Black No of events	n = 16 ; % = 59	n = 6 ; % = 46
White No of events	n = 9 ; % = 33	n = 5 ; % = 38

Characteristic	Prone (N = 28)	Standard care (N = 13)
Other No of events	n = 2 ; % = 8	n = 2 ; % = 16
Hispanic or Latino No of events	n = 7 ; % = 26	n = 3 ; % = 23
None No of events	n = 2 ; % = 15	n = 5 ; % = 19
Chronic lung disease No of events	n = 6 ; % = 22	n = 3 ; % = 23
Chronic renal disease No of events	n = 7 ; % = 26	n = 2 ; % = 15
Diabetes No of events	n = 10 ; % = 37	n = 5 ; % = 38
Heart failure No of events	n = 5 ; % = 19	n = 4 ; % = 31
BMI Median (IQR)	29 (26 to 39)	31 (28 to 38)
BMI > 30 kg/m2 No of events	n = 14 ; % = 52	n = 6 ; % = 46
Smoking history: unknown No of events	n = 2 ; % = 7	n = 0 ; % = 0
Smoking history: never No of events	n = 19 ; % = 70	n = 7 ; % = 54
1-5 cigarette pack-years No of events	n = 3 ; % = 11	n = 1 ; % = 8
6 or more cigarette pack-years No of events	n = 3 ; % = 11	n = 5 ; % = 38
Pneumonia severity index Median (IQR)	72 (57 to 95)	81 (67 to 84)
Hours from presentation to eligibility Median (IQR)	4 (1 to 24)	7 (2 to 26)

Characteristic	Prone (N = 28)	Standard care (N = 13)
Oxygen saturation at baseline Median (IQR)	92 (89 to 94)	93 (91 to 95)
Room air No of events	n = 0 ; % = 0	n = 1 ; % = 8
< 4 L nasal cannula No of events	n = 15 ; % = 56	n = 7 ; % = 54
4–6 L nasal cannula No of events	n = 11 ; % = 41	n = 3 ; % = 23
Medium flow nasal cannula No of events	n = 0 ; % = 0	n = 2 ; % = 15
Humidified high-flow nasal cannula No of events	n = 0 ; % = 0	n = 0 ; % = 0
Bilevel positive airway pressure No of events	n = 1 ; % = 4	n = 0 ; % = 0

Outcomes

Adverse events

Outcome	Prone, , N = 28	Standard care, , N = 13
Serious adverse events No of events	n = 0 ; % = 0	n = 0 ; % = 0
Anterior pressure wound No of events	n = 0 ; % = 0	n = 0 ; % = 0
Loss of intravenous catheter No of events	n = 1 ; % = 4	n = 0 ; % = 0
Emergent intubation outside of ICU No of events	n = 0 ; % = 0	n = 0 ; % = 0

Oxygen support required 48 hours after baseline

Outcome	Prone, , N = 28	Standard care, , N = 13
Intubated No of events	n = 0 ; % = 0	n = 0 ; % = 0

Hospitalisation-related outcomes

Outcome	Prone, , N = 28	Standard care, , N = 13
Required ICU admission within 48 hours No of events	n = 8 ; % = 30	n = 3 ; % = 23
Required ICU admission during hospitalisation No of events	n = 8 ; % = 30	n = 6 ; % = 46
Required intubation during hospitalisation No of events	n = 0 ; % = 0	n = 0 ; % = 0
Hospital length of stay (days) Median (IQR)	6 (3 to 12)	5 (2 to 9)

Mortality

Outcome	Prone, , N = 28	Standard care, , N = 13
Discharge disposition: expired No of events	n = 0 ; % = 0	n = 0 ; % = 0

Risk of bias assessments

Ehrmann, 2021

Bibliographic Reference	Ehrmann, Stephan; Li, Jie; Ibarra-Estrada, Miguel; Perez, Yonatan; Pavlov, Ivan; McNicholas, Bairbre; Roca, Oriol; Mirza, Sara; Vines, David; Garcia-Salcido, Roxana; Aguirre-Avalos, Guadalupe; Trump Matthew, W; Nay, Mai-Anh; Dellamonica, Jean; Nseir, Saad; Mogri, Idrees; Cosgrave, David; Jayaraman, Dev; Masclans Joan, R; Laffey John, G; Tavernier, Elsa; Awake Prone Positioning, Meta-Trial; Group; Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial.; The Lancet. Respiratory medicine; 2021

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns (*In the standard care group, one patient out of ten underwent awake prone positioning. These protocol violations could have led to an underestimation of the efficacy of awake prone positioning in the intention-to-treat population*)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes. In the standard care group, one patient out of ten underwent awake prone positioning. These protocol violations could have led to an underestimation of the efficacy of awake prone positioning in the intention-to-treat population)*
Overall bias and Directness	Overall Directness	Directly applicable

Fralick et al.

Bibliographic Reference	Fralick, Mike; Colacci, Michael; Munshi, Laveena; Venus, Kevin; Fidler, Lee; Hussein, Haseena; Britto, Karen; Fowler, Rob; Costa, Bruno; da; Dhalla, Irfan; Yaffe, Richard; Dunbar-Yaffe; Day, Laura; Branfield; MacMillan, Thomas; Zipursky, Jonathan; Carpenter, Travis; Tang, Terence; Cooke, Amanda; Hensel, Rachel; Bregger, Melissa; Gordon, Alexis; Worndl, Erin; Go, Stephanie; Mandelzweig, Keren; Castellucci, Lana; Tamming, Daniel; Razak, Fahad; Verma, Amol; Investigators, COVID; PRONE; Prone positioning of patients with moderate hypoxia due to COVID-19: A multicenter pragmatic randomized trial; medrxiv preprint

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns (*Poor adherence to time spent prone. As authors acknowledge 'The most common reason for the lack of adherence was patient discomfort.'*)
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Overall bias and Directness	Overall Directness	Directly applicable

Jayakumar, 2021

Bibliographic Reference	Jayakumar, Devachandran; Ramachandran Dnb, Pratheema; Rabindrarajan Dnb, Ebenezer; Vijayaraghavan Md, Bharath Kumar Tirupakuzhi; Ramakrishnan Ab, Nagarajan; Venkataraman Ab, Ramesh; Standard Care Versus Awake Prone Position in Adult Nonintubated Patients With Acute Hypoxemic Respiratory Failure Secondary to COVID-19 Infection-A Multicenter Feasibility Randomized Controlled Trial.; Journal of intensive care medicine; 2021; 8850666211014480

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Some concerns

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	*(53% (16 out of 30) in the supine group spent some hours in the prone position)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Only 43% could adhere to the protocol which required 6 hours of cumulative prone positioning in the prone group.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes. 53% (16 out of 30) in the supine group spent some hours in the prone position Only 43% could adhere to the protocol which required 6 hours of cumulative prone positioning in the prone group.)*
Overall bias and Directness	Overall Directness	Directly applicable

Kaur, 2021

Bibliographic Reference	Kaur, Ramandeep; Vines, David L; Mirza, Sara; Elshafei, Ahmad; Jackson, Julie A; Harnois, Lauren J; Weiss, Tyler; Scott, J Brady; Trump, Matthew W; Mogri, Idrees; Cerda, Flor; Alolaiwat, Amnah A; Miller, Amanda R; Klein, Andrew M; Oetting, Trevor W; Morris, Lindsey; Heckart, Scott; Capouch, Lindsay; He, Hangyong; Li, Jie; Early versus late awake prone positioning in non-intubated patients with COVID-19.; Critical care (London, England); 2021; vol. 25 (no. 1); 340

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended	Low

Section	Question	Answer
intended interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(This study was a post-hoc analysis: The results of this study were known before a decision was made to publish them.)*
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes. This study was a post-hoc analysis: The results of this study were known before a decision was made to publish them.)*
Overall bias and Directness	Overall Directness	Directly applicable

Rosen, 2021

Bibliographic Reference	Rosen, Jacob; von Oelreich, Erik; Fors, Diddi; Jonsson Fagerlund, Malin; Taxbro, Knut; Skorup, Paul; Eby, Ludvig; Campoccia Jalde, Francesca; Johansson, Niclas; Bergstrom, Gustav; Frykholm, Peter; PROFLO Study, Group; Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial.; Critical care (London, England); 2021; vol. 25 (no. 1); 209

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Although adherence was not measured it was reported as low)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes. Although adherence was not measured it was reported as low)*
Overall bias and Directness	Overall Directness	Partially direct *(PICO states participants on low oxygen levels but this study included patients with moderate to severe respiratory failure and use of NIV in both groups early after enrolment)*

Kharat, 2021

Bibliographic Reference	Kharat, Aileen; Dupuis-Lozeron, Elise; Cantero, Chloe; Marti, Christophe; Grosgurin, Olivier; Lolachi, Sanaz; Lador, Frederic; Plojoux, Jerome; Janssens, Jean-Paul; Soccal, Paola M; Adler, Dan; Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial.; ERJ open research; 2021; vol. 7 (no. 1)

Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
1b. Bias arising from the timing of identification and recruitment of individual participants in relation	Risk of bias judgement for the timing of identification and recruitment of individual participants in relation	Low

Section	Question	Answer
to timing of randomisation	to timing of randomisation	
2. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	High *(This study was not blinded so bias could have been introduced when recording outcomes. Intervention and assessments of end-points were limited to a 24-h time frame and measured in the supine position. Therefore, measurement of outcomes may have been inaccurate.)*
5. Bias in selection of the reported result	Risk of bias for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(This study was not blinded so bias could have been introduced when recording outcomes. Duration of prone positioning was self-reported by study participants. Intervention and assessments of end-points were limited to a 24-h time frame and measured in the supine position. Therefore, measurement of outcomes may have been inaccurate)*
Overall bias and Directness	Overall Directness	Directly applicable

Taylor, 2020

Bibliographic Reference	Taylor, Stephanie Parks; Bundy, Henry; Smith, William M; Skavroneck, Sara; Taylor, Brice; Kowalkowski, Marc A; Awake-Prone Positioning Strategy for Non-Intubated Hypoxic Patients with COVID-19: A Pilot Trial with Embedded Implementation Evaluation.; Annals of the American Thoracic Society; 2020

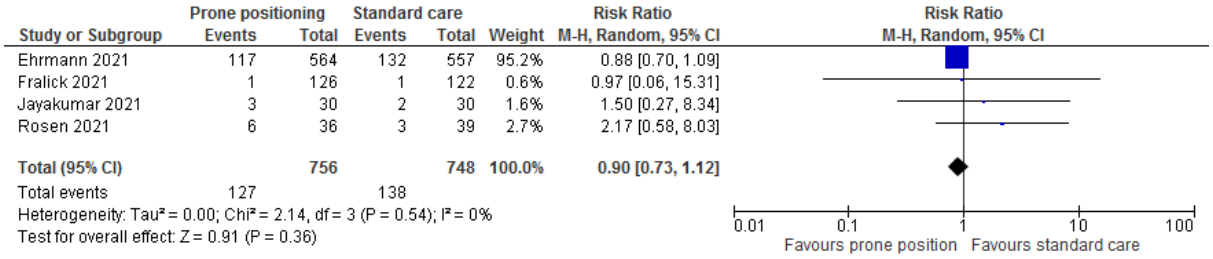
Critical appraisal - GUT Cochrane Risk of Bias tool (RoB 2.0) Cluster trials

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
1b. Bias arising from the timing of	Risk of bias judgement for the timing of	Some concerns *(Medical teams were randomised rather*

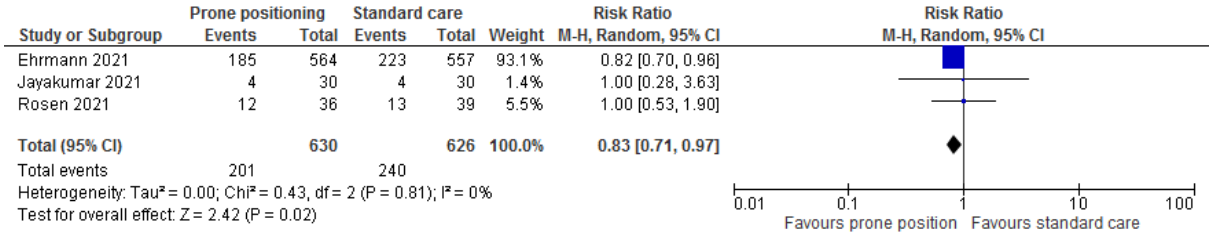
Section	Question	Answer
identification and recruitment of individual participants in relation to timing of randomisation	identification and recruitment of individual participants in relation to timing of randomisation	*than patients. This means that it might have been possible to predict which team each patient would be assigned to.)*
2. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	High *(23% of participants in the usual care arm attempted the prone position within 48 hours compared to 37% in the intervention arm)*
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Low
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(This study was not blinded so bias could have been introduced when recording outcomes.)*
5. Bias in selection of the reported result	Risk of bias for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Medical teams were randomised rather than patients. This means that it might have been possible to predict which team each patient would be assigned to. This study was not blinded so bias could have been introduced when recording outcomes. 23% of participants in the usual care arm attempted the prone position within 48 hours compared to 37% in the intervention arm. Therefore, the intervention arm and control arms were very similar with regards to the amount of prone positioning)*
Overall bias and Directness	Overall Directness	Partially applicable *(37 to 41% of participants had suspected COVID-19.)*

Appendix G: Forest Plots

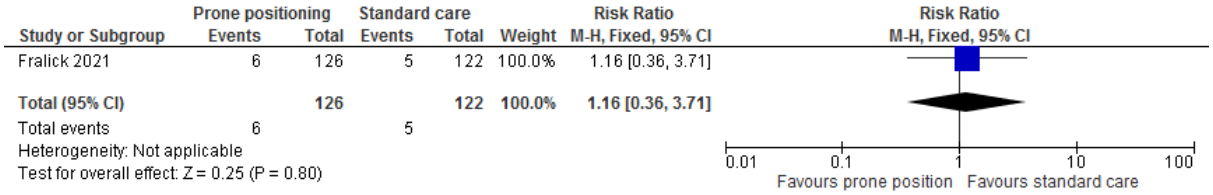
Mortality



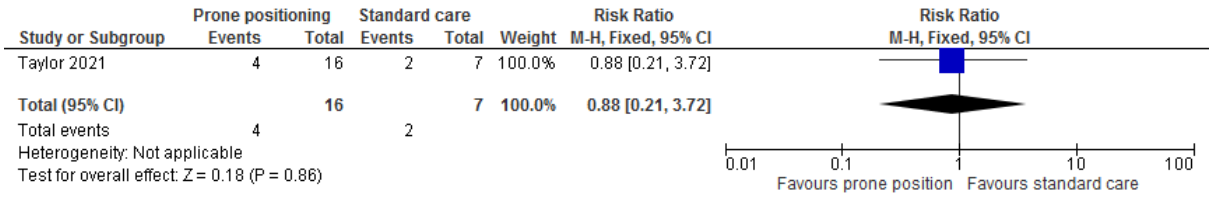
Intubation



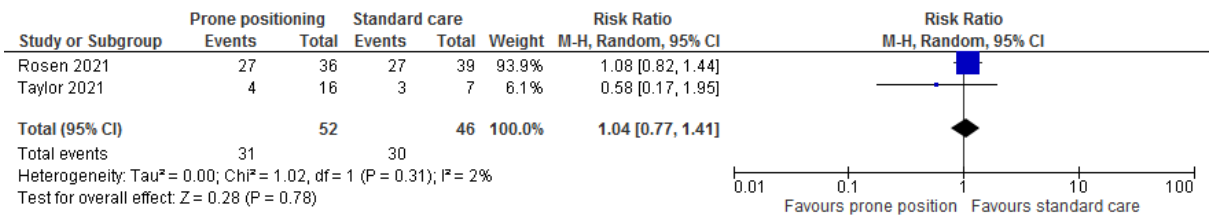
Mechanical ventilation (intubation or bilevel positive airway pressure)



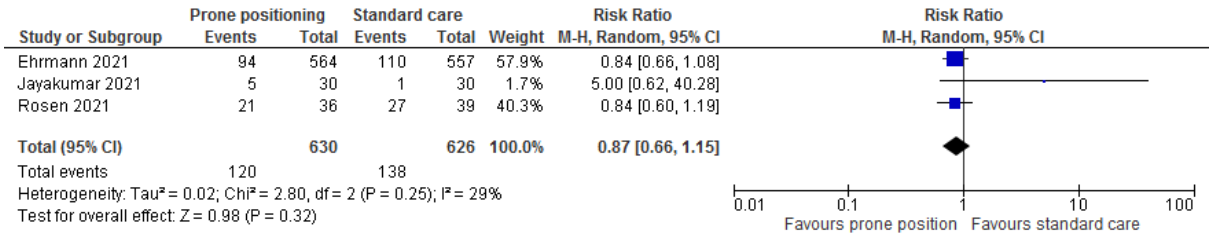
ICU admission required within 48 hours



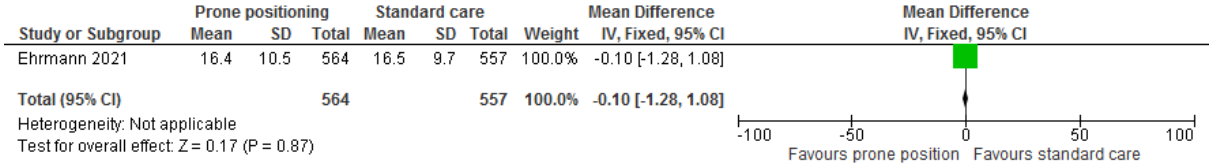
ICU admission during hospitalisation



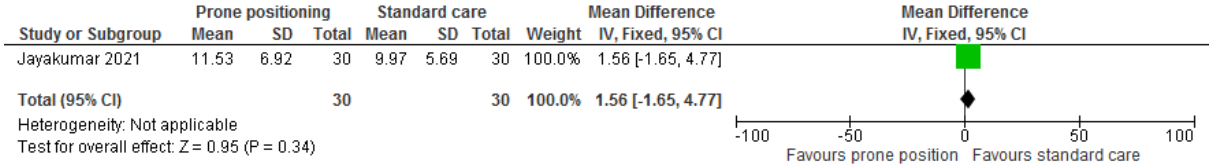
Use of non-invasive ventilation



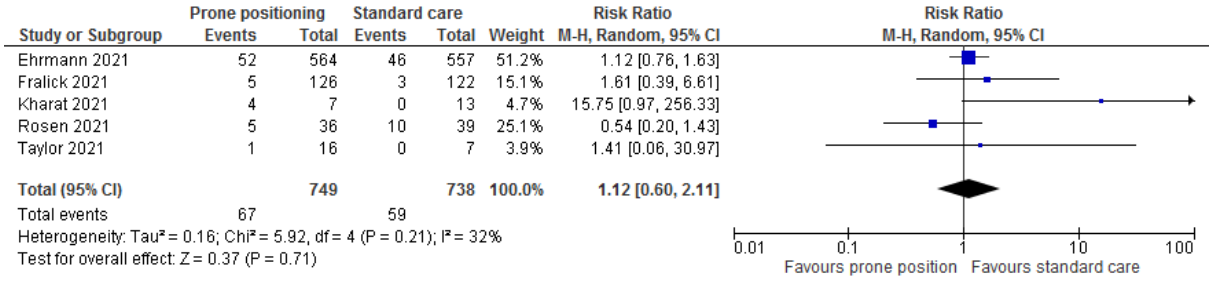
Hospital length of stay (days)



ICU length of stay (days)



Adverse events (all)



Appendix H: GRADE profiles

Awake prone positioning compared to standard care for COVID-19

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With standard care	With awake prone positioning	Relative effect (95% CI)	Risk with standard care	Risk difference with awake prone positioning
Mortality											
1504 (4 RCTs)	very serious[a]	not serious	not serious	serious[b]	none	Very low	138/748 (18.4%)	127/756 (16.8%)	**RR 0.90** (0.73 to 1.12)	184 per 1,000	**18 fewer per 1,000** (from 50 fewer to 22 more)
Intubation											
1256 (3 RCTs)	very serious[a]	not serious	not serious	not serious	none	Low	240/626 (38.3%)	201/630 (31.9%)	**RR 0.83** (0.71 to 0.97)	383 per 1,000	**65 fewer per 1,000** (from 111 fewer to 12 fewer)
Mechanical ventilation (intubation or bilevel positive airway pressure)											
248 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	5/122 (4.1%)	6/126 (4.8%)	**RR 1.16** (0.36 to 3.71)	41 per 1,000	**7 more per 1,000** (from 26 fewer to 111 more)
Use of non-invasive ventilation											

Certainty assessment							Summary of findings				
1256 (3 RCTs)	very serious[a]	not serious	not serious	serious[b]	none	Very low	138/626 (22.0%)	120/630 (19.0%)	**RR 0.87** (0.66 to 1.15)	220 per 1,000	**29 fewer per 1,000** (from 75 fewer to 33 more)

ICU admission during hospitalisation

98 (2 RCTs)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	30/46 (65.2%)	31/52 (59.6%)	**RR 1.04** (0.77 to 1.41)	652 per 1,000	**26 more per 1,000** (from 150 fewer to 267 more)

ICU admission required within 48 hours

23 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	2/7 (28.6%)	4/16 (25.0%)	**RR 0.88** (0.21 to 3.72)	286 per 1,000	**34 fewer per 1,000** (from 226 fewer to 777 more)

Adverse events (all)

1487 (5 RCTs)	very serious[a]	not serious	not serious	serious[b]	none	Very low	59/738 (8.0%)	67/749 (8.9%)	**RR 1.12** (0.60 to 2.11)	80 per 1,000	**10 more per 1,000** (from 32 fewer to 89 more)

Hospital length of stay (days)

1121 (1 RCT)	very serious[a]	not serious	not serious	serious[b]	none	Very low	557	564	-		MD **0.1 days fewer** (1.28 fewer to 1.08 more)

Hospital length of stay (days)

75 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	Very low	Awake prone positioning: Median [IQR] 16 [11-22] Standard care: Median [IQR] 18 [11-30]				

Hospital length of stay (days)

Certainty assessment							Summary of findings				
41 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	Very low	Awake prone positioning: Median [IQR] 6 [3-12] Standard care: Median [IQR] 5 [2-9]				

Hospital length of stay (days)

248 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	Very low	Awake prone positioning: Median [IQR] 5 [3-9] Standard care: Median [IQR] 4 [3-8]				

ICU length of stay

60 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	30	30	-		MD **1.56 more** (1.65 fewer to 4.77 more)

ICU length of stay (days)

75 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	Very low	Awake prone positioning: Median [IQR] 5 [4-13] Standard care: Median [IQR] 11 [3-22]				

Time from enrolment to non-invasive ventilation (days)

75 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Awake prone positioning: Median [IQR] 0.23 [0.05-1.2] Standard care: Median [IQR] 0.25 [0.1-1.1]				

Ventilator-free days

75 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Awake prone positioning: Median [IQR] 30 [11-30] Standard care: Median [IQR] 30 [11-30]				

Time from enrolment to invasive mechanical ventilation (days)

75 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Awake prone positioning: Median [IQR] 2 [1-6] Standard care: Median [IQR] 2 [1-5]				

Hospital length of stay (days)

248 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Hazard ratio (95% CI) 0.91 (0.69 to 1.2)				

Intubation within 30 days after enrolment

Certainty assessment							Summary of findings
75 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Hazard ratio (95% CI) 1.01 (0.46 to 2.21)

Intubation within 30 days after enrolment (patients with PaO2/FiO2 ratio 15 kPa or less) (unadjusted analysis)

NR (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Hazard ratio (95% CI) 0.94 (0.35 to 2.50)

Intubation within 30 days after enrolment (patients with PaO2/FiO2 ratio 15 kPa or less) (adjusted for age)

NR (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Hazard ratio (95% CI) 0.51 (0.25 to 1.89)

Time to intubation (days)

408 (1 RCT)	very serious[a]	not serious	not serious	not serious	none	Low	Hazard ratio (95% CI) 0.75 (0.62 to 0.91)

Time to death (days)

249 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	Very low	Hazard ratio (95% CI) 0.87 (0.68 to 1.11)

Time to death (days)

249 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	Very low	Awake prone positioning: Median [IQR] 12 [9.8-19] Standard care: Median [IQR] 14 [9.8-19]

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. greater than 33.3% of weight comes from outcomes assessed as high risk of bias
b. Confidence interval crosses line of no effect
c. Confidence interval crosses line of no effect, fewer than 300 people contribute to outcome
d. IQR overlap, fewer than 300 people contribute to outcome

Appendix I: Recommendations for research

Question	**What is the effectiveness of awake body positioning in improving outcomes for people in hospital with COVID-19 who are not intubated and have higher oxygen needs?**
Population	People in hospital with COVID-19 who are not intubated and have higher oxygen needs
Intervention(s)	Awake body positioning
Comparator(s)	Standard care or a different specified awake body position
Outcomes	• adherence to and compliance with body position (including total duration of awake body positioning and duration of each body positioning session) • patient reported outcomes including dyspnoea, anxiety, delirium, pain, discomfort, breathlessness, impact on sleep • mortality • time to non-invasive respiratory support • intubation • length of hospital stay • admission to intensive care unit • complications (for example: pneumothorax, pneumomediastinum, delirium, intolerance of positioning or haemodynamic instability)

	Subgroups: • mean duration of body positioning • people on general wards, and those with do-not-intubate goals of care • supplemental oxygen type • adults aged 50 years and older • children aged 12 years and younger • disease severity • sex • ethnic background • religion or belief • deprivation or socioeconomic status • frailty • BMI of 30 or higher • pregnant women (including gestational age) • people with learning disability or physical disability (or both) • people who use aids (for example, spectacles, hearing aids) • comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity)