Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
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EVIDENCE SUMMARY

Should high flow nasal cannula be used for patients with COVID-19 and acute respiratory failure?

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RECOMMENDATION

We suggest the use of high flow nasal cannula for patients with severe to critical COVID-19 who do not respond to conventional oxygen therapy (low flow nasal cannula/face mask). *(Low certainty of evidence; Weak recommendation)*

Consensus Issues
The use of high flow nasal cannula should only be considered when patients fail to respond to low flow nasal cannula or face mask. It is not intended to be the immediate first line respiratory support for COVID-19 patients. It was initially promoted due to its capability to deliver high oxygen concentration, particularly when coupled with the potential harm or risk of viral aerosolization with non-invasive ventilation. The comparison of the efficacy of high flow nasal cannula and non-invasive ventilation is discussed in a separate review.

PREVIOUS RECOMMENDATION

We suggest the use of high-flow nasal cannula oxygenation over non-invasive ventilation (e.g., helmet CPAP, mask NIV) in patients with COVID-19 infection and acute hypoxemic respiratory failure who do not respond to conventional oxygen therapy. *(Very low quality of evidence; Conditional recommendation)*

Consensus Issues
The use of HFNC over conventional oxygen therapy (i.e., nasal cannula, venture mask or non-rebreather mask) is not congruent to usual clinical practice. The use for HFNC is preferred for patients who are not doing well with the conventional oxygen therapy. In addition, the trial employing severe COVID-19 patients, used HFNC even if it is not yet needed at the time.

What's new in this version?

- One new pre-print randomized controlled trial was included for review to evaluate the use of high flow nasal cannula therapy in COVID-19 patients. The previous recommendation was reviewed from one randomized controlled trial and four retrospective cohort studies.
- In this updated review, the recommendation for the use of high flow nasal cannula therapy is upgraded to low certainty of evidence.

Key Findings

Two randomized controlled trials comparing the use of high flow nasal cannula (HFNC) versus conventional oxygen therapy (COT) in COVID-19 patients with acute respiratory failure showed significant improvement of PaO_2/FiO_2 ratio among patients who received HFNC. However, no significant benefit was found in terms of 30-day mortality, length of hospital stay, length of intensive care unit stay, and eventual tracheal intubation and intensive care unit admission. Certainty of evidence was low because of unclear to high-risk of selection and detection bias, and imprecision in most of the critical outcomes.

Introduction

Deaths from COVID-19 infections have been cited as the 5th most common cause of mortality among Filipinos in a recent report released by the Philippine Statistics Authority on the 1st half of 2021.[1] Acute respiratory failure has been one of the common complications in patients with COVID-19 leading to invasive mechanical ventilation. Descriptive studies done locally have reported that the most common complications in the subset of patients were from respiratory failure.[2,3] Physiological effects of high flow nasal cannula (HFNC) therapy has been shown to improve oxygenation in patients with respiratory failure compared to conventional oxygen therapy.[4] The interest in using high flow nasal cannula is based on its ability to be well tolerated among patients and its features to deliver higher concentrations of oxygen at a constant rate. [5-7]

Review Methods

A comprehensive literature search was done as of 07 November 2021 on the use of HFNC in COVID-19 using Medline, Cochrane Library, Google Scholar, clinicaltrials.gov, and medRxiv (pre-prints) with the following keywords: “high flow nasal cannula”,“COVID-19,” and “SARS-COV2”. All search yields were reviewed and appraised. Randomized controlled trials relating to the use of HFNC in COVID-19 associated acute respiratory failure were included.

Results

A total of 15 journal articles were reviewed to evaluate the evidence of HFNC therapy in COVID-19 associated respiratory failure. Of the 15 studies, ten articles were still in the process of recruitment and finalizing the publication manuscript. Only one article presented the study protocol but with no results posted as of search date. Two systematic reviews on the use of HFNC therapy were found but these articles did not fulfill the population criteria and only included acute respiratory failure not secondary to COVID-19. The remaining two studies, one of which was included in the initial evidence review, were both randomized controlled trials that satisfied the criteria for this evidence review. There were no RCTS that evaluated HFNC versus non-invasive ventilation in COVID-19 associated respiratory failure.

Two RCTs by Teng et al. [8] and Perkins et al. [9] done in China and the United Kingdom included all adult patients 18 years of age and above, diagnosed with severe to critical COVID-19 with acute respiratory failure and having peripheral oxygen saturations of less than 94%. Pregnant patients, patients for immediate intubation, and patients with chronic pulmonary and/or cardiac conditions were excluded from the studies. Teng et al. provided the initial HFNC settings used in the study: temperature of 37ºC, flow rate at 50 liters per minute, and fraction of inspired oxygen at 50%. HFNC therapy was delivered continuously for 72 hours to maintain peripheral oxygen saturation of 93% or higher. On the other hand, the HFNC settings in the study of Perkins et al. were titrated based on clinical judgement of the trial physicians.

The study of Perkins et al. also studied the efficacy of Continuous Positive Airway Pressure (CPAP) with Conventional Oxygen Therapy (COT) in reducing critical outcomes such as tracheal intubation, critical care unit admission and 30-day mortality. Findings showed benefit in decreasing the incidence of tracheal intubation (RR 0.66, 95% CI 0.47-0.93) but no difference in decrease in 30-day mortality (RR 0.91, CI 0.59-1.39). There were also no statistical benefits of using CPAP with regard to the length of ICU (MD1.01, 95% CI -0.1.11-3.14) and hospital stay (MD 1.25, 95% CI -1.36-3.97).

In the study by Teng et al., PaO_2/FiO_2 ratio was assessed on the 6th, 24th, and 72nd hour from HFNC initiation. Compared to COT, HFNC significantly improved PaO_2/FiO_2 on the 6th hour (MD 30.50 mmHg, 95% CI 23.29-37.71; p<0.00001), 24th hour (MD 34.90 mmHg, 95% CI 28.61-41.19; p<0.00001), and 72nd hour (MD 34.52 mmHg, 95% CI 29.25-39.79; p<0.00001). Only the HFNC therapy group significantly improved PaO_2/FiO_2 ratio of >300 mmHg at the 24th and 72nd hours. Only the trial by Perkins et al. provided data on 30-day mortality, need for tracheal intubation, and admission to critical care unit between HFNC and COT. No statistically significant difference was found in 30-day mortality (RR 0.94, 95% CI 0.71-1.25; p=0.67), need for tracheal intubation (RR 0.98, 95% CI 0.83-1.15; p=0.77), and admission to critical care unit (RR 1.05, 95% CI 0.93-1.17; p=0.45). Pooled results showed that length of intensive care unit stay (MD -0.21 days, 95% CI -2.00-1.59; p=0.82) and overall hospital stay (MD -0.49 days, 95% CI -3.52-2.54; p=0.75) were also statistically similar for both groups.

Other Factors in Evidence to Decision

Since the start of the COVID-19 pandemic, the country has been acquiring several HFNC machines which have been distributed to several hospitals across the country with more concentration on private and government hospitals in Metro Manila. An estimated 1,318 HFNC machines were acquired and distributed for use as of March 2021.[10-12] The use of HFNC in patients with acute hypoxemic respiratory failure has been tolerated by most patients compared to other forms of oxygen delivery devices; however, some adverse events with its use have been reported such as hemodynamic instability, pneumothorax and pneumomediastinum.[7,9]

Recommendations from Other Groups

Five Guidelines on the management of COVID-19 were identified. Their recommendations are summarized in the table below:

Group/Society/Network	Year	Recommendation	Level of Evidence/Strength of Recommendation
The Australian and New Zealand Intensive Care Society (ANZICS) [13]	2020	High flow nasal oxygen (HFNO) therapy (in ICU): HFNO is a recommended therapy for hypoxia associated with COVID-19 disease, as long as staff are wearing optimal airborne PPE	None stated
European Respiratory Journal [14]	2021	We suggest HFNC or non-invasive CPC delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxemic acute respiratory failure without an immediate indication for invasive mechanical ventilation	Very Low Quality Conditional Recommendation

National Institutes of Health [15]	2020	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)	BIIa
World Health Organization [16]	2021	In selected patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP) may be used.	Conditional Recommendation
Society of Critical Care Medicine [17] Surviving Sepsis Campaign	2021	For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, we suggest using HFNC over conventional oxygen therapy.	Weak Recommendation
		In adults with COVID-19 and acute hypoxemic respiratory failure, we suggest using HFNC over NIPPV	Weak Recommendation

Research Gaps

Despite the agreement of different international societies in recommending the use HFNC among patients with COVID-19, there is still paucity of high-quality clinical trials determining its effectiveness in preventing invasive mechanical ventilation and improving critical and clinically important outcomes. Ten trials which are currently ongoing may provide better evidence whether the use of HFNC is beneficial or detrimental.

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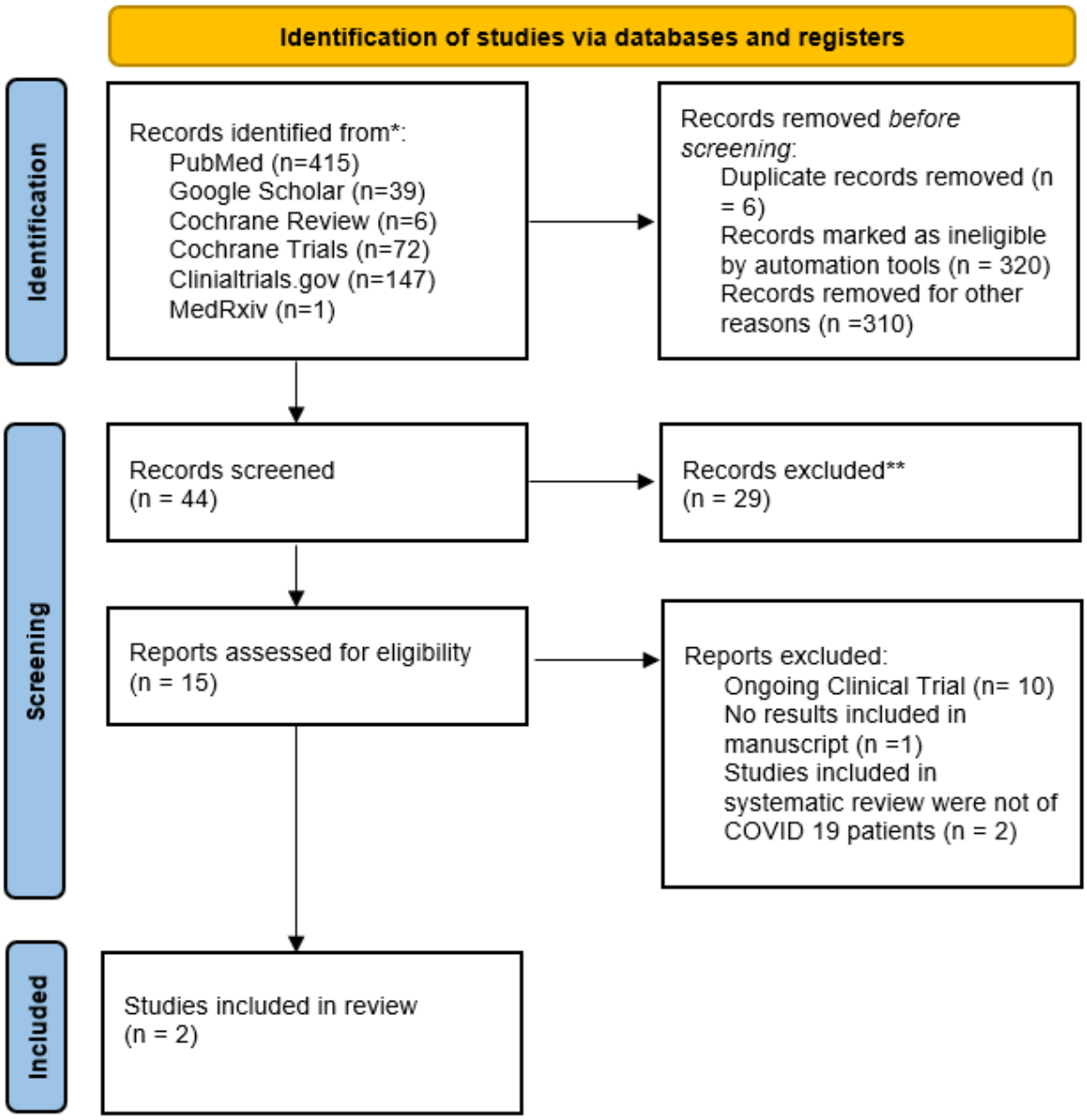
Appendix 1. Evidence to Decision

Table 1. Summary of initial judgements prior to the panel discussion (N=7)

FACTORS	JUDGEMENT					RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (7)				
Benefits	Large (3)	Moderate	Small (4)	Uncertain		• Significant improvement in PaO2/FiO2 on the 6th hour (MD 30.50 mmHg; 95% CI 23.29, 37.71; p<0.00001), 24th hour (MD 34.90 mmHg; 95% CI 28.61, 41.19; p<0.00001), and 72nd hour (MD 34.52 mmHg; 95% CI 29.25, 39.79; p<0.00001). • Only the HFNC therapy group significantly improved PaO_2/FiO_2 ratio of >300 mmHg at the 24^{th} and 72^{nd} hours
Harm	Large	Small (2)	Uncertain (5)			• No evidence
Certainty of Evidence	High	Moderate	Low (7)	Very low		
Balance of effects	Favors drug (5)	Does not favor drug	Uncertain (2)			• The use of HFNC in patients with acute hypoxemic respiratory failure has been tolerated by most patients compared to other forms of oxygen delivery devices, however, some adverse events with its use have been reported such as hemodynamic instability, pneumothorax and pneumomediastinum

Values	Important uncertainty or variability	Possibly important uncertainty or variability (2)	Possibly NO important uncertainty or variability (4)	No important uncertainty or variability (1)			
Resources Required	Uncertain	Large cost (2)	Moderate Cost (5)	Negligible cost	Moderate savings	Large savings	• the country has been acquiring several HFNC machines which have been distributed to several hospitals across the country with more concentration on private and government hospitals in Metro Manila. (1 billion peso funding for 2,550 HFNC machines)
Certainty of evidence of required resources	No included studies (6)	Very low (1)	Low	Moderate	High		
Cost effectiveness	No included studies (5)	Favors the comparison	Does not favor either the intervention or the comparison	Favors the intervention (2)			
Equity	Uncertain (7)	Reduced	Probably no impact	Increased			
Acceptability	Uncertain (1)	No	Yes (6)				
Feasibility	Uncertain	No	Yes (7)				• As of March 24, there are 1,318 HFNC machines available in hospitals in Metro Manila.

Appendix 2. PRISMA Flow Diagram



Appendix 3. Characteristics of Included Studies

Study ID Title Author	Study Design	Setting/Country	Total number of Patients Included	Population	Intervention	Comparator/Control	Outcomes
The value of high-flow nasal cannula oxygen therapy in treating novel coronavirus pneumonia Teng et. Al (2020)	Randomized controlled trial	Fuyang, China	22	Age >28 years Met the diagnostic criteria for patients with evere COVID-19	Admitted to ICU HFNC oxygen therapy machine model: Optiflow PT101AZ Parameters: Temp 37 oC Flow Rate: 50LPM Oxygen concentration 50% Parameters were adjusted according to blood oxygen saturation level (SpO2), blood gas and tolerance, maintaining SpO2 above 93 Duration of continuous treatment for all patients was >72 hours	Conventional Oxygen therapy: Admitted to ICU Nasal catheter or common mask (including venturi and oxygen storage mask) Initial O2 absorption flow at 5lpm (adjusted according to the condition of SpO2 above 93%) Duration of treatment >72 hours *All patients were given Lopinavir/ritonavir tablets and interferon alpha as antiviral treatment for regulation of gastrointestinal flora and protection of organ function	Comparison of HR, RR and PaO2/FiO2 at each time point between 2 groups Comparison of infection indexes between two groups before and after oxygen therapy Comparison of length of ICU stay and total length of hospitalizarion between thr two groups

An adaptive randomized controlled trial of non-invasive respiratory strategies in acute respiratory failure patients with COVID-19 Perkins et. Al (2021) (PREPRINT)	Parallel group, open-label, three-arm, adaptive, randomized controlled trial	London, United Kingdom	1259	Adults >18 years old hospitalized with COVID-19 Acute respirator failure defined as SpO2 of <94% despite receiving a fraction of inspired oxygen of at least 0.4 Deemed suitable for tracheal intubation of treatment escalation was required	Participants randomized to High Flow Nasal Cannula started treatment as soon as possible	Conventional oxygen therapy (via face mask or nasal cannulae)	Primary Outcome Composite outcome of tracheal intubation or mortality within 30-days of randomization Secondary Outcomes Incidence of tracheal intubation and mortality at 30 days Time to tracheal intubation Duration of invasive mechanical ventilation Time to death Mortality Incidence of intensive care unit admission Length of stay

Appendix 4. Risk of Bias Assessment of Included Studies

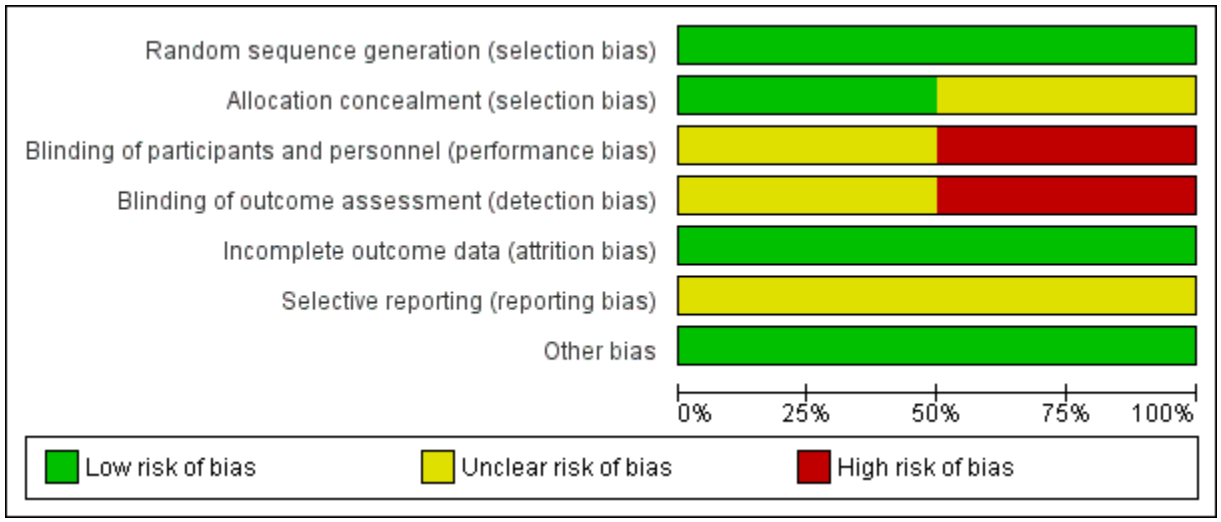


Figure 3-1 Risk of Bias Graph of Included Studies

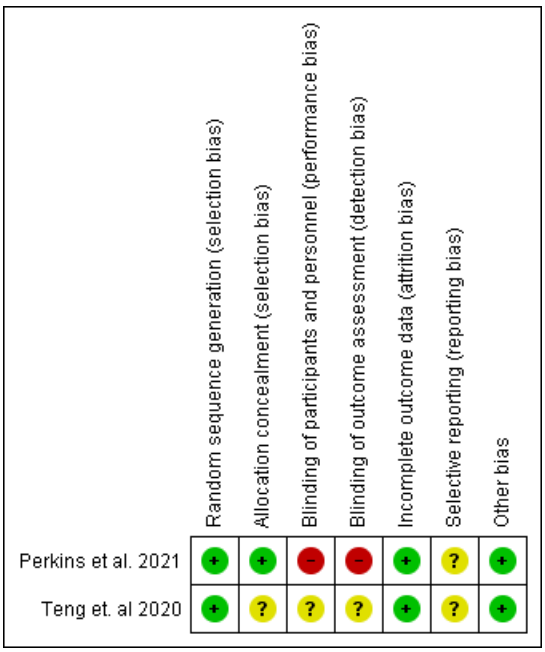


Figure 3-2 Risk of Bias Summary of Included Studies

Appendix 5. Forest Plots of Pooled Results

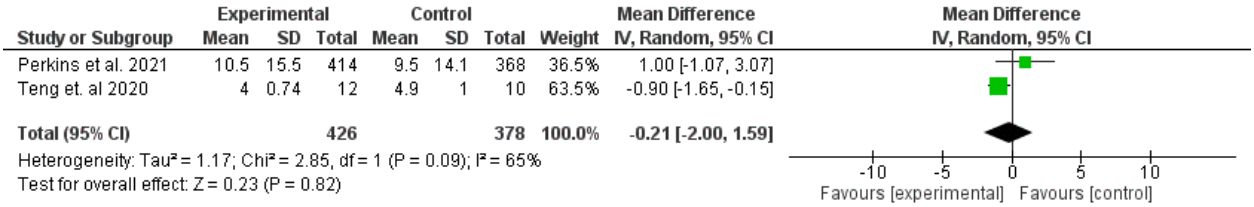


Figure 4-1 Forest plot for Intensive Care Unit Length of Stay

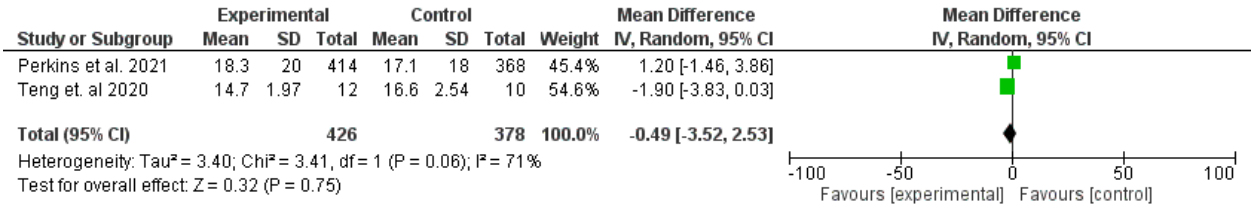


Figure 4-2 Forest plot for Overall Hospital Length of Stay

Appendix 6. GRADE Evidence Profile

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HFNC	COT	Relative (95% CI)	Absolute (95% CI)		
30-day Mortality												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	78/415 (18.8%)	74/370 (20.0%)	**RR 0.94** (0.71 to 1.25)	**12 fewer per 1,000** (from 58 fewer to 50 more)	⨁⨁⨁◯ Moderate	CRITICAL
Tracheal Intubation												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	169/414 (40.8%)	154/368 (41.8%)	**RR 0.98** (0.83 to 1.15)	**8 fewer per 1,000** (from 71 fewer to 63 more)	⨁⨁⨁◯ Moderate	CRITICAL
Critical Care Unit Admission												
1	randomised trials	serious[b]	not serious	not serious	not serious	none	253/416 (60.8%)	214/368 (58.2%)	**RR 1.05** (0.93 to 1.17)	**29 more per 1,000** (from 41 fewer to 99 more)	⨁⨁⨁◯ Moderate	CRITICAL

ICU Length of Stay

2	randomised trials	serious[b]	not serious	not serious	serious[c]	none	428	380	-	MD **0.21 days lower** (2 lower to 1.59 higher)	⨁⨁◯◯ Low	IMPORTANT

Hospital Length of Stay

2	randomised trials	serious[b]	not serious	not serious	serious[c]	none	428	380	-	MD **0.49 days lower** (3.52 lower to 2.54 higher)	⨁⨁◯◯ Low	IMPORTANT

PaO2/FiO2 at 6 hours

1	randomised trials	serious[b]	not serious	not serious	not serious	none	12	10	-	MD **30.5 mmHg higher** (23.29 higher to 37.71 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

PaO2/FiO2 at 24 hours

1	randomised trials	serious[b]	not serious	not serious	not serious	none	12	10	-	MD **34.9 mmHg higher** (28.61 higher to 41.19 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

PaO2/FiO2 at 72 hours

1	randomised trials	serious[b]	not serious	not serious	not serious	none	12	10	-	MD **34.52 mmHg higher** (29.25 higher to 39.79 higher)	⨁⨁⨁◯ Moderate	IMPORTANT

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

Explanations

a. Risk estimates cross line of no effect

b. Unclear to high-risk selection and performance bias

c. Mean difference estimates cross line of no difference

Appendix 7: Characteristics of Ongoing Clinical Trials

Title Identifier Expected Completion Date	Intervention	Comparator/Control	Patients/Population Recruited	Outcomes
High-Flow Nasal Therapy Versus Conventional Oxygen Therapy in Patients With COVID-19: A Randomized Controlled Trial (The COVID-HIGH Trial) NCT04655638 Expected completion date: October 2021	High flow nasal therapy	Conventional oxygen therapy	Inclusion Criteria: • Age ≥ 18 years old • Tested positive for SARS-CoV-2 using real-time reverse transcriptase PCR (RT-PCR) nasopharyngeal swabs • Clinical signs of acute respiratory infection and radiological evidence of pneumonia • Hospital admission in any ward or Emergency Department within 48 h • SpO2 ≤ 92% or PaO2/FiO2 < 300 in room air and need for oxygen therapy according to clinical judgment, at the screening	Primary Outcome Measures : 1. Proportion of patients needing escalation of treatment during hospital stay [Time Frame: 28 days] Proportion of patients needing escalation of treatment (i.e. noninvasive ventilation - including CPAP - or intubation). Secondary Outcome Measures : 1. Proportion of patients needing intubation during hospital stay [Time Frame: 28 days] 2. Proportion of patients who receive CPAP during hospital stay [Time Frame: 28 days] Proportion of patients who receive continuous positive airway pressure during hospital stay

				3. Proportion of patients who receive NIV during hospital stay [Time Frame: 28 days] Proportion of patients undergone noninvasive ventilation (e.g. BiLevel, PSV) 4. Proportion of patients admitted to intensive care unit during hospital stay [Time Frame: 28 days] 5. Proportion of patients who terminate the study protocols for improvement [Time Frame: 28 days] 6. Length of stay in hospital [Time Frame: 28 days] 7. Time to escalation of treatment to CPAP/NIV during hospital stay [Time Frame: 28 days] 8. Time to escalation of treatment to intubation/invasive ventilation during hospital stay [Time Frame: 28 days] 9. Length of stay in ICU [Time Frame: 28 day] 10. Days free from CPAP/NIV during hospital stay [Time Frame: 28 days]

				11. Ventilator-free days during hospital stay [Time Frame: 28 days] 12. Oxygen-free days during hospital stay [Time Frame: 28 days] 13. 28-day mortality [Time Frame: 28 days from hospital admission] 14. 60-day mortality [Time Frame: 60 days from hospital admission] 15. Hospital mortality [Time Frame: 28 days] 16. Treatment interruption due to intolerance during study treatment [Time Frame: 28 days] 17. Dyspnea score (BORG scale) during hospital stay [Time Frame: 28 days] [0= no dyspnea to 10= severe dyspnea] - daily collection 18. National Early Warning Score 2 (NEWS2) during hospital stay [Time Frame: 28 days] Daily collection of Six simple physiological parameters that form the basis of the scoring system: respiration rate, oxygen saturation, systolic

				blood pressure, pulse rate, level of consciousness or new confusion, temperature. A score is allocated to each parameter, with the magnitude of the score reflecting how extremely the parameter varies from the norm. The score is then aggregated and uplifted by 2 points for people requiring supplemental oxygen to maintain their recommended oxygen saturation. Range of values: 0 (best) - 23 (worst) points. 19. ROX index during hospital stay [Time Frame: 28 days] SpO2/FiO2/Respiratory rate - daily collection
A Trial of High-Flow Nasal Cannula vs. Conventional Oxygen Therapy in Patients With SARS-CoV-2-Related Acute Respiratory Failure: the HiFlo-COVID Trial NCT04609462	High flow nasal cannula	Conventional oxygen therapy	Inclusion Criteria: • Adults > 18 years. • Emergency or ICU admission with suspected/confirmed SARS-CoV-2 infection.	Primary Outcome Measures : 1. Intubation rate [Time Frame: 28 days]. 2. Clinical recovery [Time Frame: 28 days] Modified 7-point ordinal scale: An ordinal scale of 7 points where 1= Ambulatory/no limitation of activities and 7= Death. Low

Completed: February 2021 – no results posted			• Moderate/severe acute respiratory failure: • PaO2/FiO2 < 200. • Use of accessory muscles. • Breathing rate > 25 x minute. • Have a progression < 6 hours since meeting the definition of moderate/severe acute respiratory failure secondary to suspected/confirmed SARS-CoV-2 infection.	scores denote a better outcome and high scores denote a worse outcome. Time to reduction in scale score will be measured (daily scale scoring). Secondary Outcome Measures : 1. Proportion of patients with requirement of early mechanical ventilation. [Time Frame: 7 and 14 days] 2. Mechanical ventilation-free days [Time Frame: 28 days] 3. Renal replacement therapy-free days [Time Frame: 28 days] 4. Length of ICU stay [Time Frame: 28 days] 5. Length of hospital stay [Time Frame: 28 days] 6. All-cause day-28 mortality [Time Frame: 28 days] 7. Proportion of serious adverse events [Time Frame: 28 days] 8. Proportion of bacterial - fungal infections [Time Frame: 28 days]

Comparison of High Flow Nasal Cannula (HFNC), Face-mask Non-Invasive Ventilation (NIV) & Helmet NIV in COVID-19 ARDS Patients NCT04715243 Estimated Study completion date: December 30, 2021	Intervention 1: high flow nasal cannula Intervention 2: helmet NIV	Face-mask NIV	Inclusion Criteria: • > 18 years of age • confirmed COVID-19 • Within 48 hours of presentation in the emergency department, high dependency area or intensive care unit (ICU) • ARDS according to Berlin definition (P/F < 300) or O2 saturation < 90% or RR > 30/min) in room air • Standard oxygen therapy at flow rate < 15L/min x 60 minutes	Primary Outcome Measures : 1. Rate of endotracheal intubation [Time Frame: within the study period with an average of one month.] Secondary Outcome Measures : 1. Hospital mortality [Time Frame: 90 days from the hospital mortality.] 2. Hospital length of stay [Time Frame: Throughout the study completion. An average of 90 days.] 3. Ventilator free days [Time Frame: Throughout the study completion. An average of 90 days.]
A randomised controlled trial of high flow nasal oxygen versus non rebreathing oxygen face mask therapy in acute hypoxemic respiratory failure CTRI/2020/12/029803 *Not yet recruiting*	Intervention 1: high flow nasal cannula	Conventional oxygen therapy	All adult patients aged 18 years and above diagnosed as acute hypoxemic respiratory failure with covid positive status	Treatment failure
Randomized Controlled Trial to evaluate the effectiveness of HFNC and standard non-	High flow nasal cannula	Standard non-rebreathing mask	Adult patients with COVID-19 pneumonia	Time to progression to severe disease

rebreathing mask for oxygen therapy in moderate category COVID 19 pneumonia CTRI/2021/01/030829 *Not yet recruiting*				PaO2/FiO2 ratio, patient tolerance & acceptability will be assessed and Length of hospital stay will be recorded
COMPARISON USE OF HIGH-FLOW NASAL CANNULA AND NON INVASIVE VENTILATION IN PATIENTS WITH COVID-19: A RANDOMIZED COMPARATIVE STUDY CTRI/2020/11/029356 *Not yet recruiting*	High flow nasal cannula vs NIV	High flow nasal cannula vs NIV	Patients with COVID-19 rtPCR positive who requires HFNO and NIV as first line therapy	Reduction in respiratory distress signs like decrease in respiratory rate and increase in saturation SpO2 90%. Improvement in hemodynamic stability such as Heart rate, respiratory rate and blood pressure mprovement in chest x-ray/High Resolution Computerised Tomography. ICU stay and outcome of HFNO and NIV. Incidence of failed HFNO and NIV who needs intubation
Efficacy of awake prone positioning with high flow nasal cannula versus prone positioning with non-rebreathing mask in COVID-19 patients. A prospective comparative study CTRI/2020/12/029587 *Not yet recruiting*	Awake prone positioning with high flow nasal cannula	Awake prone positioning with non-rebreathing mask	Adult Confirmed COIVD19 positive patients admitted to ICU for acute hypoxemic respiratory failure	Intubation rates Intubation-free ICU stay Time to require NIV

n adult patients with known or suspected COVID-19, does the use of Continuous Positive Airway Pressure (CPAP) or high-flow nasal oxygen (HFNO), compared with standard care reduce mortality or need for tracheal intubation? ISRCTN16912075 *Ongoing recruitment*	Arm 1: Continuous positive airway pressure (CPAP), administered according to local protocol/guidelines. Administration will be left to clinical discretion. Arm 2: High flow nasal oxygen (HFNO) will be administered according to local protocol/guidelines. Administration will be left to clinical discretion.	Arm 3: Standard care. Standard oxygen therapy according to local protocol/guidelines	Current participant inclusion criteria as of 04/05/2021: 1. Adults =18 years 2. Hospital inpatient with suspected or proven COVID-19 3. FiO2 =0.4 and SpO2 =94% 4. Plan for escalation to intubation if needed	Composite outcome comprising tracheal intubation or mortality within 30 days. Mortality will be reported from hospital records up until discharge and tracked after discharge. Intubation will be obtained from hospital data Current secondary outcome measures as of 04/05/2021: All outcome measures are assessed at up to 30-days or hospital discharge, whichever is later, and obtained from hospital records unless otherwise specified. 1. Intubation rate 2. Time to intubation 3. Time to death (mortality), obtained from hospital record or other source 4. Mortality in critical care (level 2/3) 5. Mortality during hospital stay 6. Mortality at 30 days, obtained from hospital record or other source 7. Length of stay in critical care (level 2/3) 8. Length of stay in hospital 9. Duration of invasive ventilation 10. Admission to ICU
Evaluation of the effectiveness of high flow nasal cannula (HFNC) oxygen delivery in comparison with non-invasive ventilation (NIV) in patients with COVID-19	HFNC	NIV	Adults with COVID-19 pneumonia	Partial pressure of carbon dioxide. Timepoint: Before the intervention, 24 hours after the intervention and 48 hours after the intervention. Oxygen saturation

IRCT20160516027929N8 *Recruitment status completed, but no available results*				
High flow nasaloxygen versus Continuous Positive Airway Pressure Helmet Evaluation: A Randomized Crossover Trial in COVID-19 Pneumonia NCT04381923 Estimated study completion date: December 15, 2022	HFNO (active comparator, arm 1)	Helmet CPAP (active comparator, arm 2)	Adult patients with confirmed COVID-19 with an Sp02 < 92% on ≥ 6 liters NC admitted to a Penn Medicine advanced respiratory unit. An advanced respiratory unit is a unit capable of non-invasive respiratory support such as an ICU or intermediate care unit.	Ventilator-free days ICU and hospital length of stay Intubation Renal replacement therapy Mortality